J Am Soc Nephrol 11: S1–S86, 2000

# 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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1046-6673/1110-0001

Journal of the American Society of Nephrology

## 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 nonimmunologic 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-

*Table 1.* Table of contents



curring 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) | Screen for graft dysfunction |
| | 3 to 6 mo | 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 reevaluation 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 injures 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 | 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).<br>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).<br>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).<br>Patients should be informed of the significance of increases in serum creatinine levels and the need for monitoring (C).<br>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).<br>Periodic screening with more accurate methods for assessment of GFR is optional (C). |

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 $\leq$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 (*de novo* 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).<br>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).<br>Dipsticks that measure protein concentrations are suitable for screening, although protein/creatinine ratios are more accurate (B).<br>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).<br>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 semiquantitative 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, $\geq$2) (86), 20% (85), 24% (Banff chronic grade, $\geq$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 multifactoral, 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).<br>Renal function, BP, and blood glucose levels should be measured periodically (B).<br>Therapeutic blood level monitoring is beneficial (B).<br>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).<br>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).<br>Lipoprotein levels, complete blood counts, and platelet levels should be measured periodically (B).<br>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/m$^2$ twice daily (204). The authors of one study recommended that the dose for children should be 600 mg/m$^2$ twice daily when MMF is used in combination with CsA, 300 mg/m$^2$ twice daily when MMF is used with tacrolimus, and 500 mg/m$^2$ 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/m$^2$ 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, *e.g.*, 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/$\mu$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. Hepatoxicity, 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, *e.g.,* 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 histories 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 $\mu$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 | 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).<br>● low-risk patients may proceed to surgery without further evaluation (B).<br>● intermediate-risk patients undergoing vascular surgery should undergo dipyridamole thallium (or sestamibi) or dobutamine echocardiography (B).<br>● intermediate-risk patients undergoing nonvascular surgery should undergo dipyridamole thallium (or sestamibi) or dobutamine echocardiography (C).<br>● High-risk patients should be considered for revascularization before the planned surgery if the need for surgery is not urgent (C).<br>Some high-risk patients may benefit from perioperative management using a pulmonary artery catheter (B).<br>Elective surgery should probably be postponed for patients who have experienced strokes or transient ischemic attacks in the previous 6 mo (B).<br>There are insufficient data to determine whether identification of individuals with asymptomatic carotid artery disease should be part of the presurgical evaluation (C). |

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 ≤135/85 mmHg for renal transplant recipients without proteinuria and should possibly be ≤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 μM 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 μM for men and 10.4 μM 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 palycythemia 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/cm$^2$ for the lumbar sacral spine and 0.600 g/cm$^2$ 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).<br>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 guidelines 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 than 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 recommend 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).<br>Follow-up surveillance, with biopsies of lesions and prompt treatment of warts, is recommended (A).<br>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 *de novo* 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).<br>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).<br>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).<br>There are insufficient data to recommend for or against measuring EBV gene expression in tissue, *e.g.*, the renal allograft, to screen for PTLD among renal transplant recipients (C).<br>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

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| 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 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 examinations 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

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| 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 $\alpha$-fetoprotein levels every 6 to 12 mo for patients with liver disease could assist in early detection of hepatocellular carcinomas (C).<br>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 $\alpha$-fetoprotein can be detected in some patients with early stages of hepatocellular carcinoma (770). The sensitivity of serum $\alpha$-fetoprotein analyses for the detection of small hepatocellular carcinomas is low (between 20 and 60%) (770,772). Serum $\alpha$-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 $\alpha$-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

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| 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 *in situ* 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 $\geq$18 yr of age and girls $<$18 yr of age who are sexually active should undergo pelvic examinations, with Pap smears, annually (A).<br>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).<br>Colposcopy screening for cervical cancer is not recommended (D).<br>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 $\alpha$-fetoprotein, plasma urokinase-type plasminogen activator, serum des-$\gamma$-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

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| 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 | Women 50 to 69 yr of age should undergo screening mammography every 1 to 2 yr, with or without clinical breast examinations (A).<br>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).<br>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).<br>Women <50 yr of age who are at high risk (*e.g.,* 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). |

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

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| 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 $\geq$50 yr of age should undergo screening for colorectal cancer with annual fecal occult blood testing and flexible sigmoidoscopy performed every 5 yr (A).<br>Patients who are at higher risk for colorectal carcinoma may need more frequent screening for colorectal carcinoma (A).<br>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 $\geq$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

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|---|---|
| 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).<br>Men at increased risk, *e.g.*, 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 ultrasonography 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 $\geq$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 $\geq$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).<br>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 Biotec, 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]

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|---|---|
| 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, *e.g.,* shell vial cultures (C), and methods to detect CMV antigenemia (C).<br>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 immunodominant 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).<br>Health care workers with close contact with renal transplant recipients should also receive annual influenza vaccinations, to protect themselves and their patients (A).<br>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).<br>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]

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|---|---|
| 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, *e.g.*, 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; $P$ = 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 alternative, 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/sulfamethoxozole (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 | *Pneumocystis carinii* pneumonia causes substantial morbidity and death after renal transplantation. |
| Rationale | Infection is potentially fatal. Prophylaxis is effective and relatively safe. |
| Recommendations | Chemoprophylaxis with trimethoprim/sulfamethoxozole is strongly recommended. For patients who cannot tolerate trimethoprim/sulfamethoxozole, dapsone, pentamidine, or atovaquone should be considered (A).<br>Chemoprophylaxis should be used during periods of intensive immunosuppression, *e.g.*, 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 *de novo* 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).<br>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).<br>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).<br>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).<br>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 $\alpha$-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 enzyme 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. *Haemophilus influenzae* is a common pathogen in children, and is not unusual in immunocompromised adults. *Varicella* is very common. The incidences of both *H. influenzae* and *Varicella* 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 $\leq$12 yr of age and twice (4 to 8 wk apart) if $\geq$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.

## Acknowledgments

We thank the following reviewers for their helpful suggestions and comments: Drs. Margaret J. Bia, William M. Bennett (for the American Society of Nephrology), Daniel C. Brennan, William E. Braun, Jay A. Fishman, Donald E. Hricik, Alan S. Kliger (for the Renal Physicians Association), Andrew S. Levey, Connie C. Manske, Mariana S. Markel, Sharon Moe, John F. Neylan, Brian J. G. Pereira, Israel Penn, David N. Rush, Charles L. Smith, Amir H. Tejani (for the North American Pediatric Renal Transplant Cooperative Study), Rocco C. Venuto, and Matthew R. Weir.

## Endorsements

These guidelines were endorsed by the American Society of Nephrology, the American Society of Pediatric Nephrology, the National Kidney Foundation, the North American Pediatric Renal Transplant Cooperative Study, and the Renal Physicians Association.

## References

1. Kasiske BL, Ramos EL, Gaston RS, Bia MJ, Danovitch GM, Bowen PA, Lundin PA, Murphy K: The evaluation of renal transplant candidates: Clinical practice guidelines. *J Am Soc Nephrol* 6: 1–34, 1995
2. Canadian Task Force on the Periodic Health Examination: Task Force Report on the Periodic Health Examination. *Can Med Assoc J* 121: 1193–1254, 1979
3. United States Preventive Services Task Force: *Guide to Clinical Preventive Services: An Assessment of the Effectiveness of 169 Interventions*. Baltimore, Williams & Wilkins, 1989
4. Benfield MR, McDonald R, Sullivan EK, Stablein DM, Tejani A: The 1997 Annual Renal Transplantation in Children Report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). *Pediatr Transplant* 3: 152–167, 1999
5. Cecka JM: The UNOS Scientific Renal Transplant Registry: Ten Years of Kidney Transplants. In: *Clinical Transplants 1997*, edited by Cecka JM, Terasaki PI, Los Angeles, UCLA Tissue Typing Laboratory, 1998, pp 1–14
6. Pescovitz MD, Barone G, Choc MGJ, Hricik DE, Hwang DS, Jin JH, Klein JB, Marsh CL, Min DI, Pollak R, Pruett TL, Stinson JB, Thompson JS, Vasquez E, Waid T, Wombolt DG, Wong RL: Safety and tolerability of cyclosporine microemulsion versus cyclosporine: Two-year data in primary renal allograft recipients: A report of the Neoral Study Group. *Transplantation* 63: 778–780, 1997
7. Basgoz N, Rubin RH: Prevention and treatment of infection in kidney transplant recipients. In: *Therapy in Nephrology and Hypertension*, edited by Brady HR, Wilcox CS, Philadelphia, W.B. Saunders Co., 1999, pp 634–640
8. Rubin RH: Infectious diseases in transplantation/pre- and post-transplantation. In: *Primer on Transplantation*, edited by Norman DJ, Suki WN, Thorofare, NJ, American Society of Transplant Physicians, 1998, pp 141–154
9. Halloran PF, Melk A, Barth C: Rethinking chronic allograft nephropathy: The concept of accelerated senescence. *J Am Soc Nephrol* 10: 167–181, 1999
10. Massy ZA, Guijarro C, Wiederkehr MR, Ma JZ, Kasiske BL: Chronic renal allograft rejection: Immunologic and nonimmunologic risk factors. *Kidney Int* 49: 518–524, 1996
11. Sanders CE, Julian BA, Gaston RS, Deierhoi MH, Diethelm AG, Curtis JJ: Benefits of continued cyclosporine through an indigent drug program. *Am J Kidney Dis* 28: 572–577, 1996
12. Cecka JM, Gjertson DW, Terasaki PI: Pediatric renal transplantation: A review of the UNOS data: United Network for Organ Sharing. *Pediatr Transplant* 1: 55–64, 1997
13. Tejani A, Stablein D, Alexander S, Fine R, Harmon W: Analysis of rejection outcomes and implications: A report of the North American Pediatric Renal Transplant Cooperative Study. *Transplantation* 59: 500–504, 1995
14. Broyer M, Chantler C, Donckerwolcke R, Ehrich JHH, Rizzoni G, Schärer K: The paediatric registry of the European Dialysis and Transplant Association: 20 years' experience. *Pediatr Nephrol* 7: 758–768, 1993
15. Davis ID, Bunchman TE, Grimm PC, Benfield MR, Briscoe DM, Harmon WE, Alexander SR, Avner ED: Pediatric renal transplantation: Indications and special considerations: A position paper from the Pediatric Committee of the American Society of Transplant Physicians. *Pediatr Transplant* 2: 117–129, 1998
16. Warady BA, Alexander SR, Watkins S, Kohaut E, Harmon WE: Optimal care of the pediatric end-stage renal disease patient on dialysis. *Am J Kidney Dis* 33: 567–583, 1999
17. Schurman SJ, Stablein DM, Perlman SA, Warady BA: Center volume effects in pediatric renal transplantation: A report of the North American Pediatric Renal Transplant Cooperative Study. *Pediatr Nephrol* 13: 373–378, 1999
18. Excerpts from the United States Renal Data System 1998 Annual Data Report. *Am J Kidney Dis* 32 (2 Suppl 1): S1–S162, 1998
19. De Geest S, Borgermans L, Gemoets H, Abraham I, Vlaminck H, Evers G, Vanrenterghem Y: Incidence, determinants, and consequences of subclinical noncompliance with immunosuppressive therapy in renal transplant recipients. *Transplantation* 59: 340–347, 1995
20. Gaston RS, Hudson SL, Ward M, Jones P, Macon R: Late renal allograft loss: Non-compliance masquerading as chronic rejection. *Transplant Proc* 31: 21S–23S, 1999
21. Cramer JA: Relationship between medication compliance and medical outcomes. *Am J Health Syst Pharm* 52: S27–S29, 1995
22. Burke BA, Chavers BM, Gillingham KJ, Kashtan CE, Manivel JC, Mauer SM, Nevins TE, Matas AJ: Chronic renal allograft rejection in the first 6 months posttransplant. *Transplantation* 60: 1413–1417, 1995
23. Bumgardner GL, Wilson GA, Tso PL, Henry ML, Elkhammas EA, Davies EA, Qiu W, Ferguson RM: Impact of serum lipids on long-term graft and patient survival after renal transplantation. *Transplantation* 60: 1418–1421, 1995
24. Traindl O, Falger S, Reading S, Banyai M, Liebisch B, Gisinger J, Templ E, Mayer G, Kovarik J: The effects of lisinopril on renal function in proteinuric renal transplant recipients. *Transplantation* 55: 1309–1313, 1993
25. Bochicchio T, Sandoval G, Ron O, Pérez-Grovas H, Bordes J, Herrera-Acosta J: Fosinopril prevents hyperfiltration and decreases proteinuria in post-transplant hypertensives. *Kidney Int* 38: 873–879, 1990
26. Salahudeen AK, Hostetter TH, Raatz SK, Rosenberg ME: Effects of dietary protein in patients with chronic renal transplant rejection. *Kidney Int* 41: 183–190, 1992
27. Kootte AMM, 't Hart-Eerdmans M, Paul LC: Dietary protein manipulation or cyclosporin therapy in chronic renal allograft rejection. *Clin Transplant* 2: 152–159, 1988
28. Rosenblum ND, Harmon WE, Levey RH: Treatment of chronic renal allograft rejection with cyclosporine and prednisone. *Transplantation* 45: 232–234, 1988

29. Rowe PA, Foster MC, Morgan AG: Use of cyclosporine in chronic renal allograft rejection. *Transplantation* 46: 783–784, 1988
30. Rocher LL, Hodgson RJ, Merion RM, Swartz RD, Keavey S, Turcotte JG, Campbell DA Jr: Amelioration of chronic renal allograft dysfunction in cyclosporine-treated patients by addition of azathioprine. *Transplantation* 47: 249–254, 1989
31. Isoniemi HM, Ahonen J, Tikkanen MJ, van Willebrand EO, Krogerus L, Eklund BH, Hockerstedt KV, Salmela KE, Hayry PJ: Long-term consequences of different immunosuppressive regimens for renal allografts. *Transplantation* 55: 494–499, 1993
32. Kalil RSN, Heim-Duthoy KL, Kasiske BL: Patients with a low income have reduced renal allograft survival. *Am J Kidney Dis* 20: 63–69, 1992
33. Ross EA, Wilkinson A, Hawkins R, Danovitch GM: The plasma creatinine concentration is not an accurate reflection of the glomerular filtration rate in stable renal transplant patients receiving cyclosporine. *Am J Kidney Dis* 10: 113–117, 1987
34. Tomlanovich S, Golbetz H, Perlroth M, Stinson E, Myers BD: Limitations of creatinine in quantifying the severity of cyclosporine-induced chronic nephropathy. *Am J Kidney Dis* 8: 332–337, 1986
35. Schuck O, Matl I, Nadvornikova H, Teplan V, Skibova J: Cyclosporine A treatment and evaluation of glomerular filtration rate in patients with a transplanted kidney. *Int J Clin Pharmacol Ther Toxicol* 30: 195–201, 1992
36. Nankivell BJ, Gruenewald SM, Allen RD, Chapman JR: Predicting glomerular filtration rate after kidney transplantation. *Transplantation* 59: 1683–1689, 1995
37. Nankivell BJ, Chapman JR, Allen RD: Predicting glomerular filtration rate after simultaneous pancreas and kidney transplantation. *Clin Transplant* 9: 129–134, 1995
38. Bedros F, Kasiske BL: Estimating GFR from serum creatinine in renal transplant recipients. *J Am Soc Nephrol* 9: 666A, 1998
39. Aufricht C, Balbisi A, Gerdov C, Muller T, Lothaller MA, Balzar E: Formula creatinine clearance as a substitute for 24-hour creatine clearance in children with kidney transplantation [German]. *Klin Paediatr* 207: 59–62, 1995
40. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation: Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 130: 461–470, 1999
41. Schuck O, Teplan V, Vitko S, Matl J, Skibova J, Stollova M: Predicting glomerular function from adjusted serum creatinine in renal transplant patients. *Int J Clin Pharmacol Ther* 35: 33–37, 1997
42. al-Harbi N, Lireman D: Comparison of three different methods of estimating the glomerular filtration rate in children after renal transplantation. *Am J Nephrol* 17: 68–71, 1997
43. Berg U: Evaluation of the formula clearance as a measure of the glomerular filtration rate in cyclosporin-treated children following renal transplantation. *Transplant Int* 4: 72–76, 1991
44. Kasiske BL: Creatinine excretion after renal transplantation. *Transplantation* 48: 424–428, 1989
45. Mobb GE, Veitch PS, Bell PRF: Are serum creatinine levels adequate to identify the onset of chronic cyclosporine A nephrotoxicity? *Transplant Proc* 22: 1708–1710, 1990
46. Risch L, Blumberg A, Huber A: Rapid and accurate assessment of glomerular filtration rate in patients with renal transplants using serum cystatin C. *Nephrol Dial Transplant* 14: 1991–1996, 1999
47. Bökenkamp A, Domanetzki M, Zinck R, Schumann G, Byrd D, Brodehl J: Cystatin C serum concentrations underestimate glomerular filtration rate in renal transplant recipients. *Clin Chem* 45: 1866–1868, 1999
48. Dalmeida W, Suki WN: Measurement of GFR with non-radioisotopic radio contrast agents. *Kidney Int* 34: 725–728, 1988
49. Zaltzman JS, Whiteside C, Cattran DC, Lopez FM, Logan AG: Accurate measurement of impaired glomerular filtration using single-dose oral cimetidine. *Am J Kidney Dis* 27: 504–511, 1996
50. Marcen R, Serrano P, Teruel JL, Rivera ME, Mitjavila M, Navarro J, Orofino L, Sabater J, Ortuno J: Oral cimetidine improves the accuracy of creatinine clearance in transplant patients on cyclosporine. *Transplant Proc* 26: 2624–2625, 1994
51. Olsen NV, Ladefoged SD, Feldt-Rasmussen B, Fogh-Andersen N, Jordening H, Munck O: The effects of cimetidine on creatinine excretion, glomerular filtration rate and tubular function in renal transplant recipients. *Scand J Clin Lab Investig* 49: 155–159, 1989
52. Hirata-Dulas CAI, Halstenson CE, Kasiske BL: Improvement in the accuracy and precision of creatinine clearance as a measure of glomerular filtration rate with oral cimetidine in renal transplant recipients. *Clin Transplant* 7: 552–558, 1993
53. Lewis R, Kerr N, Van Buren C, Lowry P, Sandler C, Frazier OH, Powers P, Herson J, Corriere J Jr, Kerman R, Kahan B: Comparative evaluation of urographic contrast media, inulin, and $^{99m}$Tc-DTPA clearance methods for determination of glomerular filtration rate in clinical transplantation. *Transplantation* 48: 790–796, 1989
54. Kabasakal L, Yapar AF, Ozker K, Alkan E, Atay S, Ozcelik N, Onsel C: Simplified technetium-99m-EC clearance in adults from a single plasma sample. *J Nucl Med* 38: 1784–1786, 1997
55. Hutchings VM, Sweny P, Fernando ON, Constable AR: Measurement of glomerular filtration rate without blood sampling: Validation in renal transplant patients. *Br J Radiol* 57: 347–349, 1984
56. Reinig JW, Gordon L, Frey D, Garrick E, Daniel WT: Glomerular filtration rate in transplantation patients: Estimation of renal function using Tc-99m DTPA. *Radiology* 156: 505–507, 1985
57. Cheigh JS, Mouradian J, Susin M, Stubenbord WT, Tapia L, Riggio RR, Stenzel KH, Rubin AL: Kidney transplant nephrotic syndrome: Relationship between allograft histopathology and natural course. *Kidney Int* 18: 358–365, 1980
58. First MR, Vaidya PN, Maryniak RK, Weiss MA, Munda R, Fidler JP, Penn I, Alexander JW: Proteinuria following transplantation: Correlation with histopathology and outcome. *Transplantation* 38: 607–612, 1984
59. Bear RA, Aprile M, Sweet J, Cole EH: Proteinuria in renal transplant recipients: Incidence, cause, prognostic importance. *Transplant Proc* 20: 1235–1236, 1988
60. Vathsala A, Verani R, Schoenberg L, Lewis RM, Van Buren CT, Kerman RH, Kahan BD: Proteinuria in cyclosporine-treated renal transplant recipients. *Transplantation* 49: 35–41, 1990
61. Castelao AM, Grinó JM, Serón D, Andrés E, Gil-Vernet S, Bover J, Carrera M, Torras J, Alsina J: Pathological differen-

tial diagnostics of proteinuria and late failure after renal transplantation. *Transplant Proc* 24: 110–112, 1992
62. Kim HC, Park SB, Lee SH, Park KK, Park CH, Cho WH: Proteinuria in renal transplant recipients: Incidence, cause, and prognostic importance. *Transplant Proc* 26: 2134–2135, 1994
63. Cusumano AM, Iotti R, Turin M, Davalos M, Jost L, Vilches A: Incidence, etiology and prognostic value of persistent significant proteinuria in kidney transplants [Spanish]. *Medicina (B Aires)* 56: 346–352, 1996
64. Peddi VR, Dean DE, Hariharan S, Cavallo T, Schroeder TJ, First MR: Proteinuria following renal transplantation: Correlation with histopathology and outcome. *Transplant Proc* 29: 101–103, 1997
65. Hohage H, Kleyer U, Bruckner D, August C, Zidek W, Spieker C: Influence of proteinuria on long-term transplant survival in kidney transplant recipients. *Nephron* 75: 160–165, 1997
66. Fontán MP, Rodríguez-Carmona A, Falcón TG, Valdés F: Early proteinuria in renal transplant recipients treated with cyclosporin. *Transplantation* 67: 561–568, 1999
67. Yildiz A, Erkoc R, Sever MS, Turkmen A, Ecder ST, Turk S, Kilicarslan I, Ark E: The prognostic importance of severity and type of post-transplant proteinuria. *Clin Transplant* 13: 241–244, 1999
68. Eddy AA: Experimental insights into the tubulointerstitial disease accompanying primary glomerular lesions. *J Am Soc Nephrol* 5: 1273–1287, 1994
69. Zoja C, Donadelli R, Colleoni S, Figliuzzi MBS, Morigi M, Remuzzi G: Protein overload stimulate RANTES production by proximal tubular cells depending on NF-κB activation. *Kidney Int* 53: 1608–1615, 1998
70. Perna A, Remuzzi G: Abnormal permeability to proteins and glomerular lesions: A meta-analysis of experimental and human studies. *Am J Kidney Dis* 27: 34–41, 1996
71. Kannel WB, Stampfer MJ, Castelli WP, Verter J: The prognostic significance of proteinuria: The Framingham study. *Am Heart J* 108: 1347–1352, 1984
72. Bulpitt CJ, Beevers DG, Butler A, Coles EC, Hunt D, Munro-Faure AD, Newson RB, O'Riordan PW, Petrie JC, Rajagopalan B, Rylance PB, Twallin G, Webster J, Dollery CT: The survial of treated hypertensive patients and their causes of death: A report from the DHSS Hypertensive Care Computing Project (DHCCP). *J Hypertens* 4: 93–99, 1986
73. Samuelsson O, Wilhelmsen L, Elmfeldt D, Pennert K, Wedel H, Wikstrand J, Berglund G: Predictors of cardiovascular morbidity in treated hypertension: Results from the primary preventive trial in Goteborg, Sweden. *J Hypertens* 3: 167–176, 1985
74. Keane WF, Eknoyan G: Proteinuria, albuminuria, risk, assessment, detection, elimination (PARADE): A position paper of the National Kidney Foundation. *Am J Kidney Dis* 33: 1004–1010, 1999
75. Rell K, Linde J, Morzycka-Michalik M, Gaciong Z, Lao M: Effect of enalapril on proteinuria after kidney transplantation. *Transplant Int* 6: 213–217, 1993
76. Barnas U, Schmidt A, Haas M, Oberbauer R, Mayer G: The effects of prolonged angiotensin-converting enzyme inhibition on excretory kidney function and proteinuria in renal allograft recipients with chronic progressive transplant failure. *Nephrol Dial Transplant* 11: 1822–1824, 1996
77. Borchhardt K, Haas N, Yilmaz N, Oberbauer R, Schmidt A, Barnas U, Mayer G: Low dose angiotensin converting enzyme inhibition and glomerular permselectivity in renal transplant recipients. *Kidney Int* 52: 1622–1625, 1997
78. Lufft V, Kliem V, Hamkens A, Bleck JS, Eisenberger U, Petersen R, Ehlerding G, Maschek H, Pichlmayr R, Brunkhorst R: Antiproteinuric efficacy of fosinopril after renal transplantation is determined by the extent of vascular and tubulointerstitial damage. *Clin Transplant* 12: 409–415, 1998
79. Calvino J, Lens XM, Romero R, Sanchez-Guisande D: Long-term anti-proteinuric effect of losartan in renal transplant recipients treated for hypertension. *Nephrol Dial Transplant* 15: 82–86, 2000
80. Moore RR Jr, Hirata-Dulas CA, Kasiske BL: Use of urine specific gravity to improve screening for albuminuria. *Kidney Int* 52: 240–243, 1997
81. Thistlethwaite JRJ, Woodle ES, Mayes JT, Stuart JK, Heffron TG, Spargo BH, Stuart FP: Aggressive needle biopsy protocol prevents loss of renal allografts to undetected rejection during early posttransplant dysfunction. *Transplant Proc* 21: 1890–1892, 1989
82. Gaber LW, Gaber AO, Hathaway DK, Vera SR, Shokouh-Amiri MH: Routine early biopsy of allografts with delayed function: Correlation of histopathology and transplant outcome. *Clin Transplant* 10: 629–634, 1996
83. Jain S, Curwood V, White SA, Williams ST, Doughman T, Nicholson ML: Weekly protocol renal transplant biopsies allow detection of sub-clinical acute rejection episodes in patients with delayed graft function. *Transplant Proc* 32: 191, 2000
84. Seron D, Moreso F, Ramon JM, Hueso M, Condom E, Fulladosa X, Bover J, Gil-Vernet S, Castelao AM, Alsina J, Grinyo JM: Protocol renal allograft biopsies and the design of clinical trials aimed to prevent or treat chronic allograft nephropathy. *Transplantation* 69: 1849–1855, 2000
85. Legendre C, Thervet E, Skhiri H, Mamzer-Bruneel MF, Cantarovich F, Noel LH, Kreis H: Histologic features of chronic allograft nephropathy revealed by protocol biopsies in kidney transplant recipients. *Transplantation* 65: 1506–1509, 1998
86. Rush D, Nickerson P, Gough J, McKenna R, Grimm P, Cheang M, Trpkov K, Solez K, Jeffery J: Beneficial effects of treatment of early subclinical rejection: A randomized study. *J Am Soc Nephrol* 9: 2129–2134, 1998
87. Solez K, Vincenti F, Filo RS: Histopathologic findings from 2-year protocol biopsies from a U.S. multicenter kidney transplant trial comparing tacrolimus versus cyclosporine: A report of the FK506 Kidney Transplant Study Group. *Transplantation* 66: 1736–1740, 1998
88. Kuypers DRJ, Chapman JR, O'Connell PJ, Allen RDM, Nankivell BJ: Predictors of renal transplant histology at three months. *Transplantation* 67: 1222–1230, 1999
89. Gecim IE, Rowlands P, McDicken I, Bakran A, Sells RA, Gladman M, Gillies J: Core needle biopsy in renal transplantation. *Int Urol Nephrol* 27: 357–363, 1995
90. Kolb LG, Velosa JA, Bergstralh EJ, Offord KP: Percutaneous renal allograft biopsy: A comparison of two needle types and analysis of risk factors. *Transplantation* 57: 1742–1746, 1994
91. Riehl J, Maigatter S, Kierdorf H, Schmitt H, Maurin N, Sieberth HG: Percutaneous renal biopsy: Comparison of manual and automated puncture techniques with native and transplanted kidneys. *Nephrol Dial Transplant* 9: 1568–1574, 1994
92. Beckingham IJ, Nicholson ML, Kirk G, Veitch PS, Bell PR: Comparison of three methods to obtain percutaneous needle core biopsies of a renal allograft. *Br J Surg* 81: 898–899, 1994

93. Nickerson P, Jeffery J, Gough J, Grimm P, McKenna R, Birk P, Rush D: Effect of increasing baseline immunosuppression on the prevalence of clinical and subclinical rejection: A pilot study. *J Am Soc Nephrol* 10: 1801–1805, 1999
94. Rush DN, Nickerson P, Jeffery JR, McKenna RM, Grimm PC, Gough J: Protocol biopsies in renal transplantation: Research tool or clinically useful? *Curr Opin Nephrol Hypertens* 7: 691–694, 1998
95. Sobh MA, Moustafa FE, Ghoneim MA: Fine-needle aspiration biopsy: A reproducibility study and a correlation with the Tru-cut biopsy in the evaluation of renal allotransplants. *Nephrol Dial Transplant* 2: 562–567, 1987
96. Helderman JH, Hernandez J, Sagalowsky A, Dawidson I, Glennie J, Womble D, Toto RD, Brinker K, Hull AR: Confirmation of the utility of fine needle aspiration biopsy of the renal allograft. *Kidney Int* 34: 376–381, 1988
97. Reinholt FP, Bohman SO, Wilczek H, von Willebrand E, Hayry P: Fine-needle aspiration cytology and conventional histology in 200 renal allografts. *Transplantation* 49: 910–912, 1990
98. Danovitch GM, Nast CC, Wilkinson A, Rosenthal T: Evaluation of fine-needle aspiration biopsy in the diagnosis of renal transplant dysfunction. *Am J Kidney Dis* 17: 206–210, 1991
99. Gray DW, Richardson A, Hughes D, Fuggle S, Dunnill M, Higgins R, McWhinnie D, Morris PJ: A prospective, randomized, blind comparison of three biopsy techniques in the management of patients after renal transplantation. *Transplantation* 53: 1226–1232, 1992
100. Oliveira JG, Ramos JP, Xavier P, Magalhaes MC, Mendes AA, Guerra LE: Analysis of fine-needle aspiration biopsies by flow cytometry in kidney transplant patients. *Transplantation* 64: 97–102, 1997
101. Oliveira G, Xavier P, Murphy B, Neto S, Mendes A, Sayegh MH, Guerra LE: Cytokine analysis of human renal allograft aspiration biopsy culture supernatants predicts acute rejection. *Nephrol Dial Transplant* 13: 417–422, 1998
102. Canadian Multicentre Transplant Study Group: A randomized clinical trial of cyclosporine in cadaveric renal transplantation. *N Engl J Med* 309: 809–815, 1983
103. Canadian Multicentre Transplant Study Group: A randomized clinical trial of cyclosporine in cadaveric renal transplantation: Analysis at three years. *N Engl J Med* 314: 1219–1225, 1986
104. European Multicenter Trial Group: Cyclosporin in cadaveric renal transplantation: One-year follow-up of a multicentre trial. *Lancet* 2: 986–989, 1983
105. Calne RY: Cyclosporin in cadaveric renal transplantation: 5-year follow-up of a multicentre trial. *Lancet* 2: 506–507, 1987
106. Najarian JS, Fryd DS, Strand M, Canafax DM, Ascher NL, Payne WD, Simmons RL, Sutherland DER: A single institution, randomized, prospective trial of cyclosporine versus azathioprine-antilymphocyte globulin for immunosuppression in renal allograft recipients. *Ann Surg* 201: 142–157, 1985
107. Ponticelli C, Civati G, Tarantino A, Quarto dP, Corbetta G, Minetti L, Vegeto A, Belli L: Randomized study with cyclosporine in kidney transplantation: 10-year follow-up. *J Am Soc Nephrol* 7: 792–797, 1996
108. Savoldi S, Kahan BD: Relationship of cyclosporine pharmacokinetic parameters to clinical events in human renal transplantation. *Transplant Proc* 18: 120–128, 1986
109. Kasiske BL, Heim-Duthoy K, Rao KV, Awni WM: The relationship between cyclosporine pharmacokinetic parameters and subsequent acute rejection in renal transplant recipients. *Transplantation* 46: 716–722, 1988
110. Dunn J, Grevel J, Napoli K, Lewis RM, Van Buren CT, Kahan BD: The impact of steady-state cyclosporine concentrations on renal allograft outcome. *Transplantation* 49: 30–34, 1990
111. Grevel J, Kahan BD: Area under the curve monitoring of cyclosporine therapy: The early posttransplant period. *Ther Drug Monit* 13: 89–95, 1991
112. Lindholm A, Lundgren G, Fehrman I, Weibull H, Brynger H, Frodin L, Flatmark A: Influence of early cyclosporine dosage and plasma and whole blood levels on acute rejections in cadaveric renal allograft recipients. *Transplant Proc* 20: 444–446, 1988
113. Lindholm A, Welsh M, Rutzky L, Kahan BD: The adverse impact of high cyclosporine clearance rates on the incidences of acute rejection and graft loss. *Transplantation* 55: 985–993, 1993
114. Lindholm A, Kahan BD: Influence of cyclosporine pharmacokinetics, trough concentrations, and AUC monitoring on outcome after kidney transplantation. *Clin Pharmacol Ther* 54: 205–218, 1993
115. Meyer MM, Munar M, Udeaja J, Bennett W: Efficacy of area under the curve cyclosporine monitoring in renal transplantation. *J Am Soc Nephrol* 4: 1306–1315, 1993
116. Nankivell BJ, Hibbins M, Chapman JR: Diagnostic utility of whole blood cyclosporine measurements in renal transplantation using triple therapy. *Transplantation* 58: 989–996, 1994
117. Khauli RB, Wilson JM, Baker SP, Valliere SA, Lovewell TD, Stoff JS: Triple therapy in cadaveric renal transplantation: Role of induction cyclosporine and targeted levels to avoid rejection. *J Urol* 153: 1805–1809, 1995
118. Masri MA, Dhawan VS, Hayes K, Karim T, Pingle A: Cyclosporine dosage according to pharmacokinetic profiles leads to better graft and patient survival rates and a decrease in cyclosporine consumption. *Transplant Proc* 24: 1718–1720, 1992
119. Matas AJ, Gillingham KJ, Chavers BM, Nevins T, Kashtan C, Mauer SM, Payne WD, Gruessner R, Najarian JS: The importance of early cyclosporine levels in pediatric kidney transplantation. *Clin Transplant* 10: 482–486, 1996
120. Senel MF, Van Buren CT, Welsh M, Kahan BD: Impact of early cyclosporin average blood concentration on early kidney transplant failure. *Transplant Int* 11: 46–52, 1998
121. Harmon WE, Sullivan EK: Cyclosporine dosing and its relationship to outcome in pediatric renal transplantation. *Kidney Int* 43[Suppl]: S50–S55, 1993
122. Tejani A: Steady improvement in renal allograft survival among North American children: A five year appraisal by the North American Pediatric Renal Transplant Cooperative Study. *Kidney Int* 48: 551–553, 1995
123. Tejani A, Sullivan EK: Higher maintenance cyclosporine dose decreases the risk of graft failure in North American children: A report of the North American Pediatric Renal Transplant Cooperative Study. *J Am Soc Nephrol* 7: 550–555, 1996
124. Kahan BD, Kramer WG, Wideman C, Flechner SM, Lorber MI, Van Buren CT: Demographic factors affecting the pharmacokinetics of cyclosporine estimated by radioimmunoassay. *Transplantation* 41: 459–464, 1986
125. Kelles A, Van Damme-Lombaerts R, Tjandra-Maga TB, Van Damme B: Long-term cyclosporin A pharmacokinetic profiles in pediatric renal transplant recipients. *Transplant Int* 9: 546–550, 1996
126. Kahan BD, Welsh M, Schoenberg L, Rutzky LP, Katz SM,

Urbauer DL, Van Buren CT: Variable oral absorption of cyclosporine: A biopharmaceutical risk factor for chronic renal allograft rejection. *Transplantation* 62: 599–606, 1996
127. Awni WM, Kasiske BL, Heim-Duthoy K, Rao KV: Long-term cyclosporine pharmacokinetic changes in renal transplant recipients: Effects of binding and metabolism. *Clin Pharmacol Ther* 45: 41–48, 1989
128. Lindholm A, Welsh M, Alton C, Kahan BD: Demographic factors influencing cyclosporine pharmacokinetic parameters in patients with uremia: Racial differences in bioavailability. *Clin Pharmacol Ther* 52: 359–371, 1992
129. von Ahsen N, Helmhold M, Schutz E, Eisenhauer T, Armstrong VW, Oellerich M: Cyclosporin A trough levels correlate with serum lipoproteins and apolipoproteins: Implications for therapeutic drug monitoring of cyclosporin A. *Ther Drug Monit* 19: 140–145, 1997
130. Kahan BD: Cyclosporine. *N Engl J Med* 321: 1725–1738, 1989
131. Ohlman S, Lindholm A, Hagglund H, Sawe J, Kahan BD: On the intraindividual variability and chronobiology of cyclosporine pharmacokinetics in renal transplantation. *Eur J Clin Pharmacol* 44: 265–269, 1993
132. Mochon M, Cooney G, Lum B, Caputo GC, Dunn S, Goldsmith B, Baluarte HJ, Polinsky MS, Kaiser BA: Pharmacokinetics of cyclosporine after renal transplant in children. *J Clin Pharmacol* 36: 580–586, 1996
133. Grevel J, Welsh MS, Kahan BD: Cyclosporine monitoring in renal transplantation: Area under the curve monitoring is superior to trough-level monitoring. *Ther Drug Monit* 11: 246–248, 1989
134. Cantarovich F, Bizollon C, Cantarovich D, LeFrancois N, Dubernard JM, Traeger J: Cyclosporine plasma levels six hours after oral administration: A useful tool for monitoring therapy. *Transplantation* 45: 389–394, 1988
135. Mahalati K, Belitsky P, Sketris I, West K, Panek R: Neoral monitoring by simplified sparse sampling area under the concentration-time curve: Its relationship to acute rejection and cyclosporine nephrotoxicity early after kidney transplantation. *Transplantation* 68: 55–62, 1999
136. David-Neto E, Lemos FB, Furusawa EA, Schwartzman BS, Cavalcante JS, Yagyu EM, Romano P, Ianhez LE: Impact of cyclosporin A pharmacokinetics on the presence of side effects in pediatric renal transplantation. *J Am Soc Nephrol* 11: 343–349, 2000
137. Sallas WM: Development of limited sampling strategies for characteristics of a pharmacokinetic profile. *J Pharmacokinet Biopharm* 23: 515–529, 1995
138. Warrens AN, Waters JB, Salama AD, Lechler RI: Improving the therapeutic monitoring of cyclosporin A. *Clin Transplant* 13: 193–200, 1999
139. Dello SL, Campagnano P, Federici G, Rizzoni G: Cyclosporine A monitoring in children: Abbreviated area under curve formulas and C2 level. *Pediatr Nephrol* 13: 95–97, 1999
140. Yoshimura N, Kahan BD: Pharmacodynamic assessment of the *in vivo* cyclosporine effect on interleukin-2 production by lymphocytes in kidney transplant recipients. *Transplantation* 40: 661–666, 1985
141. Reisman L, Lieberman KV, Martinelli GP, Bowles KE, Schanzer H, Burrows L: Immunopharmacodynamic profiles in children with renal allografts receiving cyclosporine therapy. *Am J Kidney Dis* 12: 104–109, 1988
142. Koutouby R, Zucker C, Zucker K, Burke G, Nery J, Roth D, Esquenazi V, Miller J: Molecular monitoring of the immunosuppressive effects of cyclosporine in renal transplant patients by using a quantitative polymerase chain reaction. *Hum Immunol* 36: 227–234, 1993
143. Piccinini G, Gaspari F, Signorini O, Remuzzi G, Perico N: Recovery of blood mononuclear cell calcineurin activity segregates two populations of renal transplant patients with different sensitivities to cyclosporine inhibition. *Transplantation* 61: 1526–1531, 1996
144. van den Berg AP, Twilhaar WN, Mesander G, van Son WJ, van der Bij W, Klompmaker IJ, Slooff MJ, The TH, de Leij LH: Quantitation of immunosuppression by flow cytometric measurement of the capacity of T cells for interleukin-2 production. *Transplantation* 65: 1066–1071, 1998
145. Batiuk TD, Urmson J, Vincent D, Yatscoff RW, Halloran PF: Quantitating immunosuppression: Estimating the 50% inhibitory concentration for *in vivo* cyclosporine in mice. *Transplantation* 61: 1618–1624, 1996
146. Batiuk TD, Kung L, Halloran PF: Evidence that calcineurin is rate-limiting for primary human lymphocyte activation. *J Clin Investig* 100: 1894–1901, 1997
147. Halloran PF, Helms LM, Kung L, Noujaim J: The temporal profile of calcineurin inhibition by cyclosporine *in vivo*. *Transplantation* 68: 1356–1361, 1999
148. Kovarik JM, Mueller EA, van Bree JB, Arns W, Renner E, Kutz K: Within-day consistency in cyclosporine pharmacokinetics from a microemulsion formulation in renal transplant patients. *Ther Drug Monit* 16: 232–237, 1994
149. Kovarik JM, Mueller EA, Richard F, Niese D, Halloran PF, Jeffery J, Paul LC, Keown PA: Evidence for earlier stabilization of cyclosporine pharmacokinetics in *de novo* renal transplant patients receiving a microemulsion formulation. *Transplantation* 62: 759–763, 1996
150. Kahan BD, Dunn J, Fitts C, Van Buren D, Wombolt D, Pollak R, Carson R, Alexander JW, Choc M, Wong R, Hwang DS: Reduced inter- and intrasubject variability in cyclosporine pharmacokinetics in renal transplant recipients treated with a microemulsion formulation in conjunction with fasting, low-fat meals, or high-fat meals. *Transplantation* 59: 505–511, 1995
151. Bokenkamp A, Offner G, Hoyer PF, Vester U, Wonigeit K, Brodehl J: Improved absorption of cyclosporin A from a new microemulsion formulation: Implications for dosage and monitoring. *Pediatr Nephrol* 9: 196–198, 1995
152. Wahlberg J, Wilczek HE, Fauchald P, Nordal KP, Heaf JG, Olgaard K, Hansen JM, Lokkegaard H, Mueller EA, Kovarik JM: Consistent absorption of cyclosporine from a microemulsion formulation assessed in stable renal transplant recipients over a one-year study period. *Transplantation* 60: 648–652, 1995
153. Barone G, Chang CT, Choc MGJ, Klein JB, Marsh CL, Meligeni JA, Min DI, Pescovitz MD, Pollak R, Pruett TL, Stinson JB, Thompson JS, Vasquez E, Waid T, Wombolt DG, Wong RL: The pharmacokinetics of a microemulsion formulation of cyclosporine in primary renal allograft recipients: The Neoral Study Group. *Transplantation* 61: 875–880, 1996
154. Pollak R, Wong RL, Chang CT: Cyclosporine bioavailability of Neoral and Sandimmune in white and black *de novo* renal transplant recipients: Neoral Study Group. *Ther Drug Monit* 21: 661–663, 1999
155. Pollard SG, Lear PA, Ready AR, Moore RH, Johnson RW: Comparison of microemulsion and conventional formulations

of cyclosporine A in preventing acute rejection in *de novo* kidney transplant patients: The U.K. Neoral Renal Study Group. *Transplantation* 68: 1325–1331, 1999
156. Shah MB, Martin JE, Schroeder TJ, First RM: The evaluation of the safety and tolerability of two formulations of cyclosporine, Neoral and Sandimmune: A meta-analysis. *Transplantation* 67: 1411–1417, 1999
157. Shapiro R, Jordan M, Scantlebury V, Fung J, Jensen C, Tzakis A, McCauley J, Carroll P, Ricordi C, Demetris AJ, Mitchell S, Jain A, Iwaki Y, Kobayashi M, Reyes J, Todo S, Hakala TR, Simmons RL, Starzl TE: FK 506 in clinical kidney transplantation. *Transplant Proc* 23: 3065–3067, 1991
158. Vincenti F, Laskow DA, Neylan JF, Mendez R, Matas AJ: One-year follow-up of an open-label trial of FK506 for primary kidney transplantation: A report of the U.S. Multicenter FK506 Kidney Transplant Study Group. *Transplantation* 61: 1576–1581, 1996
159. Pirsch JD, Miller J, Deierhoi MH, Vincenti F, Filo RS: A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation: FK506 Kidney Transplant Study Group. *Transplantation* 63: 977–983, 1997
160. Mayer AD, Dmitrewski J, Squifflet JP, Besse T, Grabensee B, Klein B, Eigler FW, Heemann U, Pichlmayr R, Behrend M, Vanrenterghem Y, Donck J, van Hooff J, Christiaans M, Morales JM, Andres A, Johnson RW, Short C, Buchholz B, Rehmert N, Land W, Schleibner S, Forsythe JL, Talbot D, Pohanka E: Multicenter randomized trial comparing tacrolimus (FK506) and cyclosporine in the prevention of renal allograft rejection: A report of the European Tacrolimus Multicenter Renal Study Group. *Transplantation* 64: 436–443, 1997
161. Johnson C, Ahsan N, Gonwa T, Halloran P, Stegall M, Hardy M, Metzger R, Shield C III, Rocher L, Scandling J, Sorensen J, Mulloy L, Light J, Corwin C, Danovitch G, Wachs M, van Veldhuisen P, Salm K, Tolzman D, Fitzsimmons WE: Randomized trial of tacrolimus (Prograf) in combination with azathioprine or mycophenolate mofetil versus cyclosporine (Neoral) with mycophenolate mofetil after cadaveric kidney transplantation. *Transplantation* 69: 834–841, 2000
162. Knoll GA, Bell RC: Tacrolimus versus cyclosporin for immunosuppression in renal transplantation: Meta-analysis of randomised trials. *Br Med J* 318: 1104–1107, 1999
163. Pirsch JD: Cytomegalovirus infection and posttransplant lymphoproliferative disease in renal transplant recipients: Results of the U.S. Multicenter FK506 Kidney Transplant Study Group. *Transplantation* 68: 1203–1205, 1999
164. Hedayat S, Kershner RP, Su G: Relationship of whole-blood FK506 concentrations to rejection and toxicity in liver and kidney transplants. *J Biopharm Stat* 6: 411–424, 1996
165. Katari SR, Magnone M, Shapiro R, Jordan M, Scantlebury V, Vivas C, Gritsch A, McCauley J, Starzl T, Demetris AJ, Randhawa PS: Clinical features of acute reversible tacrolimus (FK 506) nephrotoxicity in kidney transplant recipients. *Clin Transplant* 11: 237–242, 1997
166. Randhawa PS, Shapiro R, Jordan ML, Starzl TE, Demetris AJ: The histopathological changes associated with allograft rejection and drug toxicity in renal transplant recipients maintained on FK506: Clinical significance and comparison with cyclosporine. *Am J Surg Pathol* 17: 60–68, 1993
167. Randhawa PS, Tsamandas AC, Magnone M, Jordan M, Shapiro R, Starzl TE, Demetris AJ: Microvascular changes in renal allografts associated with FK506 (tacrolimus) therapy. *Am J Surg Pathol* 20: 306–312, 1996
168. Kershner RP, Fitzsimmons WE: Relationship of FK506 whole blood concentrations and efficacy and toxicity after liver and kidney transplantation. *Transplantation* 62: 920–926, 1996
169. Laskow DA, Vincenti F, Neylan JF, Mendez R, Matas AJ: An open-label, concentration-ranging trial of FK506 in primary kidney transplantation: A report of the United States Multicenter FK506 Kidney Transplant Study Group. *Transplantation* 62: 900–905, 1996
170. Shimizu T, Tanabe K, Tokumoto T, Ishikawa N, Shinmura H, Oshima T, Toma H, Yamaguchi Y: Clinical and histological analysis of acute tacrolimus (TAC) nephrotoxicity in renal allografts. *Clin Transplant* 13[Suppl 1]: 48–53, 1999
171. Shapiro R, Scantlebury VP, Jordan ML, Vivas C, Ellis D, Lombardozzi-Lane S, Gilboa N, Gritsch HA, Irish W, McCauley J, Fung JJ, Hakala TR, Simmons RL, Starzl TE: Pediatric renal transplantation under tacrolimus-based immunosuppression. *Transplantation* 67: 299–303, 1999
172. Salm P, Taylor PJ, Clark A, Balderson GA, Grygotis A, Norris RL, Lynch SV, Shaw LM, Pond SM: High-performance liquid chromatography-tandem mass spectrometry as a reference for analysis of tacrolimus to assess two immunoassays in patients with liver and renal transplants. *Ther Drug Monit* 19: 694–700, 1997
173. Rudant E, Bezie Y, Bonhomme-Faivre L, Manuel N, Rucay P, Fredj G, Bismuth H: Study of the correlation between MEIA and ELISA methods for FK 506 determination in liver transplant recipients. *J Clin Pharmacol Ther* 22: 135–140, 1997
174. Taylor PJ, Hogan NS, Lynch SV, Johnson AG, Pond SM: Improved therapeutic drug monitoring of tacrolimus (FK506) by tandem mass spectrometry. *Clin Chem* 43: 2189–2190, 1997
175. Alak AM: Measurement of tacrolimus (FK506) and its metabolites: A review of assay development and application in therapeutic drug monitoring and pharmacokinetic studies. *Ther Drug Monit* 19: 338–351, 1997
176. Zhang Q, Simpson J, Aboleneen HI: A specific method for the measurement of tacrolimus in human whole blood by liquid chromatography/tandem mass spectrometry. *Ther Drug Monit* 19: 470–476, 1997
177. Braun F, Lorf T, Schutz E, Christians U, Grupp C, Sattler B, Canelo R, Sewing KF, Armstrong VW, Oellerich M, Ringe B: Clinical relevance of monitoring tacrolimus: Comparison of microparticle enzyme immunoassay, enzyme-linked immunosorbent assay, and liquid chromatography mass spectrometry in renal transplant recipients converted from cyclosporine to tacrolimus. *Transplant Proc* 28: 3175–3176, 1996
178. Jusko WJ: Analysis of tacrolimus (FK 506) in relation to therapeutic drug monitoring. *Ther Drug Monit* 17: 596–601, 1995
179. Gruber SA, Hewitt JM, Sorenson AL, Barber DL, Bowers L, Rynders G, Arrazola L, Matas AJ, Rosenberg ME, Canafax DM: Pharmacokinetics of FK506 after intravenous and oral administration in patients awaiting renal transplantation. *J Clin Pharmacol* 34: 859–864, 1994
180. Venkataramanan R, Swaminathan A, Prasad T, Jain A, Zuckerman S, Warty V, McMichael J, Lever J, Burckart G, Starzl T: Clinical pharmacokinetics of tacrolimus. *Clin Pharmacokinet* 29: 404–430, 1995
181. Hubner GI, Eismann R, Sziegoleit W: Drug interaction between mycophenolate mofetil and tacrolimus detectable within

therapeutic mycophenolic acid monitoring in renal transplant patients. *Ther Drug Monit* 21: 536–539, 1999
182. Pirsch J, Bekersky I, Vincenti F, Boswell G, Woodle ES, Alak A, Kruelle M, Fass N, Facklam D, Mekki Q: Coadministration of tacrolimus and mycophenolate mofetil in stable kidney transplant patients: Pharmacokinetics and tolerability. *J Clin Pharmacol* 40: 527–532, 2000
183. Böttiger Y, Brattström C, Tydén G, Säwe J, Groth C-G: Tacrolimus whole blood concentrations correlate closely to side-effects in renal transplant recipients. *Br J Clin Pharmacol* 48: 445–448, 1999
184. Paterson DL, Singh N: Interactions between tacrolimus and antimicrobial agents. *Clin Infect Dis* 25: 1430–1440, 1997
185. Filler G, Grygas R, Mai I, Stolpe HJ, Greiner C, Bauer S, Ehrich JH: Pharmacokinetics of tacrolimus (FK 506) in children and adolescents with renal transplants. *Nephrol Dial Transplant* 12: 1668–1671, 1997
186. Jusko WJ, Thomson AW, Fung J, McMaster P, Wong SH, Zylber-Katz E, Christians U, Winkler M, Fitzsimmons WE, Lieberman R: Consensus document: Therapeutic monitoring of tacrolimus (FK-506). *Ther Drug Monit* 17: 606–614, 1995
187. Wong KM, Shek CC, Chau KF, Li CS: Abbreviated tacrolimus area-under-the-curve monitoring for renal transplant recipients. *Am J Kidney Dis* 35: 660–666, 2000
188. Groth CG, Backman L, Morales JM, Calne R, Kreis H, Lang P, Touraine JL, Claesson K, Campistol JM, Durand D, Wramner L, Brattstrom C, Charpentier B: Sirolimus (rapamycin)-based therapy in human renal transplantation: Similar efficacy and different toxicity compared with cyclosporine: Sirolimus European Renal Transplant Study Group. *Transplantation* 67: 1036–1042, 1999
189. Kahan BD, Julian BA, Pescovitz MD, Vanrenterghem Y, Neylan J: Sirolimus reduces the incidence of acute rejection episodes despite lower cyclosporine doses in Caucasian recipients of mismatched primary renal allografts: A phase II trial: Rapamune Study Group. *Transplantation* 68: 1526–1532, 1999
190. Kreis H, Cisterne JM, Land W, Wramner L, Squifflet JP, Abramowicz D, Campistol JM, Morales JM, Grinyo JM, Mourad G, Berthoux FC, Brattstrom C, Lebranchu Y, Vialtel P: Sirolimus in association with mycophenolate mofetil induction for the prevention of acute graft rejection in renal allograft recipients. *Transplantation* 69: 1252–1260, 2000
191. Svensson JO, Brattstrom C, Sawe J: Determination of rapamycin in whole blood by HPLC. *Ther Drug Monit* 19: 112–116, 1997
192. Kahan BD, Napoli KL, Kelly PA, Podbielski J, Hussein I, Urbauer DL, Katz SH, Van Buren CT: Therapeutic drug monitoring of sirolimus: Correlations with efficacy and toxicity. *Clin Transplant* 14: 97–100, 2000
193. Holt DW, Lee T, Johnston A: Measurement of sirolimus in whole blood using high-performance liquid chromatography with ultraviolet detection. *Clin Ther* 22[Suppl B]: B38–B48, 2000
194. Maleki S, Graves S, Becker S, Horwatt R, Hicks D, Stroshane RM, Kincaid H: Therapeutic monitoring of sirolimus in human whole-blood samples by high-performance liquid chromatography. *Clin Ther* 22[Suppl B]: B25–B37, 2000
195. Ferron GM, Mishina EV, Zimmerman JJ, Jusko WJ: Population pharmacokinetics of sirolimus in kidney transplant patients. *Clin Pharmacol Ther* 61: 416–428, 1997
196. Brattstrom C, Sawe J, Tyden G, Herlenius G, Claesson K, Zimmerman J, Groth CG: Kinetics and dynamics of single oral doses of sirolimus in sixteen renal transplant recipients. *Ther Drug Monit* 19: 397–406, 1997
197. Davis DL, Soldin SJ: An immunophilin-binding assay for sirolimus. *Clin Ther* 22[Suppl B]: B62–B70, 2000
198. Davis DL, Murthy JN, Napoli KL, Kahan BD, Gallant-Haidner H, Yatscoff RW, Soldin SJ: Comparison of steady-state trough sirolimus samples by HPLC and a radioreceptor assay. *Clin Biochem* 33: 31–36, 2000
199. Zimmerman JJ, Kahan BD: Pharmacokinetics of sirolimus in stable renal transplant patients after multiple oral dose administration. *J Clin Pharmacol* 37: 405–415, 1997
200. Kaplan B, Meier-Kriesche HU, Napoli KL, Kahan BD: The effects of relative timing of sirolimus and cyclosporine microemulsion formulation coadministration on the pharmacokinetics of each agent. *Clin Pharmacol Ther* 63: 48–53, 1998
201. Jusko WJ, Ferron GM, Mis SM, Kahan BD, Zimmerman JJ: Pharmacokinetics of prednisolone during administration of sirolimus in patients with renal transplants. *J Clin Pharmacol* 36: 1100–1106, 1996
202. Zimmerman JJ, Ferron GM, Lim HK, Parker V: The effect of a high-fat meal on the oral bioavailability of the immunosuppressant sirolimus (rapamycin). *J Clin Pharmacol* 39: 1155–1161, 1999
203. Yatscoff RW, Aspeslet LJ, Gallant HL: Pharmacodynamic monitoring of immunosuppressive drugs. *Clin Chem* 44: 428–432, 1998
204. Weber LT, Schutz E, Lamersdorf T, Shipkova M, Niedmann PD, Oellerich M, Zimmerhackl LB, Staskewitz A, Mehls O, Armstrong VW, Tonshoff B: Therapeutic drug monitoring of total and free mycophenolic acid (MPA) and limited sampling strategy for determination of MPA-AUC in paediatric renal transplant recipients: The German Study Group on Mycophenolate Mofetil (MMF) Therapy. *Nephrol Dial Transplant* 14[Suppl 4]: 34–35, 1999
205. Filler G, Zimmering M, Mai I: Pharmacokinetics of mycophenolate mofetil are influenced by concomitant immunosuppression. *Pediatr Nephrol* 14: 100–104, 2000
206. European Mycophenolate Mofetil Cooperative Study Group: Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. *Lancet* 345: 1321–1325, 1995
207. Sollinger HW, U.S. Renal Transplant Mycophenolate Mofetil Study Group: Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. *Transplantation* 60: 225–232, 1995
208. Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group: A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. *Transplantation* 61: 1029–1037, 1996
209. Halloran P, Mathew T, Tomlanovich S, Groth C, Hooftman L, Barker C: Mycophenolate mofetil in renal allograft recipients: A pooled efficacy analysis of three randomized, double-blind, clinical studies in prevention of rejection. *Transplantation* 63: 39–47, 1997
210. Mathew TH: A blinded, long-term, randomized multicenter study of mycophenolate mofetil in cadaveric renal transplantation: Results at three years. *Transplantation* 65: 1450–1454, 1998
211. Sarmiento JM, Dockrell DH, Schwab TR, Munn SR, Paya CV: Mycophenolate mofetil increases cytomegalovirus invasive

organ disease in renal transplant patients. *Clin Transplant* 14: 136–138, 2000
212. Rostaing L, Izopet J, Sandres K, Cisterne JM, Puel J, Durand D: Changes in hepatitis C virus RNA viremia concentrations in long-term renal transplant patients after introduction of mycophenolate mofetil. *Transplantation* 69: 991–994, 2000
213. Shaw LM, Nowak I: Mycophenolic acid: Measurement and relationship to pharmacologic effects. *Ther Drug Monit* 17: 685–689, 1995
214. Langman LJ, LeGatt DF, Yatscoff RW: Blood distribution of mycophenolic acid. *Ther Drug Monit* 16: 602–607, 1994
215. Seebacher G, Weigel G, Wolner E, Mallinger R, Grimm M, Laufer G, El Menyawi I, Griesmacher A, Muller MM: A simple HPLC method for monitoring mycophenolic acid and its glucuronidated metabolite in transplant recipients. *Clin Chem Lab Med* 37: 409–415, 1999
216. Mourad M, Chaib-Eddour D, Malaise J, Konig J, Squifflet JP, Wallemacq PE: Analytical and clinical evaluation of the EMIT mycophenolic acid immunoassay in kidney transplantation. *Transplant Proc* 32: 404–406, 2000
217. Hood KA, Zarembski DG: Mycophenolate mofetil: A unique immunosuppressive agent. *Am J Health Syst Pharm* 54: 285–294, 1997
218. Bullingham RE, Nicholls AJ, Kamm BR: Clinical pharmacokinetics of mycophenolate mofetil. *Clin Pharmacokinet* 34: 429–455, 1998
219. Johnson AG, Rigby RJ, Taylor PJ, Jones CE, Allen J, Franzen K, Falk MC, Nicol D: The kinetics of mycophenolic acid and its glucuronide metabolite in adult kidney transplant recipients. *Clin Pharmacol Ther* 66: 492–500, 1999
220. MacPhee IA, Spreafico S, Bewick M, Davis C, Eastwood JB, Johnston A, Lee T, Holt DW: Pharmacokinetics of mycophenolate mofetil in patients with end-stage renal failure. *Kidney Int* 57: 1164–1168, 2000
221. Weber LT, Shipkova M, Lamersdorf T, Niedmann PD, Wiesel M, Mandelbaum A, Zimmerhackl LB, Schutz E, Mehls O, Oellerich M, Armstrong VW, Tonshoff B: Pharmacokinetics of mycophenolic acid (MPA) and determinants of MPA free fraction in pediatric and adult renal transplant recipients: German Study Group on Mycophenolate Mofetil Therapy in Pediatric Renal Transplant Recipients. *J Am Soc Nephrol* 9: 1511–1520, 1998
222. Weber LT, Lamersdorf T, Shipkova M, Niedmann PD, Wiesel M, Zimmerhackl LB, Staskewitz A, Schutz E, Mehls O, Oellerich M, Armstrong VW, Tonshoff B: Area under the plasma concentration-time curve for total, but not for free, mycophenolic acid increases in the stable phase after renal transplantation: A longitudinal study in pediatric patients: German Study Group on Mycophenolate Mofetil Therapy in Pediatric Renal Transplant Recipients. *Ther Drug Monit* 21: 498–506, 1999
223. Oellerich M, Shipkova M, Schutz E, Wieland E, Weber L, Toshoff B, Armstrong VW: Pharmacokinetic and metabolic investigations of mycophenolic acid in pediatric patients after renal transplantation: Implications for therapeutic drug monitoring: German Study Group on Mycophenolate Mofetil Therapy in Pediatric Renal Transplant Recipients. *Ther Drug Monit* 22: 20–26, 2000
224. Jacqz-Aigrain E, Khan SE, Baudouin V, Popon M, Zhang D, Maisin A, Loirat C: Pharmacokinetics and tolerance of mycophenolate mofetil in renal transplant children. *Pediatr Nephrol* 14: 95–99, 2000
225. Mignat C: Clinically significant drug interactions with new immunosuppressive agents. *Drug Saf* 16: 267–278, 1997
226. Zucker K, Rosen A, Tsaroucha A, de Faria L, Roth D, Ciancio G, Esquenazi V, Burke G, Tzakis A, Miller J: Unexpected augmentation of mycophenolic acid pharmacokinetics in renal transplant patients receiving tacrolimus and mycophenolate mofetil in combination therapy, and analogous *in vitro* findings. *Transplant Immunol* 5: 225–232, 1997
227. Jamil B, Nicholls K, Becker GJ, Walker RG: Impact of acute rejection therapy on infections and malignancies in renal transplant recipients. *Transplantation* 68: 1597–1603, 1999
228. Smak GP, van Gelder T, Hesse CJ, van der Mast BJ, van Besouw NM, Weimar W: Mycophenolic acid plasma concentrations in kidney allograft recipients with or without cyclosporin: A cross-sectional study. *Nephrol Dial Transplant* 14: 706–708, 1999
229. Hale MD, Nicholls AJ, Bullingham RE, Hene R, Hoitsma A, Squifflet JP, Weimar W, Vanrenterghem Y, van der Woude FJ, Verpooten GA: The pharmacokinetic-pharmacodynamic relationship for mycophenolate mofetil in renal transplantation. *Clin Pharmacol Ther* 64: 672–683, 1998
230. van Gelder T, Hilbrands LB, Vanrenterghem Y, Weimar W, de Fijter JW, Squifflet JP, Hene RJ, Verpooten GA, Navarro MT, Hale MD, Nicholls AJ: A randomized double-blind, multicenter plasma concentration controlled study of the safety and efficacy of oral mycophenolate mofetil for the prevention of acute rejection after kidney transplantation. *Transplantation* 68: 261–266, 1999
231. van Besouw NM, van der Mast BJ, Smak Gregoor PJ, Hesse CJ, Ijzermans JN, van Gelder T, Weimar W: Effect of mycophenolate mofetil on erythropoiesis in stable renal transplant patients is correlated with mycophenolic acid trough levels. *Nephrol Dial Transplant* 14: 2710–2713, 1999
232. Filler G, Ehrich J: Mycophenolate mofetil for rescue therapy in acute renal transplant rejection in children should always be monitored by measurement of trough concentration [Letter]. *Nephrol Dial Transplant* 12: 374–375, 1997
233. Langman LJ, LeGatt DF, Halloran PF, Yatscoff RW: Pharmacodynamic assessment of mycophenolic acid-induced immunosuppression in renal transplant recipients. *Transplantation* 62: 666–672, 1996
234. Bullingham RE, Nicholls A, Hale M: Pharmacokinetics of mycophenolate mofetil (RS61443): A short review. *Transplant Proc* 28: 925–929, 1996
235. Opelz G, Dohler B: Critical threshold of azathioprine dosage for maintenance immunosuppression in kidney graft recipients: Collaborative Transplant Study. *Transplantation* 69: 818–821, 2000
236. Sandrini S, Maiorca R, Scolari F, Cancarini G, Setti G, Gaggia P, Cristinelli L, Zubani R, Bonardelli S, Maffeis R, Portolani N, Nodari F, Giulini SM: A prospective randomized trial on azathioprine addition to cyclosporine versus cyclosporine monotherapy at steroid withdrawal, 6 months after renal transplantation. *Transplantation* 69: 1861–1867, 2000
237. Haesslein HC, Peirce JC, Lee HM, Hume DM: Leukopenia and azathioprine management in renal homotransplantation. *Surgery* 71: 598–604, 1972
238. Pollack R, Nishikawa RA, Mozes MF, Jonesson O: Azathioprine-induced leukopenia: Clinical significance in renal transplantation. *J Surg Res* 29: 258–264, 1980
239. Nicholls AJ, Davidson RJ: Development of macrocytosis during azathioprine therapy after renal transplantation: A corre-

lation of renal function with MCV. *Transplantation* 27: 220–221, 1979
240. McGrath BP, Ibels LS, Raik E, Hargrave MJ: Erythroid toxicity of azathioprine: Macrocytosis and selective marrow hypoplasis. *Q J Med* 44: 57–63, 1975
241. Read AE, Wiesner RH, LaBrecque DR, Tifft JG, Mullen KD, Sheer RL, Petrelli M, Ricanati ES, McCullough AJ: Hepatic veno-occlusive disease associated with renal transplantation and azathioprine therapy. *Ann Intern Med* 104: 651–655, 1986
242. Katzka DA, Saul SH, Jorkasky D, Sigal H, Reynolds JC, Soloway RD: Azathioprine and hepatic venocclusive disease in renal transplant patients. *Gastroenterology* 90: 446–454, 1986
243. Assini JF, Hamilton R, Strosberg JM: Adverse reactions to azathioprine mimicking gastroenteritis. *J Rheumatol* 13: 1117–1118, 1986
244. Cochrane D, Adamson AR, Halsey JP: Adverse reactions to azathioprine mimicking gastroenteritis [Letter]. *J Rheumatol* 14: 1075, 1987
245. Rossi SJ, Schroeder TJ, Hariharan S, First MR: Prevention and management of the adverse effects associated with immunosuppressive therapy. *Drug Saf* 9: 104–131, 1993
246. Frick TW, Fryd DS, Goodale RL, Simmons RL, Sutherland DER, Najarian JS: Lack of association between azathioprine and acute pancreatitis in renal transplantation patients [Letter]. *Lancet* 337: 251–252, 1991
247. Weller S, Thürmann P, Rietbrock P, Großman J, Scheuermann E-H: HPLC analysis of azathioprine metabolites in red blood cells, plasma and urine in renal transplant recipients. *Int J Clin Pharmacol Ther* 33: 639–645, 1995
248. Ohlman S, Lafolie P, Lindholm A, Liliemark J, Tydén G, Peterson C: Large interindividual variability in bioavailability of azathioprine in renal transplant recipients. *Clin Transplant* 7: 65–70, 1993
249. Chan GLC, Erdmann GR, Gruder SA, Matas AJ, Canafax DM: Azathioprine metabolism: Pharmacokinetics of 6-mercaptopurine, 6-thiouric acid and 6-thioguanine nucleotides in reanl transplant patients. *J Clin Pharmacol* 30: 358–363, 1990
250. Lennard L, Brown CB, Fox M, Maddocks JL: Azathioprine metabolism in kidney transplant recipients. *Br J Clin Pharmacol* 18: 693–700, 1984
251. Bergan S, Bentdal O, Sodal G, Brun A, Rugstad HE, Stokke O: Patterns of azathioprine metabolites in neutrophils, lymphocytes, reticulocytes, and erythrocytes: Relevance to toxicity and monitoring in recipients of renal allografts. *Ther Drug Monit* 19: 502–509, 1997
252. Bergan S, Rugstad HE, Bentdal O, Stokke O: Monitoring of azathioprine treatment by determination of 6-thioguanine nucleotide concentrations in erythrocytes. *Transplantation* 58: 803–808, 1994
253. Bergan S, Rugstad HE, Bentdal Ø, Sodal G, Hartmann A, Leivestad T, Stokke O: Monitored high-dose azathioprine treatment reduces acute rejection episodes after renal transplantation. *Transplantation* 66: 334–339, 1998
254. Lennard L, Van Loon JA, Weinshilboum RM: Pharmacogenetics of acute azathioprine toxicity: Relationship to thiopurine methyltransferase genetic polymorphism. *Clin Pharmacol Ther* 46: 149–154, 1989
255. Mircheva J, Legendre C, Soria-Royer C, Thervet E, Beaune P, Kreis H: Monitoring of azathioprine-induced immunosuppression with thiopurine methyltransferase activity in kidney transplant recipients. *Transplantation* 60: 639–642, 1995
256. Schütz E, Gummert J, Armstrong VW, Mohr FW, Oellerich M: Azathioprine pharmacogenetics: The relationship between 6-thioguanine nucleotides and thiopurine methyltransferase in patients after heart and kidney transplantation. *Eur J Clin Chem Clin Biochem* 34: 199–205, 1996
257. Chocair PR, Duley JA, Simmonds HA, Cameron JS: The importance of thiopurine methyltransferase activity for the use of azathioprine in transplant recipients. *Transplantation* 53: 1051–1056, 1992
258. Dervieux T, Medard Y, Baudouin V, Maisin A, Zhang D, Loirat C, Jacqz-Aigrain E: Monitoring azathioprine therapy in pediatric renal transplant patients with red blood cell thiopurine methyltransferase. *Transplant Proc* 32: 361–363, 2000
259. Bergan S, Rugstad HE, Klemetsdal B, Giverhaug T, Bentdal O, Sodal G, Hartmann A, Aarbakke J, Stokke O: Possibilities for therapeutic drug monitoring of azathioprine: 6-Thioguanine nucleotide concentrations and thiopurine methyltransferase activity in red blood cells. *Ther Drug Monit* 19: 318–326, 1997
260. Boulieu R, Lenoir A, Bertocchi M, Mornex JF: Intracellular thiopurine nucleotides and azathioprine myelotoxicity in organ transplant patients. *Br J Clin Pharmacol* 43: 116–118, 1997
261. Pol S, Cavalcanti R, Carnot F, Legendre C, Driss F, Chaix ML, Thervet E, Chkoff N, Brechot C, Berthelot P, Kreis H: Azathioprine hepatitis in kidney transplant recipients: A predisposing role of chronic viral hepatitis. *Transplantation* 61: 1774–1776, 1996
262. Bradley PP, Warden GD, Maxwell JG, Rothstein G: Neutropenia and thrombocytopenia in renal allograft recipients treated with trimethoprim-sulfamethoxazole. *Ann Intern Med* 93: 560–562, 1980
263. Griffin PJ, Da Costa CA, Salaman JR: A controlled trial of steroids in cyclosporine-treated renal transplant recipients. *Transplantation* 43: 505–508, 1987
264. Maiorca R, Cristinelli L, Brunori G, Setti G, Salerni B, De Nobili U, Mittempergher F: Prospective controlled trial of steroid withdrawal after six months in renal transplant patients treated with cyclosporine. *Transplant Proc* 20: 121–125, 1988
265. Tarantino A, Aroldi A, Stucchi L, Montagnino G, Mascaretti L, Vegeto A, Ponticelli C: A randomized prospective trial comparing cyclosporine monotherapy with triple-drug therapy in renal transplantation. *Transplantation* 52: 53–57, 1991
266. Sinclair NR: Low-dose steroid therapy in cyclosporine-treated renal transplant recipients with well-functioning grafts: The Canadian Multicentre Transplant Study Group. *Can Med Assoc J* 147: 645–657, 1992
267. Hollander AA, Hene RJ, Hermans J, Van Es LA, van der Woude FJ: Late prednisone withdrawal in cyclosporine-treated kidney transplant patients: A randomized study. *J Am Soc Nephrol* 8: 294–301, 1997
268. Ratcliffe PJ, Dudley CR, Higgins RM, Firth JD, Smith B, Morris PJ: Randomised controlled trial of steroid withdrawal in renal transplant recipients receiving triple immunosuppression. *Lancet* 348: 643–648, 1996
269. Ponticelli C, Tarantino A, Segoloni GP, Cambi V, Rizzo G, Altieri P, Mastrangelo F, Castagneto M, Salvadori M, Valente U, Cossu M, Federico S, Pisani F, Monagnino G, Messina M, Arisi L, Carmellini M, Piredda G, Corbetta G, for the Italian Multicentre Study Group for Renal Transplantation: A randomized study comparing three cyclosporine-based regimens in cadaveric renal transplantation. *J Am Soc Nephrol* 8: 639–646, 1997

270. Fryer JP, Granger DK, Leventhal JR, Gillingham K, Najarian JS, Matas AJ: Steroid-related complications in the cyclosporine era. *Clin Transplant* 8: 224–229, 1994
271. Hricik DE, Lautman J, Bartucci MR, Moir EJ, Mayes JT, Schulak JA: Variable effects of steroid withdrawal on blood pressure reduction in cyclosporine-treated renal transplant recipients. *Transplantation* 53: 1232–1235, 1992
272. Vathsala A, Weinberg RB, Schoenberg L, Grevel J, Goldstein RA, Van Buren CT, Lewis RM, Kahan BD: Lipid abnormalities in cyclosporine-prednisone-treated renal transplant recipients. *Transplantation* 48: 37–43, 1989
273. Satterthwaite R, Aswad S, Sunga V, Shidban H, Bogaard T, Asai P, Khetan U, Akra I, Mendez RG, Mendez R: Incidence of new-onset hypercholesterolemia in renal transplant patients treated with FK506 or cyclosporine. *Transplantation* 65: 446–449, 1998
274. McCune TR, Thacker LR II, Peters TG, Mulloy L, Rohr MS, Adams PA, Yium J, Light JA, Pruett T, Gaber AO, Selman SH, Jonsson J, Hayes JM, Wright FHJ, Armata T, Blanton J, Burdick JF: Effects of tacrolimus on hyperlipidemia after successful renal transplantation: A Southeastern Organ Procurement Foundation multicenter clinical study. *Transplantation* 65: 87–92, 1998
275. Yoshimura N, Nakai I, Ohmori Y, Aikawa I, Fukuda M, Yasumura T, Matsui S, Hamashima T, Oka T: Effect of cyclosporine on the endocrine and exocrine pancreas in kidney transplant recipients. *Am J Kidney Dis* 12: 11–17, 1988
276. Yamamoto H, Akazawa S, Yamaguchi Y, Yokota A, Yamasaki H, Nakanishi T, Tahara D, Matsuya F, Saito Y, Nagataki S: Effects of cyclosporin A and low dosages of steroid on posttransplantation diabetes in kidney transplant recipients. *Diabetes Care* 14: 867–870, 1991
277. Wagner K, Webber SA, Kurland G, Boyle GJ, Miller SA, Cipriani L, Griffith BP, Fricker FJ: New-onset diabetes mellitus in pediatric thoracic organ recipients receiving tacrolimus-based immunosuppression. *J Heart Lung Transplant* 16: 275–282, 1997
278. Furth S, Neu A, Colombani P, Plotnick L, Turner ME, Fivush B: Diabetes as a complication of tacrolimus (FK506) in pediatric renal transplant patients. *Pediatr Nephrol* 10: 64–66, 1996
279. Moxey-Mims MM, Kay C, Light JA, Kher KK: Increased incidence of insulin-dependent diabetes mellitus in pediatric renal transplant patients receiving tacrolimus (FK506). *Transplantation* 65: 617–619, 1998
280. von Kiparski A, Frei D, Uhlschmid G, Largiader F, Binswanger U: Post-transplant diabetes mellitus in renal allograft recipients: A matched-pair control study. *Nephrol Dial Transplant* 5: 220–225, 1990
281. Hricik DE, Bartucci MR, Moir EJ, Mayes JT, Schulak JA: The effects of steroid withdrawal on posttransplant diabetes mellitus in cyclosporine-treated renal transplant recipients. *Transplantation* 51: 374–377, 1991
282. Boudreaux JP, McHugh L, Canafax DM, Ascher N, Sutherland DER, Payne W, Simmons RL, Najarian JS, Fryd DS: The impact of cyclosporine and combination immunosuppression on the incidence of posttransplant diabetes in renal allograft recipients. *Transplantation* 44: 376–381, 1987
283. Sumrani NB, Delaney V, Daskalakis P, Davis R, Friedman EA, Hong JH, Sommer BG: Retrospective analysis of posttransplantation diabetes mellitus in black renal allograft recipients. *Diabetes Care* 14: 760–762, 1991
284. McKee M, Segev D, Wise B, Case B, Neu A, Fivush B, Colombani P: Initial experience with FK506 (tacrolimus) in pediatric renal transplant recipients. *J Pediatr Surg* 32: 688–690, 1997
285. Shapiro R, Jordan ML, Scantlebury VP, Vivas C, Fung JJ, McCauley J, Randhawa P, Demetris AJ, Irish W, Mitchell S, Hakala TR, Simmons RL, Starzl TE: A prospective randomized trial of FK506-based immunosuppression after renal transplantation. *Transplantation* 59: 485–490, 1995
286. Grotz WH, Mundinger FA, Gugel B, Exner V, Kirste G, Schollmeyer PJ: Bone fracture and osteodensitometry with dual energy X-ray absorptiometry in kidney transplant recipients. *Transplantation* 58: 912–915, 1994
287. Hardie I, Matsunami C, Hilton A, Dyer J, Rumbach O: Ocular complications in renal transplant recipients. *Transplant Proc* 24: 177, 1992
288. Hokken-Koelega AC, Van Zaal MA, de Ridder MA, Wolff ED, De Jong MC, Donckerwolcke RA, de Muinck K, Drop SL: Growth after renal transplantation in prepubertal children: Impact of various treatment modalities. *Pediatr Res* 35: 367–371, 1994
289. Broyer M, Guest G, Gagnadoux MF: Growth rate in children receiving alternate-day corticosteroid treatment after kidney transplantation. *J Pediatr* 120: 721–725, 1992
290. Jabs K, Sullivan EK, Avner ED, Harmon WE: Alternate-day steroid dosing improves growth without adversely affecting graft survival or long-term graft function: A report of the North American Pediatric Renal Transplant Cooperative Study. *Transplantation* 61: 31–36, 1996
291. Ellis D: Clinical use of tacrolimus (FK-506) in infants and children with renal transplants. *Pediatr Nephrol* 9: 487–494, 1995
292. Tejani A, Cortes L, Sullivan EK: A longitudinal study of the natural history of growth post-transplantation. *Kidney Int* 53[Suppl]: S103–S108, 1996
293. Veenstra DL, Best JH, Hornberger J, Sullivan SD, Hricik DE: Incidence and long-term cost of steroid-related side effects after renal transplantation. *Am J Kidney Dis* 33: 829–839, 1999
294. Pirsch JD, Armbrust MJ, Knechtle SJ, Reed A, D'Alessandro AM, Sollinger HW, Belzer FO: Effect of steroid withdrawal on hypertension and cholesterol levels in living related recipients. *Transplant Proc* 23: 1363–1364, 1991
295. Hariharan S, Schroeder TJ, Weiskittel P, Alexander JW, First MR: Prednisone withdrawal in HLA-identical and one haplotype-matched live-related donor and cadaver renal transplant recipients. *Kidney Int* 43[Suppl]: S30–S35, 1993
296. Landmann J, Renner N, Gachter A, Thiel G, Harder F: Cyclosporin A and osteonecrosis of the femoral head. *J Bone Joint Surg Am Vol* 69: 1226–1228, 1987
297. Thiel G, Harder F, Loertscher R, Brunisholz M, Landmann J, Brunner F, Follat F, Wenk M, Mihatsch M: Cyclosporine alone or in combination with prednisone in cadaveric renal transplantation. *Transplant Proc* 16: 1187–1190, 1984
298. Albert FW, Schmidt U: Cyclopsorine therapy with or without steroids in cadaveric kidney transplantation: A prospective randomized one-center study. *Tranplant Proc* 17: 2669–2670, 1987
299. Johnson RW, Mallick NP, Bakran A, Pearson RC, Scott PD, Dyer P, Donaghue D, Morris D, Gokal R: Cadaver renal transplantation without maintenance steroids. *Transplant Proc* 21: 1581–1582, 1989

300. Schulak JA, Mayes JT, Moritz CE, Hricik DE: A prospective randomized trial of prednisone versus no prednisone maintenance therapy in cyclosporine-treated and azathioprine-treated renal transplant patients. *Transplantation* 49: 327–332, 1990
301. Hricik DE, O'Toole MA, Schulak JA, Herson J: Steroid-free immunosuppression in cyclosporine-treated renal transplant recipients: A meta-analysis. *J Am Soc Nephrol* 4: 1300–1305, 1993
302. Reisman L, Lieberman KV, Burrows L, Schanzer H: Follow-up of cyclosporine-treated pediatric renal allograft recipients after cessation of prednisone. *Transplantation* 49: 76–80, 1990
303. Ingulli E, Sharma V, Singh A, Suthanthiran M, Tejani A: Steroid withdrawal, rejection and the mixed lymphocyte reaction in children after renal transplantation. *Kidney Int* 43[Suppl]: S36–S39, 1993
304. Tornatore KM, Morse GD, Jusko WJ, Walshe JJ: Methylprednisolone disposition in renal transplant recipients receiving triple-drug immunosuppression. *Transplantation* 48: 962–965, 1989
305. Hill MR, Szefler SJ, Ball BD, Bartoszek M, Brenner AM: Monitoring glucocorticoid therapy: A pharmacokinetic approach. *Clin Pharmacol Ther* 48: 390–398, 1990
306. Grevel J: Optimisation of immunosuppressive therapy using pharmacokinetic principles. *Clin Pharmacokinet* 23: 380–390, 1992
307. Tornatore KM, Reed KA, Venuto RC: Assessment of methylprednisolone pharmacokinetics and cortisol response during the early and chronic postrenal transplant periods. *Transplantation* 60: 1607–1611, 1995
308. Tornatore KM, Reed KA, Venuto RC: Methylprednisolone and cortisol metabolism during the early post-renal transplant period. *Clin Transplant* 9: 427–432, 1995
309. Tornatore KM, Reed KA, Venuto RC: Repeated assessment of methylprednisolone pharmacokinetics during chronic immunosuppression in renal transplant recipients. *Ann Pharmacother* 29: 120–124, 1995
310. Gambertoglio JG, Frey FJ, Holford NH, Birnbaum JL, Lizak PS, Vincenti F, Feduska NJ, Salvatierra OJ, Amend WJJ: Prednisone and prednisolone bioavailability in renal transplant patients. *Kidney Int* 21: 621–626, 1982
311. Tornatore KM, Biocevich DM, Reed K, Tousley K, Singh JP, Venuto RC: Methylprednisolone pharmacokinetics, cortisol response, and adverse effects in black and white renal transplant recipients. *Transplantation* 59: 729–736, 1995
312. Tornatore KM, Biocevich DM, Reed KA, Tousley K, Gray V, Singh JP, Murray BM, Venuto RC: Post-transplant diabetes mellitus and methylprednisolone pharmacokinetics in African-American and Caucasian renal transplant recipients. *Clin Transplant* 9: 289–296, 1995
313. Rocci ML, Tietze KJ, Lee J, Harris H, Danzeisen J, Burke JF: The effect of cyclosporine on the pharmacokinetics of prednisolone in renal transplant patients. *Transplantation* 45: 656–660, 1988
314. Legler UF, Benet LZ: Marked alterations in dose-dependent prednisolone kinetics in women taking oral contraceptives. *Clin Pharmacol Ther* 39: 425–429, 1986
315. Frey BM, Schaad HJ, Frey FJ: Pharmacokinetic interaction of contraceptive steroids with prednisone and prednisolone. *Eur J Clin Pharmacol* 26: 505–511, 1984
316. Zurcher RM, Frey BM, Frey FJ: Impact of ketoconazole on the metabolism of prednisolone. *Clin Pharmacol Ther* 45: 366–372, 1989
317. Ulrich B, Frey FJ, Speck RF, Frey BM: Pharmacokinetics/pharmacodynamics of ketoconazole-prednisolone interaction. *J Pharmacol Exp Ther* 260: 487–490, 1992
318. Moore LW, Alloway RR, Acchiardo SR, Vera SR, Shokouh-Amiri M, Gaber AO: Clinical observations of metabolic changes occurring in renal transplant recipients receiving ketoconazole. *Transplantation* 61: 537–541, 1996
319. Gambertoglio JG, Holford NH, Kapusnik JE, Nishikawa R, Saltiel M, Stanik-Lizak P, Birnbaum JL, Hau T, Amend WJJ: Disposition of total and unbound prednisolone in renal transplant patients receiving anticonvulsants. *Kidney Int* 25: 119–123, 1984
320. Bergrem H, Jervell J, Flatmark A: Prednisolone pharmacokinetics in cushingoid and non-cushingoid kidney transplant patients. *Kidney Int* 27: 459–464, 1985
321. Gambertoglio JG, Vincenti F, Feduska NJ, Birnbaum J, Salvatierra OJ, Amend WJJ: Prednisolone disposition in cushingoid and noncushingoid kidney transplant patients. *J Clin Endocrinol Metab* 51: 561–565, 1980
322. Frey FJ, Amend WJJ, Lozada F, Frey BM, Benet LZ: Endogenous hydrocortisone, a possible factor contributing to the genesis of cushingoid habitus in patients on prednisone. *J Clin Endocrinol Metab* 53: 1076–1080, 1981
323. Tornatore KM, Logue G, Venuto RC, Davis PJ: Cortisol pharmacodynamics after methylprednisolone administration in young and elderly males. *J Clin Pharmacol* 37: 304–311, 1997
324. Tornatore KM, Reed K, Walshe JJ, Venuto RC: Cortisol pharmacodynamic response to long-term methylprednisolone in renal transplant recipients. *Pharmacotherapy* 14: 111–118, 1994
325. Kasiske BL: Risk factors for accelerated atherosclerosis in renal transplant recipients. *Am J Med* 84: 985–992, 1988
326. Kasiske BL, Guijarro C, Massy ZA, Wiederkehr MR, Ma JZ: Cardiovascular disease after renal transplantation. *J Am Soc Nephrol* 7: 158–165, 1996
327. Aakhus S, Dahl K, Widerøe TE: Cardiovascular morbidity and risk factors in renal transplant patients. *Nephrol Dial Transplant* 14: 648–654, 1999
328. Adams HP Jr, Dawson G, Coffman TJ, Corry RJ: Stroke in renal transplant recipients. *Arch Neurol* 43: 113–115, 1986
329. Lemmers MJ, Barry JM: Major role for arterial disease in morbidity and mortality after kidney transplantation in diabetic recipients. *Diabetes Care* 14: 295–301, 1991
330. Raine AEG: Hypertension and ischaemic heart disease in renal transplant recipients. *Nephrol Dial Transplant* 10[Suppl 1]: 95–100, 1995
331. Webb AT, Franks PJ, Reaveley DA, Greenhalgh RM, Brown EA: Prevalence of intermittent claudication and risk factors for its development in patients on renal replacement therapy. *Eur J Vasc Surg* 7: 523–527, 1993
332. Lindholm A, Albrechtsen D, Frödin L, Tufveson G, Persson NH, Lundgren G: Ischemic heart disease: Major cause of death and graft loss after renal transplantation in Scandinavia. *Transplantation* 60: 451–457, 1995
333. Massy ZA, Mamzer-Bruneel MF, Chevalier A, Millet P, Helenon O, Chadefaux-Vekemans B, Legendre C, Bader C, Drueke T, Lacour B, Kreis H: Carotid atherosclerosis in renal transplant recipients. *Nephrol Dial Transplant* 13: 1792–1798, 1998

334. Foley RN, Parfrey PS, Sarnak MJ: Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 32: S112–S119, 1998
335. Ojo AO, Hanson JA, Wolfe RA, Leichtman AB, Agodoa LY, Port FK: Long-term survival in renal transplant recipients with graft function. *Kidney Int* 57: 307–313, 2000
336. Levey AS: Controlling the epidemic of cardiovascular disease in chronic renal disease: Where do we start? *Am J Kidney Dis* 32: S5–S13, 1998
337. United States Preventive Services Task Force: Screening for asymptomatic coronary artery disease. In: *Guide to Clinical Preventive Services*, 2nd Ed., edited by Di Guiseppi C, Atkins D, Woolf S, Baltimore, Williams & Wilkins, 1996, pp 3–14
338. United States Preventive Services Task Force: Screening for asymptomatic carotid artery stenosis. In: *Guide to Clinical Preventive Services*, 2nd Ed., edited by Di Guiseppi C, Atkins D, Woolf S, Baltimore, Williams & Wilkins, 1996, pp 53–61
339. United States Preventive Services Task Force: Screening for peripheral arterial disease. In: *Guide to Clinical Preventive Services*, 2nd Ed., edited by Di Guiseppi C, Atkins D, Woolf S, Baltimore, Williams & Wilkins, 1996, pp 63–66
340. Manske CL, Wang Y, Rector T, Wilson RF, White CW: Coronary revascularisation in insulin-dependent diabetic patients with chronic renal failure. *Lancet* 340: 998–1002, 1992
341. American College of Physicians: Guidelines for assessing and managing the perioperative risk from coronary artery disease associated with major noncardiac surgery. *Ann Intern Med* 127: 309–312, 1997
342. Palda VA, Detsky AS: Perioperative assessment and management of risk from coronary artery disease. *Ann Intern Med* 127: 313–328, 1997
343. Moore WS, Barnett HJ, Beebe HG, Bernstein EF, Brener BJ, Brott T, Caplan LR, Day A, Goldstone J, Hobson RW: Guidelines for carotid endarterectomy: A multidisciplinary consensus statement from the Ad Hoc Committee, American Heart Association. *Circulation* 91: 566–579, 1995
344. Biller J, Feinberg WMCJE, Whittemore AD, Harbaugh RE, Dempsey RJ, Caplan LR, Kresowik TF, Matchar DB, Toole JF, Easton JD, Adams HP, Brass LM, Hobson RW II, Brott TG, Sternau L: Guidelines for carotid endarterectomy: A statement for healthcare professionals from a Special Writing Group of the Stroke Council, American Heart Association. *Circulation* 97: 501–509, 1998
345. McKhann GM, Goldsborough MA, Borowicz LMJ, Mellits ED, Brookmeyer R, Quaskey SA, Baumgartner WA, Cameron DE, Stuart RS, Gardner TJ: Predictors of stroke risk in coronary artery bypass patients. *Ann Thorac Surg* 63: 516–521, 1997
346. Mickleborough LL, Walker PM, Takagi Y, Ohashi M, Ivanov J, Tamariz M: Risk factors for stroke in patients undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 112: 1250–1258, 1996
347. Dashe JF, Pessin MS, Murphy RE, Payne DD: Carotid occlusive disease and stroke risk in coronary artery bypass graft surgery. *Neurology* 49: 678–686, 1997
348. Jahangiri M, Rees GM, Edmondson SJ, Lumley J, Uppal R: A surgical approach to coexistent coronary and carotid artery disease. *Heart* 77: 164–167, 1997
349. Sayers RD, Thompson MM, Underwood MJ, Graham T, Hartshorne T, Spyt TJ, Firmin RK, Bell PR: Early results of combined carotid endarterectomy and coronary artery bypass grafting in patients with severe coronary and carotid artery disease. *J R Coll Surg Edinb* 38: 340–343, 1993
350. Takach TJ, Reul GJJ, Cooley DA, Duncan JM, Ott DA, Livesay JJ, Hallman GL, Frazier OH: Is an integrated approach warranted for concomitant carotid and coronary artery disease? *Ann Thorac Surg* 64: 16–22, 1997
351. Terramani TT, Rowe VL, Hood DB, Eton D, Nuno IN, Yu H, Yellin AE, Starnes VA, Weaver FA: Combined carotid endarterectomy and coronary artery bypass grafting in asymptomatic carotid artery stenosis. *Am Surg* 64: 993–997, 1998
352. Hines GL, Scott WC, Schubach SL, Kofsky E, Wehbe U, Cabasino E: Prophylactic carotid endarterectomy in patients with high-grade carotid stenosis undergoing coronary bypass: Does it decrease the incidence of perioperative stroke? *Ann Vasc Surg* 12: 23–27, 1998
353. Ivey TD: Combined carotid and coronary disease: A conservative strategy. *J Vasc Surg* 3: 687–689, 1986
354. Gaudino M, Glieca F, Alessandrini F, Cellini C, Luciani N, Pragliola C, Schiavello R, Possati G: Individualized surgical strategy for the reduction of stroke risk in patients undergoing coronary artery bypass grafting. *Ann Thorac Surg* 67: 1246–1253, 1999
355. Collaborative overview of randomised trials of antiplatelet therapy. I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients: Antiplatelet Trialists' Collaboration. *Br Med J* 308: 81–106, 1994
356. Eccles M, Freemantle N, Mason J: North of England Evidence-Based Guideline Development Project: Guideline on the use of aspirin as secondary prophylaxis for vascular disease in primary care: North of England Aspirin Guideline Development Group. *Br Med J* 316: 1303–1309, 1998
357. Hennekens CH, Dyken ML, Fuster V: Aspirin as a therapeutic agent in cardiovascular disease: A statement for healthcare professionals from the American Heart Association. *Circulation* 96: 2751–2753, 1997
358. Aspirin therapy in diabetes: American Diabetes Association. *Diabetes Care* 20: 1772–1773, 1997
359. Gorelick PB, Sacco RL, Smith DB, Alberts M, Mustone-Alexander L, Rader D, Ross JL, Raps E, Ozer MN, Brass LM, Malone ME, Goldberg S, Booss J, Hanley DF, Toole JF, Greengold NL, Rhew DC: Prevention of a first stroke: A review of guidelines and a multidisciplinary consensus statement from the National Stroke Association. *JAMA* 281: 1112–1120, 1999
360. Johnson ES, Lanes SF, Wentworth CE, Satterfield MH, Abebe BL, Dicker LW: A metaregression analysis of the dose-response effect of aspirin on stroke. *Arch Intern Med* 159: 1248–1253, 1999
361. He J, Whelton PK, Vu B, Klag MJ: Aspirin and risk of hemorrhagic stroke: A meta-analysis of randomized controlled trials. *JAMA* 280: 1930–1935, 1998
362. United States Preventive Services Task Force: Aspirin prophylaxis for the primary prevention of myocardial infarction. In: *Guide to Clinical Preventive Services*, 2nd Ed., edited by Di Guiseppi C, Atkins D, Woolf S, Baltimore, Williams & Wilkins, 1996, pp 845–852
363. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 157: 2413–2446, 1997
364. Kasiske BL: Possible causes and consequences of hyperten-

sion in stable renal transplant patients. *Transplantation* 44: 639–643, 1987
365. Jarowenko MV, Flechner SM, Van Buren CT, Lorber MI, Kahan BD: Influence of cyclosporine on posttransplant blood pressure response. *Am J Kidney Dis* 10: 98–103, 1987
366. Peschke B, Scheuermann EH, Geiger H, Bolscher S, Kachel HG, Lenz T: Hypertension is associated with hyperlipidemia, coronary heart disease and chronic graft failure in kidney transplant recipients. *Clin Nephrol* 51: 290–295, 1999
367. Gordjani N, Offner G, Hoyer PF, Brodehl J: Hypertension after renal transplantation in patients treated with cyclosporin and azathioprine. *Arch Dis Child* 65: 275–279, 1990
368. Warholm C, Wilczek H, Pettersson E: Hypertension two years after renal transplantation: Causes and consequences. *Transplant Int* 8: 286–292, 1995
369. Sanchez J, Pallardo LM, Sanchez P, Garcia J, Orero E, Beneyto I, Cruz JM: Risk factors and prognostic significance of hypertension after renal transplantation. *Transplant Proc* 24: 2738–2739, 1992
370. Perez FM, Rodriguez-Carmona A, Garcia FT, Fernandez RC, Valdes F: Early immunologic and nonimmunologic predictors of arterial hypertension after renal transplantation. *Am J Kidney Dis* 33: 21–28, 1999
371. Budde K, Waiser J, Fritsche L, Zitzmann J, Schreiber M, Kunz R, Neumayer HH: Hypertension in patients after renal transplantation. *Transplant Proc* 29: 209–211, 1997
372. Opelz G, Wujciak T, Ritz E, for the Collaborative Transplant Study: Association of chronic kidney graft failure with recipient blood pressure. *Kidney Int* 53: 217–222, 1998
373. Sorof JM, Sullivan EK, Tejani A, Portman RJ: Antihypertensive medication and renal allograft failure: A North American Pediatric Renal Transplant Cooperative Study report. *J Am Soc Nephrol* 10: 1324–1330, 1999
374. Huysmans FT, Hoitsma AJ, Koene RA: Factors determining the prevalence of hypertension after renal transplantation. *Nephrol Dial Transplant* 2: 34–38, 1987
375. Sankari BR, Geisinger M, Zelch M, Brouhard B, Cunningham R, Novick AC: Post-transplant renal artery stenosis: Impact of therapy on long-term kidney function and blood pressure control. *J Urol* 155: 1860–1864, 1996
376. Rengel M, Gomes-Da-Silva G, Inchaustegui L, Lampreave JL, Robledo R, Echenagusia A, Vallejo JL, Valderrabano F: Renal artery stenosis after kidney transplantation: Diagnostic and therapeutic approach. *Kidney Int* 68[Suppl]: S99–S106, 1998
377. Merkus JW, Huysmans FT, Hoitsma AJ, Buskens FG, Skotnicki SH, Koene RA: Renal allograft artery stenosis: Results of medical treatment and intervention: A retrospective analysis. *Transplant Int* 6: 111–115, 1993
378. Halimi JM, Al-Najjar A, Buchler M, Birmele B, Tranquart F, Alison D, Lebranchu Y: Transplant renal artery stenosis: Potential role of ischemia/reperfusion injury and long-term outcome following angioplasty. *J Urol* 161: 28–32, 1999
379. Lacombe M: Renal artery stenosis after renal transplantation. *Ann Vasc Surg* 2: 155–160, 1988
380. Henning PH, Bewick M, Reidy JF, Rigden SP, Neild GH, Chantler C: Increased incidence of renal transplant arterial stenosis in children. *Nephrol Dial Transplant* 4: 575–580, 1989
381. Guideline Subcommittee: World Health Organization-International Society of Hypertension guidelines for the management of hypertension. *J Hypertens* 17: 151–183, 1999
382. Feldman RD, Campbell N, Larochelle P, Bolli P, Burgess ED, Carruthers SG, Floras JS, Haynes RB, Honos G, Leenen FH, Leiter LA, Logan AG, Myers MG, Spence JD, Zarnke KB: 1999 Canadian Recommendations for the Management of Hypertension: Task Force for the Development of the 1999 Canadian Recommendations for the Management of Hypertension. *Can Med Assoc J* 161[Suppl 12]: S1–S17, 1999
383. Maki DD, Ma JZ, Louis TA, Kasiske BL: Long-term effects of antihypertensive agents on proteinuria and renal function. *Arch Intern Med* 155: 1073–1080, 1995
384. Gansevoort RT, Sluiter WJ, Hemmelder MH, de Zeeuw D, de Jong PE: Antiproteinuric effect of blood-pressure-lowering agents: A meta-analysis of comparative trials. *Nephrol Dial Transplant* 10: 1963–1974, 1995
385. Giatras I, Lau J, Levey AS, for the Angiotensin-Converting-Enzyme Inhibition and Progressive Renal Disease Study Group: Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: A meta-analysis of randomized trials. *Ann Intern Med* 127: 337–345, 1997
386. Mailloux LU, Levey AS: Hypertension in patients with chronic renal disease. *Am J Kidney Dis* 32: S120–S141, 1998
387. Modena FM, Hostetter TH, Salahudeen AK, Najarian JS, Matas AJ, Rosenberg ME: Progression of kidney disease in chronic renal transplant rejection. *Transplantation* 52: 239–244, 1991
388. Cheigh JS, Haschemeyer RH, Wang JC, Riggio RR, Tapia L, Stenzel KH, Rubin AL: Hypertension in kidney transplant recipients: Effect on long-term renal allograft survival. *Am J Hypertens* 2: 341–348, 1989
389. Cosio FG, Dillon JJ, Falkenhain ME, Tesi RJ, Henry ML, Elkhammas EA, Davies EA, Bumgardner GL, Ferguson RM: Racial differences in renal allograft survival: The role of systemic hypertension. *Kidney Int* 47: 1136–1141, 1995
390. Barbagallo CM, Pinto A, Gallo S, Parrinello G, Caputo F, Sparacino V, Cefalu AB, Novo S, Licata G, Notarbartolo A, Averna MR: Carotid atherosclerosis in renal transplant recipients: Relationships with cardiovascular risk factors and plasma lipoproteins. *Transplantation* 67: 366–371, 1999
391. Gatzka CD, Schobel HP, Klingbeil AU, Neumayer HH, Schmieder RE: Normalization of circadian blood pressure profiles after renal transplantation. *Transplantation* 59: 1270–1274, 1995
392. Farmer CK, Goldsmith DJ, Cox J, Dallyn P, Kingswood JC, Sharpstone P: An investigation of the effect of advancing uraemia, renal replacement therapy and renal transplantation on blood pressure diurnal variability. *Nephrol Dial Transplant* 12: 2301–2307, 1997
393. Baumgart P, Walger P, Gemen S, von Eiff M, Raidt H, Rahn KH: Blood pressure elevation during the night in chronic renal failure, hemodialysis and after renal transplantation. *Nephron* 57: 293–298, 1991
394. van den Dorpel MA, van den Meiracker AH, Lameris TWB, Levi M, Man in 't Veld AJ, Weimar W, Schalekamp MA: Cyclosporin A impairs the nocturnal blood pressure fall in renal ransplant recipients. *Hypertension* 28: 304–307, 1996
395. Calzolari A, Giordano U, Matteucci MC, Pastore E, Turchetta A, Rizzoni G, Alpert B: Hypertension in young patients after renal transplantation: Ambulatory blood pressure monitoring versus casual blood pressure. *Am J Hypertens* 11: 497–501, 1998
396. Lipkin GW, Tucker B, Giles M, Raine AE: Ambulatory blood pressure and left ventricular mass in cyclosporin- and non-

cyclosporin-treated renal transplant recipients. *J Hypertens* 11: 439–442, 1993
397. Ogilvie RI, Burgess ED, Cusson JR, Feldman RD, Leiter LA, Myers MG: Report of the Canadian Hypertension Society Consensus Conference. 3. Pharmacologic treatment of essential hypertension. *Can Med Assoc J* 149: 575–584, 1993
398. Sever P, Beevers G, Bulpitt C, Lever A, Ramsay L, Reid J, Swales J: Management guidelines in essential hypertension: Report of the Second Working Party of the British Hypertension Society. *Br Med J* 306: 983–987, 1993
399. Sorof JM, Goldstein SL, Brewer ED, Steiger HM, Portman RJ: Use of anti-hypertensive medications and post-transplant renal allograft function in children. *Pediatr Transplant* 4: 21–27, 2000
400. Dussol B, Nicolino F, Brunet P, Leonetti F, Siles S, Berland Y: Acute transplant artery thrombosis induced by angiotensin-converting enzyme inhibitor in a patient with renovascular hypertension. *Nephron* 66: 102–104, 1994
401. Garcia TM, da Costa JA, Costa RS, Ferraz AS: Acute tubular necrosis in kidney transplant patients treated with enalapril. *Renal Fail* 16: 419–423, 1994
402. Fauchald P, Vatne K, Paulsen D, Brodahl U, Sodal G, Holdaas H, Berg KJ, Flatmark A: Long-term clinical results of percutaneous transluminal angioplasty in transplant renal artery stenosis. *Nephrol Dial Transplant* 7: 256–259, 1992
403. Sierre SD, Raynaud AC, Carreres T, Sapoval MR, Beyssen BM, Gaux JC: Treatment of recurrent transplant renal artery stenosis with metallic stents. *J Vasc Interv Radiol* 9: 639–644, 1998
404. Glicklich D, Tellis VA, Quinn T, Mallis M, Greenstein SM, Schechner R, Heller S, Freeman LM, Kutcher R, Veith FJ: Comparison of captopril scan and Doppler ultrasonography as screening tests for transplant renal artery stenosis. *Transplantation* 49: 217–219, 1990
405. Duda SH, Erley CM, Wakat JP, Huppert PE, Lauchart W, Risler T, Claussen CD: Posttransplant renal artery stenosis: Outpatient intraarterial DSA versus color aided duplex Doppler sonography. *Eur J Radiol* 16: 95–101, 1993
406. Saarinen O, Salmela K, Edgren J: Doppler ultrasound in the diagnosis of renal transplant artery stenosis: Value of resistive index. *Acta Radiol* 35: 586–589, 1994
407. Merkus JW, Hoitsma AJ, van Asten WN, Zeebregts CJ, van der Vliet, Strijk SP, Koene RA, Skotnicki SH: Echo-Doppler diagnosis of renal allograft artery stenosis. *Clin Transplant* 9: 383–389, 1995
408. Gottlieb RH, Lieberman JL, Pabico RC, Waldman DL: Diagnosis of renal artery stenosis in transplanted kidneys: Value of Doppler waveform analysis of the intrarenal arteries. *Am J Roentgenol* 165: 1441–1446, 1995
409. Loubeyre P, Cahen R, Grozel F, Trolliet P, Pouteil-Noble C, Labeeuw M, Tran Minh VA: Transplant renal artery stenosis: Evaluation of diagnosis with magnetic resonance angiography compared with color duplex sonography and arteriography. *Transplantation* 62: 446–450, 1996
410. Mousa D, Hamilton D, Miola UJ, al-Sulaiman M, Rassoul Z, Abdalla A, Rehman MA, al-Khader A: The importance of the perfusion index in the evaluation of captopril renography for transplant renal artery stenosis. *Nucl Med Commun* 15: 949–952, 1994
411. Kauffman HM, Adams MB, Hebert LA, Walczak PM: Platelet inhibitors in human renal homotransplantation: Randomized comparison of aspirin versus dipyridamole. *Transplant Proc* 12: 311–314, 1980
412. Mell MW, Alfrey EJ, Rubin GD, Scandling JD, Jeffrey RB, Dafoe DC: Use of spiral computed tomography in the diagnosis of transplant renal artery stenosis. *Transplantation* 57: 746–748, 1994
413. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Summary of the Second Report of the National Cholesterol Education Program (NCEP) (Adult Treatment Panel II). *JAMA* 269: 3015–3023, 1993
414. Kasiske BL: Hyperlipidemia in patients with chronic renal disease. *Am J Kidney Dis* 32: S142–S156, 1998
415. Tsakiris D, Caslake MJ, Briggs JD, Packard CJ, Shepherd J: Low-density lipoprotein metabolism following renal transplantation. *Transplantation* 39: 458–460, 1985
416. Chan MK, Persaud JW, Varghese Z, Fernando ON, Moorhead JF: Fat clearances and hyperlipidaemia in renal allograft recipients: The role of insulin resistance. *Clin Chim Acta* 114: 61–67, 1981
417. Ghanem H, van den Dorpel MA, Weimar W, Man in 't Veld AJ, El-kannishy MH, Jansen H: Increased low density lipoprotein oxidation in stable kidney transplant recipients. *Kidney Int* 49: 488–493, 1996
418. Aakhus S, Dahl K, Widerøe TE: Hyperlipidaemia in renal transplant patients. *J Intern Med* 239: 407–415, 1996
419. Brown JH, Murphy BG, Douglas AF, Short CD, Bhatnagar D, Mackness MI, Doherty CC, Durrington PN: Influence of immunosuppressive therapy on lipoprotein(a) and other lipoproteins following renal transplantation. *Nephron* 75: 277–282, 1997
420. Sugahara S, Koyama I, Yoshikawa Y, Dohi Y, Omoto R: Lipid and lipoprotein(a) in renal transplant recipients. *Transplant Proc* 26: 2080–2081, 1994
421. Sharma AK, Myers TA, Hunninghake DB, Matas AJ, Kashtan CE: Hyperlipidemia in long-term suvivors of pediatric renal transplantation. *Clin Transplant* 8: 252–257, 1994
422. Nicholls AJ, Cumming AM, Catto GRD, Edward N, Engeset J: Lipid relationships in dialysis and renal transplant patients. *Q J Med* 50: 149–160, 1981
423. Chatterjee SN, Chin HP, Azen SP, Blankenhorn DH, Boothe S, Massry SG: Abnormal serum lipid patterns in primary renal allograft recipients. *Surgery* 82: 655–659, 1977
424. Goldberg RB, Judelman JJ, Mindel A, Meyers AM, Salant DJ, Myburgh JA, Rabkin R, Joffe BI, Seftel HC: Hyperlipidaemia in renal transplant patients. *S Afr Med J* 50: 1291–1294, 1976
425. Massy ZA, Bader CA, Chevalier A, Chauveau P, Zingraft J, Lambrey G, Drueke T, Jungers P, Kreis H, Lacour B: Serum lipoprotein(a) levels in chronic renal failure and renal transplant patients. *J Nephrol* 7: 229–236, 1994
426. Segarra A, Chacón P, Martin M, Vilardell M, Vila J, Cotrina M, Fort J, Olmos A, Piera LL, Chacon P: Serum lipoprotein(a) levels in patients with chronic renal failure: Evolution after renal transplantation and relationship with other parameters of lipoprotein metabolism: A prospective study. *Nephron* 69: 9–13, 1995
427. Webb AT, Reaveley DA, O'Donnell M, O'Connor B, Seed M, Brown EA: Does cyclosporin increase lipoprotein(a) concentrations in renal transplant recipients? *Lancet* 341: 268–270, 1993
428. Singh A, Tejani C, Benfield M, Tejani A: Sequential analysis of the lipid profile of children post-renal transplantation. *Pediatr Transplant* 2: 216–223, 1998

429. Silverstein DM, Palmer J, Polinsky MS, Braas C, Conley SB, Baluarte HJ: Risk factors for hyperlipidemia in long-term pediatric renal transplant recipients. *Pediatr Nephrol* 14: 105–110, 2000
430. Pearson TA, Futaki V: Executive Summary: 27th Bethesda Conference: Matching the intensity of risk factor management with the hazard for coronary disease events: September 14–15, 1995. *J Am Coll Cardiol* 27: 961–963, 1996
431. Heule H, Keusch G, Uhlschmid G, Largiad r F, Binswanger U: Kardiovasculäre Krankheiten nach Nierentransplantation: Eine Analyse prädisponierender Facktoren. *Schweiz Med Wochenschr* 20: 709–716, 1981
432. Abdulmassih Z, Chevalier A, Bader C, Drüeke T, Kreis H, Lacour B: Role of lipid disturbances in the atherosclerosis of renal transplant patients. *Clin Transplant* 6: 106–113, 1992
433. Dimény E, Tufveson G, Lithell H, Larsson E, Siegbahn A, Fellström B: The influence of pretransplant lipoprotein abnormalities on the early results of renal transplantation. *Eur J Clin Investig* 23: 572–579, 1993
434. Dimény E, Fellström B, Larsson E, Tufveson G, Lithell H: Chronic vascular rejection and hyperlipoproteinemia in renal transplant patients. *Clin Transplant* 7: 482–490, 1993
435. Isoniemi H, Nurminen M, Tikkanen M, von Willebrand E, Krogerus L, Ahonen J, Eklund B, Höckerstedt K, Salmela K, Häyry P, Tikkanen MJ, Hockerstedt K, Hayry P: Risk factors predicting chronic rejection of renal allograft. *Transplantation* 57: 68–72, 1994
436. Roodnat JI, Mulder PG, Zietse R, Rischen-Vos J, van Riemsdijk IC, Ijzermans JN, Weimar W: Cholesterol as an independent predictor of outcome after renal transplantation. *Transplantation* 69: 1704–1710, 2000
437. Welch GN, Loscalzo J: Homocysteine and atherothrombosis. *N Engl J Med* 338: 1042–1050, 1998
438. Kang SS, Wong PW, Malinow MR: Hyperhomocyst(e)inemia as a risk factor for occlusive vascular disease. *Annu Rev Nutr* 12: 279–298, 1992
439. Selhub J, Jacques PF, Rosenberg IH, Rogers G, Bowman BA, Gunter EW, Wright JD, Johnson CL: Serum total homocysteine concentrations in the third National Health and Nutrition Examination Survey (1991–1994): Population reference ranges and contribution of vitamin status to high serum concentrations. *Ann Intern Med* 131: 331–339, 1999
440. van Guldener C, Janssen MJ, Stehouwer CD, Jakobs C, Bronzwaer JG, Surachno J, Donker AJ: The effect of renal transplantation on hyperhomocysteinaemia in dialysis patients, and the estimation of renal homocysteine extraction in patients with normal renal function. *Neth J Med* 52: 58–64, 1998
441. Arnadottir M, Hultberg B, Wahlberg J, Fellstrom B, Dimeny E: Serum total homocysteine concentration before and after renal transplantation. *Kidney Int* 54: 1380–1384, 1998
442. Arnadottir M, Hultberg B, Vladov V, Nilsson-Ehle P, Thysell H: Hyperhomocysteinemia in cyclosporine-treated renal transplant recipients. *Transplantation* 61: 509–512, 1996
443. Bostom AG, Gohh RY, Tsai MY, Hopkins-Garcia BJ, Nadeau MR, Bianchi LA, Jacques PF, Rosenberg IH, Selhub J: Excess prevalence of fasting and postmethionine-loading hyperhomocysteinemia in stable renal transplant recipients. *Arterioscler Thromb Vasc Biol* 17: 1894–1900, 1997
444. Woodside JV, Fogarty DG, Lightbody JH, Loughrey CM, Yarnell JW, Maxwell AP, Young IS: Homocysteine and B-group vitamins in renal transplant patients. *Clin Chim Acta* 282: 157–166, 1999
445. Fernández-Miranda C, Gómez P, Díaz-Rubio P, Estonez J, Carillo JL, Andrés A, Morales J: Plasma homocysteine levels in renal transplanted patients on cyclosporine or tacrolimus therapy: Effect of treatment with folic acid. *Clin Transplant* 14: 100–114, 2000
446. Ducloux D, Motte G, Challier B, Gibey R, Chalopin JM: Serum total homocysteine and cardiovascular disease occurrence in chronic, stable renal transplant recipients: A prospective study. *J Am Soc Nephrol* 11: 134–137, 2000
447. Ducloux D, Fournier V, Rebibou JM, Bresson-Vautrin C, Gibey R, Chalopin JM: Hyperhomocyst(e)inemia in renal transplant recipients with and without cyclosporine. *Clin Nephrol* 49: 232–235, 1998
448. Ducloux D, Ruedin C, Gibey R, Vautrin P, Bresson-Vautrin C, Rebibou JM, Chalopin JM: Prevalence, determinants, and clinical significance of hyperhomocyst(e)inaemia in renal-transplant recipients. *Nephrol Dial Transplant* 13: 2890–2893, 1998
449. Bostom AG, Gohh RY, Beaulieu AJ, Han H, Jacques PF, Selhub J, Dworkin L, Rosenberg IH: Determinants of fasting plasma total homocysteine levels among chronic stable renal transplant recipients. *Transplantation* 68: 257–261, 1999
450. Boushey CJ, Beresford SA, Omenn GS, Motulsky AG: A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: Probable benefits of increasing folic acid intakes. *JAMA* 274: 1049–1057, 1995
451. Bostom AG, Rosenberg IH, Silbershatz H, Jacques PF, Selhub J, D'Agostino RB, Wilson PW, Wolf PA: Nonfasting plasma total homocysteine levels and stroke incidence in elderly persons: The Framingham Study. *Ann Intern Med* 131: 352–355, 1999
452. Eikelboom JW, Lonn E, Genest JJ, Hankey G, Yusuf S: Homocyst(e)ine and cardiovascular disease: A critical review of the epidemiologic evidence. *Ann Intern Med* 131: 363–375, 1999
453. Massy ZA, Chadefaux-Vekemans B, Chevalier A, Bader CA, Drüeke TB, Legendre C, Lacour B, Kamoun P, Kreis H, Drueke TB: Hyperhomocysteinaemia: A significant risk factor for cardiovascular disease in renal transplant recipients. *Nephrol Dial Transplant* 9: 1103–1108, 1994
454. Olmer M, Renucci JE, Planells R, Bouchouareb D, Purgus R: Preliminary evidence for a role of apolipoprotein E alleles in identifying haemodialysis patients at high vascular risk. *Nephrol Dial Transplant* 12: 691–693, 1997
455. Bostom AG, Gohh RY, Beaulieu AJ, Nadeau MR, Hume AL, Jacques PF, Selhub J, Rosenberg IH: Treatment of hyperhomocysteinemia in renal transplant recipients. *Ann Intern Med* 127: 1089–1092, 1997
456. Arnadottir M, Hultberg B: Treatment with high-dose folic acid effectively lowers plasma homocysteine concentration in cyclosporine-treated renal transplant recipients. *Transplantation* 64: 1087, 1997
457. Sumrani NB, Delaney V, Ding ZK, Davis R, Daskalakis P, Friedman EA, Butt KM, Hong JH: Diabetes mellitus after renal transplantation in the cyclosporine era: An analysis of risk factors. *Transplantation* 51: 343–347, 1991
458. Rao M, Jacob CK, Shastry JC: Post-renal transplant diabetes mellitus: A retrospective study. *Nephrol Dial Transplant* 7: 1039–1042, 1992
459. Hjelmesaeth J, Hartmann A, Kofstad J, Stenstrom J, Leivestad

T, Egeland T, Fauchald P: Glucose intolerance after renal transplantation depends upon prednisolone dose and recipient age. *Transplantation* 64: 979–983, 1997
460. Roth D, Milgrom M, Esquenazi V, Fuller L, Burke G, Miller J: Posttransplant hyperglycemia: Increased incidence in cyclosporine-treated renal allograft recipients. *Transplantation* 47: 278–281, 1989
461. Neylan JF: Racial differences in renal transplantation after immunosuppression with tacrolimus versus cyclosporine: FK506 Kidney Transplant Study Group. *Transplantation* 65: 515–523, 1998
462. Shapiro R, Jordan ML, Scantlebury VP, Vivas C, Marsh JW, McCauley J, Johnston J, Randhawa P, Irish W, Gritsch HA, Naraghi R, Hakala TR, Fung JJ, Starzl TE: A prospective, randomized trial of tacrolimus/prednisone versus tacrolimus/prednisone/mycophenolate mofetil in renal transplant recipients. *Transplantation* 67: 411–415, 1999
463. Onwubalili JK, Obineche EN: High incidence of post-transplant diabetes mellitus in a single-centre study. *Nephrol Dial Transplant* 7: 346–349, 1992
464. Ducloux D, Motte G, Vautrin P, Bresson-Vautrin C, Rebibou JM, Chalopin JM: Polycystic kidney disease as a risk factor for post-transplant diabetes mellitus. *Nephrol Dial Transplant* 14: 1244–1246, 1999
465. Miles AM, Sumrani N, Horowitz R, Homel P, Maursky V, Markell MS, Distant DA, Hong JH, Sommer BG, Friedman EA: Diabetes mellitus after renal transplantation: As deleterious as non-transplant-associated diabetes? *Transplantation* 65: 380–384, 1998
466. Jindal RM, Sidner RA, Milgrom ML: Post-transplant diabetes mellitus: The role of immunosuppression. *Drug Saf* 16: 242–257, 1997
467. American Diabetes Association: Clinical practice recommendations 1997. *Diabetes Care* 20[Suppl 1]: S1–S70, 1997
468. Diabetes Control and Complications (DCCT) Research Group: Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. *Kidney Int* 47: 1703–1720, 1995
469. Manske CL: Hyperglycemia and intensive glycemic control in diabetic patients with chronic renal disease. *Am J Kidney Dis* 32: S157–S171, 1998
470. Kasiske BL, Klinger D: Cigarette smoking in renal transplant recipients. *J Am Soc Nephrol* 11: 753–759, 2000
471. Cosio FG, Alamir A, Yim S, Pesavento TE, Falkenhain ME, Henry ML, Elkhammas EA, Davies EA, Bumgardner GL, Ferguson RM: Patient survival after renal transplantation. I. The impact of dialysis pre-transplant. *Kidney Int* 53: 767–772, 1998
472. Arend SM, Mallat MJ, Westendorp RJ, van der Woude FJ, Van Es LA: Patient survival after renal transplantation: More than 25 years follow-up. *Nephrol Dial Transplant* 12: 1672–1679, 1997
473. Hegeman RL, Hunsicker LG: Chronic rejection in renal allografts: Importance of cardiovascular risk factors. *Clin Transplant* 9: 135–139, 1995
474. Fiore MC, Jorenby DE, Baker TB: Smoking cessation: Principles and practice based upon the AHCPR Guideline, 1996: Agency for Health Care Policy and Research. *Ann Behav Med* 19: 213–219, 1997
475. Agency for Health Care Policy and Research: Smoking cessation: Information for specialists. In: *Clinical Practice Guideline Quick Reference Guide, pp 1–10*
476. Agency for Health Care Policy and Research: The Agency for Health Care Policy and Research smoking cessation clinical practice guideline. *JAMA* 275: 1270–1280, 1996
477. Sumrani NB, Daskalakis P, Miles AM, Sarkar S, Markell MS, Hong JH, Friedman EA, Sommer BG: Erythrocytosis after renal transplantation: A prospective analysis. *ASAIO J* 39: 51–55, 1993
478. Pollak R, Maddux MS, Cohan J, Jacobsson PK, Mozes MF: Erythrocythemia following renal transplantation: Influence of diuretic therapy. *Clin Nephrol* 29: 119–123, 1988
479. Koall W, Schabitz J, Kunsch R, Nilius R: Thromboembolism risk factors in kidney transplant patients with secondary erythrocytosis in relation to hemorheologic aspects [German]. *Z Gesamte Inn Med* 43: 474–477, 1988
480. Hestin D, Legrand E, Mertes M, Renoult E, Kessler M: Polycythemia after kidney transplantation. *Presse Med* 21: 1973–1974, 1992
481. Frei D, Guttmann RD, Gorman P: A matched-pair control study of postrenal transplant polycythemia. *Am J Kidney Dis* 2: 36–42, 1982
482. Wickre CG, Norman DJ, Bennison A, Barry JM, Bennett WM: Postrenal transplant erythrocytosis: A review of 53 patients. *Kidney Int* 23: 731–737, 1983
483. Qunibi WY, Barri Y, Devol E, Al-Furayh O, Sheth K, Taher S: Factors predictive of post-transplant erythrocytosis. *Kidney Int* 40: 1153–1159, 1991
484. Gruber SA, Simmons RL, Najarian JS, Vercellotti G, Ascher NL, Dunn DL, Payne WD, Sutherland DE, Fryd DS: Erythrocytosis and thromboembolic complications after renal transplantation: Results from a randomized trial of cyclosporine versus azathioprine-antilymphocyte globulin. *Transplant Proc* 20: 948–950, 1988
485. Gruppo ISP: Polycythemia vera: The natural history of 1213 patients followed for 20 years. *Ann Intern Med* 123: 656–664, 1995
486. Schwarcz TH, Hogan LA, Endean ED, Roitman IT, Kazmers A, Hyde GL: Thromboembolic complications of polycythemia: Polycythemia vera versus smokers' polycythemia. *J Vasc Surg* 17: 518–522, 1993
487. Orlandi E, Castelli G, Brusamolino E, Canevari A, Morra E, Lazzarino M, Bernasconi C: Hemorrhagic and thrombotic complications in polycythemia vera: A clinical study. *Haematologica* 74: 45–49, 1989
488. Anger B, Haug U, Seidler R, Heimpel H: Polycythemia vera: A clinical study of 141 patients. *Blut* 59: 493–500, 1989
489. Beckingham IJ, Woodrow G, Hinwood M, Rigg KM, Morgan AG, Burden RP, Broughton-Pipkin F: A randomized placebo-controlled study of enalapril in the treatment of erythrocytosis after renal transplantation. *Nephrol Dial Transplant* 10: 2316–2320, 1995
490. Danovitch GM, Jamgotchian NJ, Eggena PH, Paul W, Barrett JD, Wilkinson A, Lee DB: Angiotensin-converting enzyme inhibition in the treatment of renal transplant erythrocytosis: Clinical experience and observation of mechanism. *Transplantation* 60: 132–137, 1995
491. Torregrosa JV, Campistol JM, Montesinos M, Rogada AG, Oppenheimer F, Andreu J: Efficacy of captopril on posttransplant erythrocytosis: Long-term follow-up. *Transplantation* 58: 311–314, 1994
492. Rell K, Koziak K, Jarzyo I, Lao M, Gaciong Z: Correction of posttransplant erythrocytosis with enalapril. *Transplantation* 57: 1059–1063, 1994

493. Islam MS, Bourbigot B, Codet JP, Songy B, Fournier G, Cledes J: Captopril induces correction of postrenal transplant erythremia. *Transplant Int* 3: 222–225, 1990
494. Gaston RS, Julian BA, Diethelm AG, Curtis JJ: Effects of enalapril on erythrocytosis after renal transplantation. *Ann Intern Med* 115: 954–955, 1991
495. Stigant CE, Cohen J, Vivera M, Zaltzman JS: ACE inhibitors and angiotensin II antagonists in renal transplantation: An analysis of safety and efficacy. *Am J Kidney Dis* 35: 58–63, 2000
496. Montanaro D, Groupuzzo M, Boscutti G, Risaliti A, Bresadola F, Mioni G: Long-term therapy for postrenal transplant erythrocytosis with ACE inhibitors: Efficacy, safety and action mechanisms. *Clin Nephrol* 53: 47–51, 2000
497. Julian BA, Brantley RRJ, Barker CV, Stopka T, Gaston RS, Curtis JJ, Lee JY, Prchal JT: Losartan, an angiotensin II type 1 receptor antagonist, lowers hematocrit in posttransplant erythrocytosis. *J Am Soc Nephrol* 9: 1104–1108, 1998
498. Midtvedt K, Stokke ES, Hartmann A: Successful long-term treatment of post-transplant erythrocytosis with losartan. *Nephrol Dial Transplant* 11: 2495–2497, 1996
499. Grekas D, Dioudis C, Valkouma D, Papoulidou F, Tourkantonis A: Theophylline modulates erythrocytosis after renal transplantation. *Nephron* 70: 25–27, 1995
500. Ilan Y, Dranitzki-Elhallel M, Rubinger D, Silver J, Popovtzer MM: Erythrocytosis after renal transplantation: The response to theophylline treatment. *Transplantation* 57: 661–664, 1994
501. Bakris GL, Sauter ER, Hussey JL, Fisher JW, Gaber AO, Winsett R: Effects of theophylline on erythropoietin production in normal subjects and in patients with erythrocytosis after renal transplantation. *N Engl J Med* 323: 86–90, 1990
502. Barenbrock M, Spieker C, Rahn KH, Zidek W: Therapeutic efficiency of phlebotomy in posttransplant hypertension associated with erythrocytosis. *Clin Nephrol* 40: 241–243, 1993
503. Friman S, Nyberg G, Blohmé I: Erythrocytosis after renal transplantation: Treatment by removal of the native kidneys. *Nephrol Dial Transplant* 5: 969–973, 1990
504. Case records of the Massachusetts General Hospital: Weekly clinicopathological exercises: Normal reference laboratory values. *N Engl J Med* 327: 718–724, 1992
505. Miles AM, Markell MS, Daskalakis P, Sumrani NB, Hong J, Sommer BG, Friedman EA: Anemia following renal transplantation: Erythropoietin response and iron deficiency. *Clin Transplant* 11: 313–315, 1997
506. Pruijt JF, Haanen JB, Hollander AA, den Ottolander GJ: Azathioprine-induced pure red-cell aplasia. *Nephrol Dial Transplant* 11: 1371–1373, 1996
507. Creemers GJ, van Boven WP, Lowenberg B, van der Heul C: Azathioprine-associated pure red cell aplasia. *J Intern Med* 233: 85–87, 1993
508. Kim CJ, Park KI, Inoue H, Yoshida T, Yoshiki T, Tomoyoshi T, Abe H, Kodama M, Sako H, Nakane Y: Azathioprine-induced megaloblastic anemia with pancytopenia 22 years after living-related renal transplantation. *Int J Urol* 5: 100–102, 1998
509. Beshara S, Birgegard G, Goch J, Wahlberg J, Wikstrom B, Danielson BG: Assessment of erythropoiesis following renal transplantation. *Eur J Haematol* 58: 167–173, 1997
510. Moore LW, Smith SO, Winsett RP, Acchiardo SR, Gaber AO: Factors affecting erythropoietin production and correction of anemia in kidney transplant recipients. *Clin Transplant* 8: 358–364, 1994
511. Tornero F, Prats D, Alvarez-Sala JL, Coronel F, Sanchez A, Barrientos A: Iron deficiency anemia after successful renal transplantation. *J Urol* 149: 1398–1400, 1993
512. Gossmann J, Thurmann P, Bachmann T, Weller S, Kachel HG, Schoeppe W, Scheuermann EH: Mechanism of angiotensin converting enzyme inhibitor-related anemia in renal transplant recipients. *Kidney Int* 50: 973–978, 1996
513. Gossmann J, Kachel HG, Schoeppe W, Scheuermann EH: Anemia in renal transplant recipients caused by concomitant therapy with azathioprine and angiotensin-converting enzyme inhibitors. *Transplantation* 56: 585–589, 1993
514. Korzets A, Zevin D, Chagnac A, Gafter U, Weinstein T, Ori Y, Levi J: Angiotensin-converting enzyme inhibition and anaemia in renal patients. *Acta Haematol* 90: 202–205, 1993
515. Sizeland PC, Bailey RR, Lynn KL, Robson RA: Anemia and angiotensin-converting enzyme inhibition in renal transplant recipients. *J Cardiovasc Pharmacol* 16[Suppl 7]: S117–S119, 1990
516. Sambataro M, Thomaseth K, Pacini G, Robaudo C, Carraro A, Bruseghin M, Brocco E, Abaterusso C, DeFerrari G, Fioretto P, Maioli M, Tonolo GC, Crepaldi G, Nosadini R: Plasma clearance rate of $^{51}$Cr-EDTA provides a precise and convenient technique for measurement of glomerular filtration rate in diabetic humans. *J Am Soc Nephrol* 7: 118–127, 1996
517. Jeffrey RF, Kendall RG, Prabhu P, Norfolk DR, Will EJ, Davison AM: Re-establishment of erythropoietin responsiveness in end-stage renal failure following renal transplantation. *Clin Nephrol* 44: 241–247, 1995
518. Nampoory MR, Johny KV, al-Hilali N, Seshadri MS, Kanagasabhapathy AS: Erythropoietin deficiency and relative resistance cause anaemia in post-renal transplant recipients with normal renal function. *Nephrol Dial Transplant* 11: 177–181, 1996
519. Rougier JP, Viron B, Ronco P, Khayat R, Michel C, Mignon F: Autoimmune haemolytic anaemia after ABO-match, ABDR full match kidney transplantation. *Nephrol Dial Transplant* 9: 693–697, 1994
520. Bapat AR, Schuster SJ, Dahlke M, Ballas SK: Thrombocytopenia and autoimmune hemolytic anemia following renal transplantation. *Transplantation* 44: 157–159, 1987
521. DeClerck YA, Ettenger RB, Ortega JA, Pennisi AJ: Macrocytosis and pure RBC anemia caused by azathioprine. *Am J Dis Child* 134: 377–379, 1980
522. Ahsan N, Holman MJ, Gocke CD, Groff JA, Yang HC: Pure red cell aplasia due to parvovirus B19 infection in solid organ transplantation. *Clin Transplant* 11: 265–270, 1997
523. Mathias RS: Chronic anemia as a complication of parvovirus B19 infection in a pediatric kidney transplant patient. *Pediatr Nephrol* 11: 355–357, 1997
524. Bertoni E, Rosati A, Zanazzi M, Azzi A, Zakrzewfka K, Guidi S, Salvadori M: Severe aplastic anaemia due to B19 parvovirus infection in renal transplant recipient. *Nephrol Dial Transplant* 10: 1462–1463, 1995
525. Aufricht C, Marik JL, Ettenger RB: Subcutaneous recombinant human erythropoietin in chronic renal allograft dysfunction. *Pediatr Nephrol* 12: 10–13, 1998
526. Van Loo A, Vanholder R, Bernaert P, De Roose J, Lameire N: Recombinant human erythropoietin corrects anaemia during the first weeks after renal transplantation: A randomized prospective study. *Nephrol Dial Transplant* 11: 1815–1821, 1996
527. Kessler M: Erythropoietin and erythropoiesis in renal trans-

plantation. *Nephrol Dial Transplant* 10[Suppl 6]: 114–116, 1995
528. Muirhead N, Cattran DC, Zaltzman J, Jindal K, First MR, Boucher A, Keown PA, Munch LC, Wong C: Safety and efficacy of recombinant human erythropoietin in correcting the anemia of patients with chronic renal allograft dysfunction. *J Am Soc Nephrol* 5: 1216–1222, 1994
529. Jindal KK, Hirsch DJ, Belitsky P, Whalen MA: Low-dose subcutaneous erythropoietin corrects the anaemia of renal transplant failure. *Nephrol Dial Transplant* 7: 143–146, 1992
530. Julian BA, Quarles LD, Niemann KM: Musculoskeletal complications after renal transplantation: Pathogenesis and treatment. *Am J Kidney Dis* 19: 99–120, 1992
531. Epstein S, Shane E, Bilezikian JP: Organ transplantation and osteoporosis. *Curr Opin Rheumatol* 7: 255–261, 1995
532. Coen G: Fracturing osteoporosis after kidney transplantation: What are the options? *Nephrol Dial Transplant* 11: 567–569, 1996
533. Massari PU: Disorders of bone and mineral metabolism after renal transplantation. *Kidney Int* 52: 1412–1421, 1997
534. Moe SM: The treatment of steroid-induced bone loss in transplantation. *Curr Opin Nephrol Hypertens* 6: 544–549, 1997
535. Julian BA, Laskow DA, Dubovsky J, Dubovsky EV, Curtis JJ, Quarles LD: Rapid loss of vertebral mineral density after renal transplantation. *N Engl J Med* 325: 544–550, 1991
536. Kwan JT, Almond MK, Evans K, Cunningham J: Changes in total body bone mineral content and regional bone mineral density in renal patients following renal transplantation. *Miner Electrolyte Metab* 18: 166–168, 1992
537. Almond MK, Kwan JT, Evans K, Cunningham J: Loss of regional bone mineral density in the first 12 months following renal transplantation. *Nephron* 66: 52–57, 1994
538. Horber FF, Casez JP, Steiger U, Czerniak A, Montandon A, Jaeger P: Changes in bone mass early after kidney transplantation. *J Bone Miner Res* 9: 1–9, 1994
539. Wolpaw T, Deal CL, Fleming-Brooks S, Bartucci MR, Schulak JA, Hricik DE: Factors influencing vertebral bone density after renal transplantation. *Transplantation* 58: 1186–1189, 1994
540. Grotz WH, Mundinger FA, Gugel B, Exner VM, Kirste G, Schollmeyer PJ: Bone mineral density after kidney transplantation: A cross-sectional study in 190 graft recipients up to 20 years after transplantation. *Transplantation* 59: 982–986, 1995
541. Grotz WH, Mundinger FA, Rasenack J, Speidel L, Olschewski M, Exner VM, Schollmeyer PJ: Bone loss after kidney transplantation: A longitudinal study in 115 graft recipients. *Nephrol Dial Transplant* 10: 2096–2100, 1995
542. Torregrosa JV, Campistol JM, Montesinos M, Pons F, Martinez de Osaba MJ: Evolution of bone mineral density after renal transplantation: Related factors. *Nephrol Dial Transplant* 10[Suppl 6]: 111–113, 1995
543. Torres A, Machado M, Concepcion MT, Martin N, Lorenzo V, Hernandez D, Rodriguez AP, Rodriguez A, de Bonis E, Gonzalez-Posada JM, Hernandez A, Salido E: Influence of vitamin D receptor genotype on bone mass changes after renal transplantation. *Kidney Int* 50: 1726–1733, 1996
544. Bagni B, Gilli P, Cavallini A, Bagni I, Marzola MC, Orzincolo C, Wahner HW: Continuing loss of vertebral mineral density in renal transplant recipients. *Eur J Nucl Med* 21: 108–112, 1994
545. Boot AM, Nauta J, Hokken-Koelega AC, Pols HA, de Ridder MA, de Muinck K: Renal transplantation and osteoporosis. *Arch Dis Child* 72: 502–506, 1995
546. Pichette V, Bonnardeaux A, Prudhomme L, Gagne M, Cardinal J, Ouimet D: Long-term bone loss in kidney transplant recipients: A cross-sectional and longitudinal study. *Am J Kidney Dis* 28: 105–114, 1996
547. Behnke B, Altrogge H, Delling G, Kruse HP, Muller-Wiefel DE: Bone mineral density in pediatric patients after renal transplantation. *Clin Nephrol* 46: 24–29, 1996
548. Velasquez-Forero F, Mondragon A, Herrero B, Pena JC: Adynamic bone lesion in renal transplant recipients with normal renal function. *Nephrol Dial Transplant* 11[Suppl 3]: 58–64, 1996
549. Grotz WH, Mundinger FA, Muller CB, Rasenack J, Schulte-Monting J, Langer MF, Schollmeyer PJ: Trabecular bone architecture in female renal allograft recipients: Assessed by computed tomography. *Nephrol Dial Transplant* 12: 564–569, 1997
550. Caglar M, Adeera L: Factors affecting bone mineral density in renal transplant patients. *Ann Nucl Med* 13: 141–145, 1999
551. Cueto-Manzano AM, Konel S, Hutchison AJ, Crowley V, France MW, Freemont AJ, Adams JE, Mawer B, Gokal R: Bone loss in long-term renal transplantation: Histopathology and densitometry analysis. *Kidney Int* 55: 2021–2029, 1999
552. Nielsen HE, Melsen F, Christensen MS: Spontaneous fractures following renal transplantation: Clinical and biochemical aspects, bone mineral content and bone morphometry. *Miner Electrolyte Metab* 2: 323–330, 1979
553. Briner VA, Thiel G, Monier-Faugere MC, Bognar B, Landmann J, Kamber V, Malluche HH: Prevention of cancellous bone loss but persistence of renal bone disease despite normal 1,25 vitamin D levels two years after kidney transplantation. *Transplantation* 59: 1393–1400, 1995
554. Ramsey-Goldman R, Dunn JE, Dunlop DD, Stuart FP, Abecassis MM, Kaufman DB, Langman CB, Salinger MH, Sprague SM: Increased risk of fracture in patients receiving solid organ transplants. *J Bone Miner Res* 14: 456–463, 1999
555. Chiu MY, Sprague SM, Bruce DS, Woodle ES, Thistlethwaite JRJ, Josephson MA: Analysis of fracture prevalence in kidney-pancreas allograft recipients. *J Am Soc Nephrol* 9: 677–683, 1998
556. Nisbeth U, Lindh E, Ljunghall S, Backman U, Fellstrom B: Increased fracture rate in diabetes mellitus and females after renal transplantation. *Transplantation* 67: 1218–1222, 1999
557. Withold W, Friedrich W, Degenhardt S: Serum bone alkaline phosphatase is superior to plasma levels of bone matrix proteins for assessment of bone metabolism in patients receiving renal transplants. *Clin Chim Acta* 261: 105–115, 1997
558. Bonnin MR, Gonzalez MT, Grino JM, Cruzado JM, Bover J, Martinez JM, Navarro MA: Changes in serum osteocalcin levels in the follow-up of kidney transplantation. *Ann Clin Biochem* 34: 651–655, 1997
559. Cvetkovic M, Mann GN, Romero DF, Liang XG, Ma Y, Jee WS, Epstein S: The deleterious effects of long-term cyclosporine A, cyclosporine G, and FK506 on bone mineral metabolism *in vivo*. *Transplantation* 57: 1231–1237, 1994
560. Dumoulin G, Hory B, Nguyen NU, Henriet MT, Bresson C, Regnard J, Saint-Hillier Y: Lack of evidence that cyclosporine treatment impairs calcium-phosphorus homeostasis and bone remodeling in normocalcemic long-term renal transplant recipients. *Transplantation* 59: 1690–1694, 1995
561. Cueto-Manzano AM, Konel S, Freemont AJ, Adams JE,

Mawer B, Gokal R, Hutchison AJ: Effect of 1,25-dihydroxyvitamin D3 and calcium carbonate on bone loss associated with long-term renal transplantation. *Am J Kidney Dis* 35: 227–236, 2000

562. Fan SL, Almond MK, Ball E, Evans K, Cunningham J: Pamidronate therapy as prevention of bone loss following renal transplantation. *Kidney Int* 57: 684–690, 2000
563. Hampers CL, Katz AI, Wilson RE, Merrill JP: Calcium metabolism and osteodystrophy after renal transplantation. *Arch Intern Med* 124: 282–291, 1969
564. Cundy T, Kanis JA, Heynen G, Morris PJ, Oliver DO: Calcium metabolism and hyperparathyroidism after renal transplantation. *Q J Med* 52: 67–78, 1983
565. Garvin PJ, Castaneda M, Linderer R, Dickhans M: Management of hypercalcemic hyperparathyroidism after renal transplantation. *Arch Surg* 120: 578–583, 1985
566. D'Alessandro AM, Melzer JS, Pirsch JD, Sollinger HW, Kalayoglu M, Vernon WB, Belzer FO, Starling JR: Tertiary hyperparathyroidism after renal transplantation: Operative indications. *Surgery* 106: 1049–1055, 1989
567. Nordal KP, Dahl E, Halse J, Attramadal A, Flatmark A: Long-term low-dose calcitriol treatment in predialysis chronic renal failure: Can it prevent hyperparathyroid bone disease? *Nephrol Dial Transplant* 10: 203–206, 1995
568. Setterberg L, Sandberg J, Elinder CG, Nordenstrom J: Bone demineralization after renal transplantation: Contribution of secondary hyperparathyroidism manifested by hypercalcaemia. *Nephrol Dial Transplant* 11: 1825–1828, 1996
569. Dumoulin G, Hory B, Nguyen NU, Bresson C, Fournier V, Bouhaddi M, Chalopin JM, Saint-Hillier Y, Regnard J: No trend toward a spontaneous improvement of hyperparathyroidism and high bone turnover in normocalcemic long-term renal transplant recipients. *Am J Kidney Dis* 29: 746–753, 1997
570. Vlcek J, Binswanger U, Keusch G, Zaruba J: Hyperparathyroidism after kidney transplantation: A retrospective case controlled study. *Klin Wochenschr* 69: 669–673, 1991
571. Schmid T, Muller P, Spelsberg F: Parathyroidectomy after renal transplantation: A retrospective analysis of long-term outcome. *Nephrol Dial Transplant* 12: 2393–2396, 1997
572. Steiner RW, Ziegler M, Halasz NA, Catherwood BD, Manolagas S, Deftos LJ: Effect of daily oral vitamin D and calcium therapy, hypophosphatemia, and endogenous 1,25-dihydroxycholecalciferol on parathyroid hormone and phosphate wasting in renal transplant recipients. *Transplantation* 56: 843–846, 1993
573. Lobo PI, Cortez MS, Stevenson W, Pruett TL: Normocalcemic hyperparathyroidism associated with relatively low 1,25 vitamin D levels post-renal transplant can be successfully treated with oral calcitriol. *Clin Transplant* 9: 277–281, 1995
574. Higgins RM, Richardson AJ, Endre ZH, Frostick SP, Morris PJ: Hypophosphataemia after renal transplantation: Relationship to immunosuppressive drug therapy and effects on muscle detected by $^{31}P$ nuclear magnetic resonance spectroscopy. *Nephrol Dial Transplant* 5: 62–68, 1990
575. Ulmann A, Chkoff N, Lacour B: Disorders of calcium and phosphorus metabolism after successful kidney transplantation. *Adv Nephrol Necker Hosp* 12: 331–340, 1983
576. Parfitt AM, Kleerekoper M, Cruz C: Reduced phosphate reabsorption unrelated to parathyroid hormone after renal transplantation: Implications for the pathogenesis of hyperparathyroidism in chronic renal failure. *Miner Electrolyte Metab* 12: 356–362, 1986
577. Rosenbaum RW, Hruska KA, Korkor A, Anderson C, Slatopolsky E: Decreased phosphate reabsorption after renal transplantation: Evidence for a mechanism independent of calcium and parathyroid hormone. *Kidney Int* 19: 568–578, 1981
578. Nielsen HE, Christensen MS, Melsen F, Torring S: Bone disease, hypophosphatemia and hyperparathyroidism after renal transplantation. *Adv Exp Med Biol* 81: 603–610, 1977
579. Moorhead JF, Wills MR, Ahmed KY, Baillod RA, Varghese Z, Tatler GL: Hypophosphataemic osteomalacia after cadaveric renal transplantation. *Lancet* 1: 694–697, 1974
580. Felsenfeld AJ, Gutman RA, Drezner M, Llach F: Hypophosphatemia in long-term renal transplant recipients: Effects on bone histology and 1,25-dihydroxycholecalciferol. *Miner Electrolyte Metab* 12: 333–341, 1986
581. Walker GS, Peacock M, Marshall DH, Giles GR, Davison AM: Factors influencing the intestinal absorption of calcium and phosphorus following renal transplantation. *Nephron* 26: 225–229, 1980
582. Farrington K, Varghese Z, Newman SP, Ahmed KY, Fernando ON, Moorhead JF: Dissociation of absorptions of calcium and phosphate after successful cadaveric renal transplantation. *Br Med J* 1: 712–714, 1979
583. Ambuhl PM, Meier D, Wolf B, Dydak U, Boesiger P, Binswanger U: Metabolic aspects of phosphate replacement therapy for hypophosphatemia after renal transplantation: Impact on muscular phosphate content, mineral metabolism, and acid/base homeostasis. *Am J Kidney Dis* 34: 875–883, 1999
584. Scoble JE, Freestone A, Varghese Z, Fernando ON, Sweny P, Moorhead JF: Cyclosporin-induced renal magnesium leak in renal transplant patients. *Nephrol Dial Transplant* 5: 812–815, 1990
585. Haag-Weber M, Schollmeyer P, Horl WH: Failure to detect remarkable hypomagnesemia in renal transplant recipients receiving cyclosporin. *Miner Electrolyte Metab* 16: 66–68, 1990
586. Ramos EL, Barri YM, Kubilis P, Peterson JC, Pfaff WW, Howard RJ, Parris CJ, Patton PR, Karlix JL: Hypomagnesemia in renal transplant patients: Improvement over time and association with hypertension and cyclosporine levels. *Clin Transplant* 9: 185–189, 1995
587. Markell MS, Altura BT, Barbour RL, Altura BM: Ionized and total magnesium levels in cyclosporin-treated renal transplant recipients: Relationship with cholesterol and cyclosporin levels. *Clin Sci* 85: 315–318, 1993
588. Vannini SD, Mazzola BL, Rodoni L, Truttmann AC, Wermuth B, Bianchetti MG, Ferrari P: Permanently reduced plasma ionized magnesium among renal transplant recipients on cyclosporine. *Transplant Int* 12: 244–249, 1999
589. Rasmussen HS, Aurup P, Goldstein K, McNair P, Mortensen PB, Larsen OG, Lawaetz H: Influence of magnesium substitution therapy on blood lipid composition in patients with ischemic heart disease: A double-blind, placebo controlled study. *Arch Intern Med* 149: 1050–1053, 1989
590. Gupta BK, Glicklich DTVA: Magnesium repletion therapy improves lipid metabolism in hypomagnesemic renal transplant recipients. *Transplantation* 67: 1485–1487, 1999
591. Barton CH, Vaziri ND, Martin DC, Choi S, Alikhani S: Hypomagnesemia and renal magnesium wasting in renal transplant recipients receiving cyclosporine. *Am J Med* 83: 693–699, 1987
592. Gores PF, Fryd DS, Sutherland DE, Najarian JS, Simmons

RL: Hyperuricemia after renal transplantation. *Am J Surg* 156: 397–400, 1988
593. Lin HY, Rocher LL, McQuillan MA, Schmaltz S, Palella TD, Fox IH: Cyclosporine-induced hyperuricemia and gout. *N Engl J Med* 321: 287–292, 1989
594. West C, Carpenter BJ, Hakala TR: The incidence of gout in renal transplant recipients. *Am J Kidney Dis* 10: 369–372, 1987
595. Edvardsson VO, Kaiser BA, Polinsky MS, Palmer JA, Quien R, Baluarte HJ: Natural history and etiology of hyperuricemia following pediatric renal transplantation. *Pediatr Nephrol* 9: 57–60, 1995
596. Hoyer PF, Lee IJ, Oemar BS, Krohn HP, Offner G, Brodehl J: Renal handling of uric acid under cyclosporin A treatment. *Pediatr Nephrol* 2: 18–21, 1988
597. Marcen R, Gallego N, Orofino L, Gamez C, Estepa MR, Sabater J, Teruel JL, Ortuno J: Impairment of tubular secretion of urate in renal transplant patients on cyclosporine. *Nephron* 70: 307–313, 1995
598. Hansen JM, Fogh-Andersen N, Leyssac PP, Strandgaard S: Glomerular and tubular function in renal transplant patients treated with and without ciclosporin A. *Nephron* 80: 450–457, 1998
599. Laine J, Holmberg C: Mechanisms of hyperuricemia in cyclosporine-treated renal transplanted children. *Nephron* 74: 318–323, 1996
600. Zurcher RM, Bock HA, Thiel G: Hyperuricaemia in cyclosporin-treated patients: GFR-related effect. *Nephrol Dial Transplant* 11: 153–158, 1996
601. Hollander AA, van Saase JL, Kootte AM, van Dorp WT, van Bockel HJ, Van Es LA, van der Woude FJ: Beneficial effects of conversion from cyclosporin to azathioprine after kidney transplantation. *Lancet* 345: 610–614, 1995
602. Gerhardt U, Grosse HM, Hohage H: Influence of hyperglycemia and hyperuricemia on long-term transplant survival in kidney transplant recipients. *Clin Transplant* 13: 375–379, 1999
603. Venkataseshan VS, Feingold R, Dikman S, Churg J: Acute hyperuricemic nephropathy and renal failure after transplantation. *Nephron* 56: 317–321, 1990
604. Cantarell MC, Capdevila L, Morlans M, Piera L: Uric acid calculus in renal transplant patients treated with cyclosporine [Letter]. *Clin Nephrol* 35: 288, 1991
605. Guijarro C, Massy ZA, Ma JZ, Wiederkehr M, Kasiske BL: Serum albumin and mortality after renal transplantation. *Am J Kidney Dis* 27: 117–123, 1996
606. Becker BN, Becker YT, Heisey DM, Leverson GE, Collins BH, Odorico JS, D'Alessandro AM, Knechtle SJ, Pirsch JD, Sollinger HW: The impact of hypoalbuminemia in kidney-pancreas transplant recipients. *Transplantation* 68: 72–75, 1999
607. Ekstrand A, Groop L, Pettersson E, Gronhagen-Riska C, Laatikainen L, Matikainen E, Seppalainen AM, Laasonen E, Summanen P, Ollus A: Metabolic control and progression of complications in insulin-dependent diabetic patients after kidney transplantation. *J Intern Med* 232: 253–261, 1992
608. Miller DG, Levine SE, D'Elia JA, Bistrian BR: Nutritional status of diabetic and nondiabetic patients after renal transplantation. *Am J Clin Nutr* 44: 66–69, 1986
609. Modlin CS, Flechner SM, Goormastic M, Goldfarb DA, Papajcik D, Mastroianni B, Novick AC: Should obese patients lose weight before receiving a kidney transplant? *Transplantation* 64: 599–604, 1997
610. Holley JL, Shapiro R, Lopatin WB, Tzakis AG, Hakala TR, Starzl TE: Obesity as a risk factor following cadaveric renal transplantation. *Transplantation* 49: 387–389, 1990
611. Blümke M, Keller E, Eble F, Nausner M, Kirste G: Obesity in kidney transplant patients as a risk factor. *Transplant Proc* 25: 2618, 1993
612. Pirsch JD, Armbrust MJ, Knechtle SJ, D'Alessandro AM, Sollinger HW, Heisey DM, Belzer FO: Obesity as a risk factor following renal transplantation. *Transplantation* 59: 631–633, 1995
613. Halme L, Eklund B, Kyllonen L, Salmela K: Is obesity still a risk factor in renal transplantation? *Transplant Int* 10: 284–288, 1997
614. Meier-Kriesche HU, Vaghela M, Thambuganipalle R, Friedman G, Jacobs M, Kaplan B: The effect of body mass index on long-term renal allograft survival. *Transplantation* 68: 1294–1297, 1999
615. Merion RM, Twork AM, Rosenberg L, Ham JM, Burtch GD, Turcotte JG, Rocher LL, Campbell DAJ: Obesity and renal transplantation. *Surg Gynecol Obstet* 172: 367–376, 1991
616. Drafts HH, Anjum MR, Wynn JJ, Mulloy LL, Bowley JN, Humphries AL: The impact of pre-transplant obesity on renal transplant outcomes. *Clin Transplant* 11: 493–496, 1997
617. Measurement of visceral protein status in assessing protein and energy malnutrition: Standard of care: Prealbumin in Nutritional Care Consensus Group. *Nutrition* 11: 169–171, 1995
618. Ingenbleek Y, Young V: Transthyretin (prealbumin) in health and disease: Nutritional implications. *Annu Rev Nutr* 14: 495–533, 1994
619. Johnson AM: Low levels of plasma proteins: Malnutrition or inflammation. *Clin Chem Lab Med* 37: 91–96, 1999
620. Potter MA, Luxton G: Prealbumin measurement as a screening tool for protein calorie malnutrition in emergency hospital admissions: A pilot study. *Clin Investig Med* 22: 44–52, 1999
621. Sreedhara R, Avram MM, Blanco M, Batish R, Mittman N: Prealbumin is the best nutritional predictor of survival in hemodialysis and peritoneal dialysis. *Am J Kidney Dis* 28: 937–942, 1996
622. Hoy WE, Sargent JA, Freeman RB, Pabico RC, McKenna BA, Sterling WA Jr: The influence of glucocorticoid dose on protein catabolism after renal transplantation. *Am J Med Sci* 291: 241–247, 1986
623. Seagraves A, Moore EE, Moore FA, Weil R III: Net protein catabolic rate after kidney transplantation: Impact of corticosteroid immunosuppression. *J Parenter Enter Nutr* 10: 453–455, 1986
624. Johnson CP, Gallagher-Lepak S, Zhu YR, Porth C, Kelber S, Roza AM, Adams MB: Factors influencing weight gain after renal transplantation. *Transplantation* 56: 822–827, 1993
625. National Heart, Lung, and Blood Institute: *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults* (Report No. 228), Bethesda, MD, National Institutes of Health, 1998
626. United States Preventive Services Task Force: Screening for obesity. In: *Guide to Clinical Preventive Services*, 2nd Ed., edited by Di Guiseppi C, Atkins D, Woolf S, Baltimore, Williams & Wilkins, 1996, pp 219–229
627. Patel MG: The effect of dietary intervention on weight gains after renal transplantation. *J Renal Nutr* 8: 137–141, 1998

628. Rizzoni G, Broyer M, Brunner FP, Brynger H, Challah S, Kramer P, Oules R, Selwood NH, Wing AJ, Balas EA: Combined Report on Regular Dialysis and Transplantation of Children in Europe, XIII, 1983. *Proc Eur Dial Transplant Assoc Eur Renal Assoc* 21: 66–95, 1985
629. Hokken-Koelega AC, Van Zaal MA, van Bergen W, de Ridder MA, Stijnen T, Wolff ED, de Jong RC, Donckerwolcke RA, Muinck Keizer-Schrama SM, Drop SL: Final height and its predictive factors after renal transplantation in childhood. *Pediatr Res* 36: 323–328, 1994
630. Betts PR, Magrath G: Growth pattern and dietary intake of children with chronic renal insufficiency. *Br Med J* 2: 189–193, 1974
631. Ingelfinger JR, Grupe WE, Harmon WE, Fernbach SK, Levey RH: Growth acceleration following renal transplantation in children less than 7 years of age. *Pediatrics* 68: 255–259, 1981
632. Fine RN: Renal transplantation for children: The only realistic choice. *Kidney Int* 17[Suppl]: S15–S17, 1985
633. Rotundo A, Nevins TE, Lipton M, Lockman LA, Mauer SM, Michael AF: Progressive encephalopathy in children with chronic renal insufficiency in infancy. *Kidney Int* 21: 486–491, 1982
634. McGraw ME, Haka-Ikse K: Neurologic-developmental sequelae of chronic renal failure in infancy. *J Pediatr* 106: 579–583, 1985
635. Crittenden MR, Holliday MA, Piel CF, Potter DE: Intellectual development of children with renal insufficiency and end stage disease. *Int J Pediatr Nephrol* 6: 275–280, 1985
636. Fennell RS, Fennell EB, Carter RL, Mings EL, Klausner AB, Hurst JR: Association between renal function and cognition in childhood chronic renal failure. *Pediatr Nephrol* 4: 16–20, 1990
637. Fennell RS, Fennell EB, Carter RL, Mings EL, Klausner AB, Hurst JR: A longitudinal study of the cognitive function of children with renal failure. *Pediatr Nephrol* 4: 11–15, 1990
638. Henning P, Tomlinson L, Rigden SP, Haycock GB, Chantler C: Long term outcome of treatment of end stage renal failure. *Arch Dis Child* 63: 35–40, 1988
639. Elzouki A, Carroll J, Butinar D, Moosa A: Improved neurological outcome in children with chronic renal disease from infancy. *Pediatr Nephrol* 8: 205–210, 1994
640. Morel P, Almond PS, Matas AJ, Gillingham KJ, Chau C, Brown A, Kashtan CE, Mauer SM, Chavers B, Nevins TE: Long-term quality of life after kidney transplantation in childhood. *Transplantation* 52: 47–53, 1991
641. Potter DE, Najarian J, Belzer F, Holliday MA, Horns G, Salvatierra O Jr: Long-term results of renal transplantation in children. *Kidney Int* 40: 752–756, 1991
642. Apajasalo M, Rautonen J, Sintonen H, Holmberg C: Health-related quality of life after organ transplantation in childhood. *Pediatr Transplant* 1: 130–137, 1997
643. McEnery PT, Gonzalez LL, Martin LW, West CD: Growth and development of children with renal transplants: Use of alternate-day steroid therapy. *J Pediatr* 83: 806–814, 1973
644. Johansson G, Sietnieks A, Janssens F, Proesmans W, Vanderschueren-Lodeweyckx M, Holmberg C, Sipila I, Broyer M, Rappaport R, Albertsson-Wikland K: Recombinant human growth hormone treatment in short children with chronic renal disease, before transplantation or with functioning renal transplants: An interim report on five European studies. *Acta Paediatr Scand Suppl* 370: 36–42, 1990
645. Rees L, Ward G, Rigden SP: Growth over 10 years following a 1-year trial of growth hormone therapy. *Pediatr Nephrol* 14: 309–314, 2000
646. Penn I: Skin disorders in organ transplant recipients: External anogenital lesions. *Arch Dermatol* 133: 221–223, 1997
647. Penn I: Neoplastic complications of transplantation. *Semin Respir Infect* 8: 233–239, 1993
648. Sheil AGR, Disney APS, Mathew TG, Amiss N: *De novo* malignancy emerges as a major cause of morbidity and late failure in renal transplantation. *Transplant Proc* 25: 1383–1384, 1993
649. London NJ, Farmery SM, Will EJ, Davison AM, Lodge JPA: Risk of neoplasia in renal transplant patients. *Lancet* 346: 403–406, 1995
650. Blohmé I, Brynger H: Malignant disease in renal transplant patients. *Transplantation* 39: 23–25, 1985
651. Penn I: Cancers in cyclosporine-treated vs azathioprine-treated patients. *Transplant Proc* 28: 876–878, 1996
652. Hartevelt MM, Bavinck JNB, Kootte AMM, Vermeer BJ, Vandenbroucke JP: Incidence of skin cancer after renal transplantation in the Netherlands. *Transplantation* 49: 506–509, 1990
653. Sheil AGR, Disney APS, Mathew TG, Amiss N, Excell L: Malignancy following renal transplantation. *Transplant Proc* 24: 1946–1947, 1992
654. Greene MH, Young TI: Malignant melanoma in renal-transplant recipients. *Lancet* 1: 1196–1199, 1981
655. Brunner FP, Landais P, Selwood NH: Malignancies after renal transplantation: The EDTA-ERA Registry experience. *Nephrol Dial Transplant* 10[Suppl 1]: 74–80, 1995
656. Kinlen J, Sheil AGR, Peto J, Doll R: Collaborative United Kingdom-Australasian study of cancer in patients treated with immunosuppressive drugs. *Br Med J* 2: 1461–1466, 1979
657. Penn I: Malignant melanoma in organ allograft recipients. *Transplantation* 61: 274–278, 1996
658. King GN, Healy CM, Glover MT, Kwan JTC, Williams DM, Leigh IM, Worthington HV, Thornhill MH: Increased prevalence of dysplastic and malignant lip lesions in renal-transplant recipients. *N Engl J Med* 332: 1052–1057, 1995
659. Penn I: *De novo* malignancies in pediatric organ transplant recipients. *Pediatr Transplant* 2: 56–63, 1998
660. Hepburn DJ, Divakar D, Bailey RR, Macdonald KJS: Cutaneous manifestations of renal transplantation in a New Zealand population. *N Z Med J* 107: 497–499, 1994
661. Brash DE, Rudolph JA, Simon JA, Lin A, McKenna GJ, Baden HP, Halperin AJ, Ponten J: A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. *Proc Natl Acad Sci USA* 88: 10124–10128, 1991
662. Gibson GE, O'Grady A, Kay EW, Leader M, Murphy GM: p53 tumor suppressor gene protein expression in premalignant and malignant skin lesions of kidney transplant recipients. *J Am Acad Dermatol* 36: 924–931, 1997
663. Sheil AGR: Malignancy in organ transplant recipients. *Transplant Proc* 28: 1162, 1996
664. Glover MT, Deeks JJ, Raftery MJ, Cunningham J, Leigh IM: Immunosuppression and risk of non-melanoma skin cancer in renal transplant recipients. *Lancet* 349: 398, 1997
665. Myskowski PL: Skin cancer and HLA antigens. *N Engl J Med* 326: 765, 1992
666. Bavinck JNB, Vermeer BJ, van der Woude FJ, Vandenbroucke JP, Schreuder GMT, Thorogood J, Persijn GG, Claas FHJ: Relation between skin cancer and HLA antigens in renal-transplant recipients. *N Engl J Med* 325: 843–848, 1991

667. Bavinck JNB, Claas FHJ: The role of HLA molecules in the development of skin cancer. *Hum Immunol* 41: 173–179, 1994
668. Bouwes-Bavinck JN, Claas FH, Hardie DR, Green A, Vermeer BJ, Hardie IR: Relation between HLA antigens and skin cancer in renal transplant recipients in Queensland, Australia. *J Investig Dermatol* 108: 708–711, 1997
669. Glover MT, Bodmer J, Bodmer W, Kennedy LJ, Brown J, Navarrete C, Kwan JTC, Leigh IM: HLA antigen frequencies in renal transplant recipients and non-immunosuppressed patients with non-melanoma skin cancer. *Eur J Cancer* 29A: 520–524, 1993
670. Shamanin V, zur Hausen H, Lavergne D, Proby CM, Leigh IM, Neumann C, Hamm H, Goos M, Haustein U-F, Jung EG, Plewig G, Wolff H, de Villiers E-M: Human papillomavirus infections in nonmelanoma skin cancers from renal transplant recipients and nonimmunosuppressed patients. *J Natl Cancer Inst* 88: 802–811, 1996
671. Stark LA, Arends MJ, McLaren KM, Benton EC, Shahidullah H, Hunter JAA, Bird CC: Prevalence of human papillomavirus DNA in cutaneous neoplasms from renal allograft recipients supports a possible viral role in tumour promotion. *Br J Cancer* 69: 222–229, 1994
672. Berkhout RJM, Tieben LM, Smits HL, Bavinck JNB, Vermeer BJ, ter Schegget J: Nested PCR approach for detection and typing of epidermodysplasia verruciformis-associated human papillomavirus types in cutaneous cancers from renal transplant recipients. *J Clin Microbiol* 33: 690–695, 1995
673. McGregor JM, Proby CM, Leigh IM: Virus infection and cancer risk in transplant recipients. *Trends Microbiol* 4: 2–4, 1996
674. McGregor JM, Farthing A, Crook T, Yu CCW, Dublin EA, Levison DA, MacDonald DM: Posttransplant skin cancer: A possible role for p53 gene mutation but not for oncogenic human papillomaviruses. *J Am Acad Dermatol* 30: 701–706, 1994
675. Mullen DL, Silverberg SG, Penn I: Squamous cell carcinoma of the skin and lip in renal homograft recipients. *Cancer* 37: 729–734, 1976
676. Euvrard S, Kanitakis J, Pouteil-Noble C, Dureau G, Touraine JL, Faure M, Claudy A, Thivolet J: Comparative epidemiologic study of premalignant and malignant epithelial cutaneous lesions developing after kidney and heart transplantation. *J Am Acad Dermatol* 33: 222–229, 1995
677. Szepietowski J, Wasik F, Szepietowski T, Wlodarczyk M, Sobczak-Radwan K, Czyz W: Excess benign melanocytic naevi in renal transplant recipients. *Dermatology* 194: 17–19, 1997
678. United States Preventive Services Task Force: Screening for skin cancer. In: *Guide to Clinical Preventive Services*, 2nd Ed., edited by Di Guiseppi C, Atkins D, Woolf S, Baltimore, Williams & Wilkins, 1996, pp 141–152
679. Miller AB, Chamberlain J, Day NE, Hakama M, Prorok PC: Report on a workshop of the UICC Project on the Evaluation of Screening for Cancer. *Int J Cancer* 46: 761–769, 1990
680. Cassileth BR, Clark WH Jr, Lusk EJ, Frederick BE, Thompson CJ, Walsh WP: How well do physicians recognize melanoma and other problem lesions? *J Am Acad Dermatol* 14: 555–560, 1986
681. Drake LA, Ceilley RI, Cornelison RL, Dobes WA, Dorner W, Goltz RW, Lewis CW, Salasche SJ, Turner ML, Arrowsmith DR, Burgdorf WHC, Sanders BS: Guidelines of care for nevi I (nevocellular nevi and seborrheic kertoses): Committee on Guidelines of Care: Task Force on Nevocellular Nevi. *J Am Acad Dermatol* 26: 629–631, 1992
682. NIH Consensus Development Panel on Early Melanoma: Diagnosis and treatment of early melanoma. *JAMA* 268: 1314–1319, 1992
683. American Cancer Society: Summary of American Cancer Society recommendations for the early detection of cancer in asymptomatic people. In: *Cancer Facts and Figures—1998*, Atlanta, American Cancer Society, 1998
684. Cowen EW, Billingsley EM: Awareness of skin cancer by kidney transplant patients. *J Am Acad Dermatol* 40: 697–701, 1999
685. Birkeland SA, Storm HH, Lamm LU, Barlow L, Blohmé I, Forsberg B, Eklund B, Fjeldborg O, Friedberg M, Frodin L, Glattre E, Halvorsen S, Holm NV, Jakobsen A, Jorgensen HE, Ladefoged J, Lindholm T, Lundgren G, Pukkala E: Cancer risk after renal transplantation in the Nordic countries, 1964–1986. *Int J Cancer* 60: 183–189, 1995
686. Penn I: Cancers of the anogenital region in renal transplant recipients: Analysis of 65 cases. *Cancer* 58: 611–616, 1986
687. Fairley CK, Sheil AGR, McNeil JJ, Ugoni AM, Disney APS, Giles GG, Amiss N: The risk of ano-genital malignancies in dialysis and transplant patients. *Clin Nephrol* 41: 101–105, 1994
688. Penn I: Tumors after renal and cardiac transplantation. *Hematol Oncol Clin North Am* 7: 431–445, 1993
689. Euvrard S, Kanitakis J, Chardonnet Y, Pouteil-Noble C, Touraine JL, Faure M, Thivolet J, Claudy A: External anogenital lesions in organ transplant recipients: A clinicopathologic virologic assessment. *Arch Dermatol* 133: 175–178, 1997
690. Ogunbiyi OA, Scholefield JH, Raftery AT, Smith JHF, Duffy S, Sharp F, Rogers K: Prevalence of anal human papillomavirus infection and intraepithelial neoplasia in renal allograft recipients. *Br J Surg* 81: 365–367, 1994
691. Shah KV: Human papillomaviruses and anogenital cancers. *N Engl J Med* 337: 1386–1388, 1997
692. Arends MJ, Benton EC, McLaren KM, Stark LA, Hunter JAA, Bird CC: Renal allograft recipients with high susceptibility to cutaneous malignancy have an increased prevalence of human papillomavirus DNA in skin tumours and a greater risk of anogenital malignancy. *Br J Cancer* 75: 722–728, 1997
693. Palefsky JM, Holly EA, Gonzales J, Lamborn K, Hollander H: Natural history of anal cytologic abnormalities and papillomavirus infection among homosexual men with Group IV HIV disease. *J AIDS* 5: 1258–1265, 1992
694. Siegel JH, Janis R, Alper JC, Schutte H, Robbins L, Blaufox MD: Disseminated visceral Kaposi's sarcoma: Appearance after human renal homograft operation. *JAMA* 207: 1493–1496, 1969
695. Penn I: Kaposi's sarcoma in transplant recipients. *Transplantation* 64: 669–673, 1997
696. Odajnyk C, Muggia FM: Treatment of Kaposi's sarcoma: Overview and analysis by clinical setting. *J Clin Oncol* 3: 1277–1285, 1985
697. Penn I: Sarcomas in organ allograft recipients. *Transplantation* 60: 1485–1491, 1995
698. Qunibi W, Akhtar M, Sheth K, Ginn HE, Al-Furayh O, DeVol EB, Taher S: Kaposi's sarcoma: The most common tumor after renal transplantation in Saudi Arabia. *Am J Med* 84: 225–232, 1988
699. Qunibi W, Barri Y, Alfurayh K, Almeshari K, Khan B, Taher

S, Sheth K: Kaposi's sarcoma in renal transplant recipients: A report on 26 cases from a single institution. *Transplant Proc* 25: 1402–1405, 1993
700. Harwood AR, Osoba D, Hofstader SL, Goldstein MB, Cardella CJ, Holecek MJ, Kunynetz R, Giammarco RA: Kaposi's sarcoma in recipients of renal transplants. *Am J Med* 67: 759–765, 1979
701. Montagnino G, Bencini PL, Tarantino A, Caputo R, Ponticelli C: Clinical features and course of Kaposi's sarcoma in kidney transplant patients: Report of 13 cases. *Am J Nephrol* 14: 121–126, 1994
702. Doutrelepont J-M, De Pauw L, Gruber SA, Dunn DL, Qunibi W, Kinnaert P, Vereerstraeten P, Penn I, Abramowicz D: Renal transplantation exposes patients with previous Kaposi's sarcoma to a high risk of recurrence. *Transplantation* 62: 463–466, 1996
703. Cathomas G, Tamm M, McGandy CE, Itin PH, Gudat F, Thiel G, Mihatsch MJ: Transplantation-associated malignancies: Restriction of human herpes virus 8 to Kaposi's sarcoma. *Transplantation* 64: 175–178, 1997
704. Moosa MR, Treurnicht FK, van Rensburg EJ, Schneider JW, Jordaan HF, Engelbrecht S: Detection and subtyping of human herpesvirus-8 in renal transplant patients before and after remission of Kaposi's sarcoma. *Transplantation* 66: 214–218, 1998
705. Farge D, Lebbe C, Marjanovic Z, Tuppin P, Mouquet C, Peraldi MN, Lang P, Hiesse C, Antoine C, Legendre C, Bedrossian J, Gagnadoux MF, Loirat C, Pellet C, Sheldon J, Golmard JL, Agbalika F, Schulz TF: Human herpes virus-8 and other risk factors for Kaposi's sarcoma in kidney transplant recipients: Groupe Cooperatif de Transplantation d'Ile de France (GCIF). *Transplantation* 67: 1236–1242, 1999
706. Frances C, Mouquet C, Marcelin AG, Barete S, Agher R, Charron D, Benalia H, Dupin N, Piette JC, Bitker MO, Calvez V: Outcome of kidney transplant recipients with previous human herpesvirus-8 infection. *Transplantation* 69: 1776–1779, 2000
707. Cattani P, Nanni G, Graffeo R, Capuano M, Cerimele F, La Parola IL, Diociaiuti A, Pozzetto U, Cerimele D, Fadda G, Castagneto M: Pretransplantation human herpes virus 8 seropositivity as a risk factor for Kaposi's sarcoma in kidney transplant recipients. *Transplant Proc* 32: 526–527, 2000
708. Kedda M-A, Margolius L, Kew MC, Swanepoel C, Pearson D: Kaposi's sarcoma-associated herpesvirus in Kaposi's sarcoma occurring in immunosuppressed renal transplant recipients. *Clin Transplant* 10: 429–431, 1996
709. Brunson ME, Balakrishnan K, Penn I: HLA and Kaposi's sarcoma in solid organ transplantation. *Hum Immunol* 29: 56–63, 1990
710. Akhtar M, Bunuan H, Ali MA, Godwin JT: Kaposi's sarcoma in renal transplant recipients. *Cancer* 53: 258–266, 1984
711. McGuinness G: Changing trends in the pulmonary manifestations of AIDS. *Radiol Clin North Am* 35: 1029–1082, 1997
712. Gunawardena KA, Al-Hasani MK, Haleem A, Al-Suleiman M, al-Khader AA: Pulmonary Kaposi's sarcoma in two recipients of renal transplants. *Thorax* 43: 653–656, 1988
713. Panicek DM, Gatsonis C, Rosenthal DI, Seeger LL, Huvos AG, Moore SG, Caudry DJ, Palmer WE, McNeil BJ: CT and MR imaging in the local staging of primary malignant musculoskeletal neoplasms: Report of the Radiology Diagnostic Oncology Group. *Radiology* 202: 237–246, 1997
714. Storm HH: Cancers of the soft tissues. *Cancer Surv* 19–20: 197–217, 1994
715. Basgoz N, Preiksaitis JK: Post-transplant lymphoproliferative disorder. *Infect Dis Clin North Am* 9: 901–923, 1995
716. Paya CV, Fung JJ, Nalesnik MA, Kieff E, Green M, Gores G, Habermann TM, Wiesner PH, Swinnen JL, Woodle ES, Bromberg JS: Epstein-Barr virus-induced posttransplant lymphoproliferative disorders: ASTS/ASTP EBV-PTLD Task Force and The Mayo Clinic Organized International Consensus Development Meeting. *Transplantation* 68: 1517–1525, 1999
717. Doak PB, Montgomerie JZ, North JDK, Smith F: Reticulum cell sarcoma after renal homotransplantation and azathioprine and prednisone therapy. *Br Med J* 4: 746–748, 1968
718. Committee on Guidelines of Care, Task Force on Basal Cell Carcinoma: Guidelines for basal cell carcinoma. *J Am Acad Dermatol* 26: 117–120, 1992
719. Wood BL, Sabath D, Broudy VC, Raghu G: The recipient origin of posttransplant lymphoproliferative disorders in pulmonary transplant patients. *Cancer* 78: 2223–2228, 1996
720. Hanto DW, Frizzera G, Purtilo DT, Sakamoto K, Sullivan JL, Saemundsen AK, Klein G, Simmons RL, Najarian JS: Clinical spectrum of lymphoproliferative disorders in renal transplant recipients and evidence for the role of Epstein-Barr virus. *Cancer Res* 41: 4253–4261, 1981
721. Ho M, Miller G, Atchison RW, Breinig MK, Dummer JS, Andiman W, Starzl TE, Eastman R, Griffith BP, Hardesty RL, Bahnson HT, Hakala TR, Rosenthal JT: Epstein-Barr virus infections and DNA hybridization studies in posttransplantation lymphoma and lymphoproliferative lesions: The role of primary infection. *J Infect Dis* 152: 876–886, 1985
722. Savage P, Waxman J: Post-transplantation lymphoproliferative disease. *Q J Med* 90: 497–503, 1997
723. Knowles DM, Cesarman E, Chadburn A, Frizzera G, Chen J, Rose EA, Michler RE: Correlative morphologic and molecular genetic analysis demonstrates three distinct categories of posttransplantation lymphoproliferative disorders. *Blood* 85: 552–565, 1995
724. Chadburn A, Chen JM, Hsu DT, Frizzera G, Cesarman E, Garrett TJ, Mears JG, Zangwill SD, Addonizio LJ, Michler RE, Knowles DM: The morphologic and molecular genetic categories of posttransplantation lymphoproliferative disorders are clinically relevant. *Cancer* 82: 1978–1987, 1998
725. Opelz G, Henderson R: Incidence of non-Hodgkin lymphoma in kidney and heart transplant recipients. *Lancet* 342: 1514–1516, 1993
726. Nalesnik M, Locker J, Jaffe R, Reyes J, Cooper M, Fung J, Starzl TE: Experience with posttransplant lymphoproliferative disorders in solid organ transplant recipients. *Clin Transplant* 6[Suppl]: 249–252, 1992
727. Shapiro R, Nalesnik M, McCauley J, Fedorek S, Jordan ML, Scantlebury VP, Jain A, Vivas C, Ellis D, Lombardozzi-Lane S, Randhawa P, Johnston J, Hakala TR, Simmons RL, Fung JJ, Starzl TE: Posttransplant lymphoproliferative disorders in adult and pediatric renal transplant patients receiving tacrolimus-based immunosuppression. *Transplantation* 68: 1851–1854, 1999
728. Nocera A, Ghio L, Dall'Amico R, Fontana I, Cardillo M, Berardinelli L, Zanon GF, Scalamogna M, Zacchello G, Valente U, Ginevri F: *De novo* cancers in paediatric renal transplant recipients: A multicentre analysis within the North Italy Transplant programme (NITp), Italy. *Eur J Cancer* 36: 80–86, 2000

729. Srivastava T, Zwick DL, Rothberg PG, Warady BA: Posttransplant lymphoproliferative disorder in pediatric renal transplantation. *Pediatr Nephrol* 13: 748–754, 1999
730. Hanto DW, Frizzera G, Gajl-Peczalska KJ, Sakamoto K, Purtilo DT, Balfour HH Jr, Simmons RL, Najarian JS: Epstein-Barr virus-induced B-cell lymphoma after renal transplantation: Acyclovir therapy and transition from polyclonal to monoclonal B-cell proliferation. *N Engl J Med* 306: 913–918, 1982
731. Lieberman J, Bucksbaum R: Using T cells to treat B-cell cancers. *N Engl J Med* 330: 1231–1233, 1994
732. Swinnen LJ, Costanzo-Nordin MR, Fisher SG, O'Sullivan EJ, Johnson MR, Heroux AL, Dizikes GJ, Pifarre R, Fisher RI: Increased incidence of lymphoproliferative disorder after immunosuppression with the monoclonal antibody OKT3 in cardiac transplant recipients. *N Engl J Med* 323: 1723–1728, 1990
733. Harmon WE, Dharnidharka VR: Lymphoproliferative disease in children. *Transplant Proc* 31: 1268–1269, 1999
734. Penn I, Porat G: Central nervous system lymphomas in organ allograft recipients. *Transplantation* 59: 240–244, 1995
735. Palmer BF, Sagalowsky AI, McQuitty DA, Dawidson I, Vazquez MA, Lu CY: Lymphoproliferative disease presenting as obstructive uropathy after renal transplantation. *J Urol* 153: 392–394, 1995
736. Goral S, Felgar R, Shappell S: Posttransplantation lymphoproliferative disorder in a renal allograft recipient. *Am J Kidney Dis* 30: 301–307, 1997
737. Nalesnik MA: Involvement of the gastrointestinal tract by Epstein-Barr virus-associated posttransplant lymphoproliferative disorders. *Am J Surg Pathol* 14[Suppl 1]: 92–100, 1990
738. Hanto DW, Gajl-Peczalska KJ, Frizzera G, Arthur DC, Balfour HH Jr, McClain K, Simmons RL, Najarian JS: Epstein-Barr virus (EBV) induced polyclonal and monoclonal B-cell lymphoproliferative diseases occurring after renal transplantation: Clinical, pathologic, and virologic findings and implications for therapy. *Ann Surg* 198: 356–369, 1983
739. Leblond V, Sutton L, Dorent R, Davi F, Bitker M-O, Gabarre J, Charlotte F, Ghoussoub J-J, Fourcade C, Fischer A, Gandjbakhch I, Binet J-L, Raphael M: Lymphoproliferative disorders after organ transplantation: A report of 24 cases observed in a single center. *J Clin Oncol* 13: 961–968, 1995
740. Penn I: *De novo* cancers in organ allograft recipients. *Curr Opin Organ Transplant* 3: 188–196, 1998
741. Preiksaitis JK, Diaz-Mitoma F, Mirzayans F, Roberts S, Tyrrell DLJ: Quantitative oropharyngeal Epstein-Barr virus shedding in renal and cardiac transplant recipients: Relationship to immunosuppressive therapy, serologic responses, and the risk of posttransplant lymphoproliferative disorder. *J Infect Dis* 166: 986–994, 1992
742. Kenagy DN, Schlesinger Y, Weck K, Ritter JH, Gaudreault-Keener MM, Storch GA: Epstein-Barr virus DNA in peripheral blood leukocytes of patients with posttransplant lymphoproliferative disease. *Transplantation* 60: 547–554, 1995
743. Rooney CM, Loftin SK, Holladay MS, Brenner MK, Krance RA, Heslop HE: Early identification of Epstein-Barr virus-associated post-transplantation lymphoproliferative disease. *Br J Haematol* 89: 98–103, 1995
744. Rowe DT, Qu L, Reyes J, Jabbour N, Yunis E, Putnam P, Todo S, Green M: Use of quantitative competitive PCR to measure Epstein-Barr virus genome load in the peripheral blood of pediatric transplant patients with lymphoproliferative disorders. *J Clin Microbiol* 35: 1612–1615, 1997
745. Crompton CH, Cheung RK, Donjon C, Miyazaki I, Feinmesser R, Hebert D, Dosch H-M: Epstein-Barr virus surveillance after renal transplantation. *Transplantation* 57: 1182–1189, 1994
746. Savoie A, Perpete C, Carpentier L, Joncas J, Alfieri C: Direct correlation between the load of Epstein-Barr virus-infected lymphocytes in the peripheral blood of pediatric transplant patients and risk of lymphoproliferative disease. *Blood* 83: 2715–2722, 1994
747. Randhawa PS, Jaffe R, Demetris AJ, Nalesnik M, Starzl TE, Chen YY, Weiss LM: Expression of Epstein-Barr virus-encoded small RNA (by the EBER-1 gene) in liver specimens from transplant recipients with post-transplantation lymphoproliferative disease. *N Engl J Med* 327: 1710–1714, 1992
748. Hubscher SG, Williams A, Davison SM, Young LS, Niedobitek G: Epstein-Barr virus in inflammatory diseases of the liver and liver allografts: An *in situ* hybridization study. *Hepatology* 20: 899–907, 1994
749. Tublin ME, Dodd GD III: Sonography of renal transplantation. *Radiol Clin North Am* 33: 447–459, 1995
750. Oliver JH III: Clinical indications, recipient evaluation, surgical considerations, and the role of CT and MR in renal transplantation. *Radiol Clin North Am* 33: 435–446, 1995
751. Naidich DP: Helical computed tomography of the thorax: Clinical applications. *Radiol Clin North Am* 32: 759–774, 1994
752. Semelka RC, Shoenut JP, Kroeker MA, MacMahon RG, Greenberg HM: Renal lesions: Controlled comparison between CT and 1.5-T MR imaging with nonenhanced and gadolinium-enhanced fat-suppressed spin-echo and breath-hold FLASH techniques. *Radiology* 182: 425–430, 1992
753. Lanfermann H, Heindel W, Schaper J, Schroder R, Hansmann ML, Lehrke R, Ernestus RI, Lackner K: CT and MR imaging in primary cerebral non-Hodgkin's lymphoma. *Acta Radiol* 38: 259–267, 1997
754. Semelka RC, Shoenut JP, Magro CM, Kroeker MA, MacMahon R, Greenberg HM: Renal cancer staging: Comparison of contrast-enhanced CT and gadolinium-enhanced fat-suppressed spin-echo and gradient-echo MR imaging. *J Magn Reson Imaging* 3: 597–602, 1993
755. Laing ADP, Gibson RE: MRI of the liver. *J Magn Reson Imaging* 8: 337–345, 1998
756. Winston CB, Schwartz LH: Advances in magnetic resonance imaging: Applications in body imaging. *Cancer Investig* 16: 413–420, 1998
757. Cao S, Cox K, Esquivel CO, Berquist W, Concepcion W, Ojogho O, Monge H, Krams S, Martinez O, So S: Posttransplant lymphoproliferative disorders and gastrointestinal manifestations of Epstein-Barr virus infection in children following liver transplantation. *Transplantation* 66: 851–856, 1998
758. Penn I: Primary kidney tumors before and after renal transplantation. *Transplantation* 59: 480–485, 1995
759. Williams JC, Merguerian PA, Schned AR, Morrison PM: Acquired renal cystic disease and renal cell carcinoma in an allograft kidney. *J Urol* 153: 395–396, 1995
760. Kliem V, Kolditz M, Behrend M, Ehlerding G, Pichlmayr R, Koch KM, Brunkhorst R: Risk of renal cell carcinoma after kidney transplantation. *Clin Transplant* 11: 255–258, 1997
761. Doublet J-D, Peraldi M-N, Gattegno B, Thibault P, Sraer J-D:

Renal cell carcinoma of native kidneys: Prospective study of 129 renal transplant patients. *J Urol* 158: 42–44, 1997
762. Heinz-Peer G, Schoder M, Rand T, Mayer G, Mostbeck GH: Prevalence of acquired cystic kidney disease and tumors in native kidneys of renal transplant recipients: A prospective US study. *Radiology* 195: 667–671, 1995
763. Bokemeyer C, Thon WF, Brunkhorst T, Kuczyk MA, Pichlmayr R, Kliem V: High frequency of urothelial cancers in patients with kidney transplantations for end-stage analgesic nephropathy. *J Cancer* 32A: 175–176, 1996
764. Levine LA, Gburek BM: Acquired cystic disease and renal adenocarcinoma following renal transplantation. *J Urol* 151: 129–132, 1994
765. Pope JC, Koch MO, Bluth RF: Renal cell carcinoma in patients with end-stage renal disease: A comparison of clinical significance in patients receiving hemodialysis and those with renal transplants. *Urology* 44: 497–501, 1994
766. Messing EM, Young TB, Hunt VB, Roecker EB, Vaillancourt AM, Hisgen WJ, Greenberg EB, Kuglitsch ME, Wegenke JD: Home screening for hematuria: Results of a multiclinic study. *J Urol* 148: 289–292, 1992
767. Cogny-Van Weydevelt F, Chautard D, Bourree Y, Ngohou C, Bacquaert-Dufour K, Delva R, Riberi P: Host renal cell carcinoma in kidney transplanted patient: Ultrasonography screening study. *Transplant Proc* 27: 1786–1788, 1995
768. Rofsky NM, Weinreb JC, Bosniak MA, Libes RB, Birnbaum BA: Renal lesion characterization with gadolinium-enhanced MR imaging: Efficacy and safety in patients with renal insufficiency. *Radiology* 180: 85–89, 1991
769. Jeng LB, Huang CC, Lai MK, Chu SH: Hepatocellular carcinoma in kidney transplantation. *Transplant Proc* 31: 1273–1274, 1999
770. Ijzermans JNM, Bac D-J: Recent developments in screening, diagnosis and surgical treatment of hepatocellular carcinoma. *Scand J Gastroenterol* 32[Suppl 223]: 50–54, 1997
771. Khakoo SI, Grellier LFL, Soni PN, Bhattacharya S, Dusheiko GM: Etiology, screening, and the treatment of hepatocellular carcinoma. *Med Clin North Am* 80: 1121–1145, 1996
772. Sarasin FP, Giostra E, Hadengue A: Cost-effectiveness of screening for detection of small hepatocellular carcinoma in Western patients with Child-Pugh class A cirrhosis. *Am J Med* 171: 422–434, 1996
773. Saini S: Imaging of the hepatobiliary tract. *N Engl J Med* 336: 1889–1894, 1998
774. Kemmerer SR, Mortele KJ, Ros PR: CT scan of the liver. *Radiol Clin North Am* 36: 247–260, 1998
775. Rummeny EJ, Marchal G: Liver imaging: Clinical applications and future perspectives. *Acta Radiol* 38: 626–630, 1997
776. ter Haar-van Eck SA, Rischen-Vos J, Chadha-Ajwani S, Huikeshoven FJM: The incidence of cervical intraepithelial neoplasia among women with renal transplant in relation to cyclosporine. *Br J Obstet Gynaecol* 102: 58–61, 1995
777. Halpert R, Fruchter RG, Sedlis A, Butt K, Boyce JG, Sillman FH: Human papillomavirus and lower genital neoplasia in renal transplant patients. *Obstet Gynecol* 68: 251–258, 1986
778. Morrison EAB, Dole P, Sun X-W, Stern L, Wright TC Jr: Low prevalence of human papillomavirus infection of the cervix in renal transplant recipients. *Nephrol Dial Transplant* 11: 1603–1606, 1996
779. National Cancer Institute: *Prevention of Cervical Cancer* [Pamphlet], Bethesda, MD, National Institutes of Health, 1998
780. National Cancer Institute: *Screening for Cervical Cancer* [Pamphlet], Bethesda, MD, National Institutes of Health, 1996
781. Porreco R, Penn I, Droegemueller W, Greer B, Makowski E: Gynecologic malignancies in immunosuppressed organ homograft recipients. *Obstet Gynecol* 45: 359–364, 1975
782. ACOG committee opinion. Recommendations on frequency of Pap test screening. Number 152–March 1995. Committee on Gynecologic Practice. American College of Obstetricians and Gynecologists. *Int J Gynaecol Obstet* 49: 210–211, 1995
783. United States Preventive Services Task Force: Screening for cervical cancer. In: *Guide to Clinical Preventive Services*, 2nd Ed., edited by Di Guiseppi C, Atkins D, Woolf S, Baltimore, Williams & Wilkins, 1996, pp 105–117
784. Fetters MD, Fischer G, Reed BD: Effectiveness of vaginal Papanicolaou smear screening after total hysterectomy for benign disease. *JAMA* 275: 940–947, 1996
785. Alloub MI, Barr BB, McLaren KM, Smith IW, Bunney MH, Smart GE: Human papillomavirus infection and cervical intraepithelial neoplasia in women with renal allografts. *Br Med J* 298: 153–156, 1989
786. Johnson K, Canadian Task Force on the Periodic Health Examination: Periodic health examination, 1995 update. 1. Screening for human papillomavirus infection in asymptomatic women. *Can Med Assoc J* 152: 483–493, 1995
787. Blessing K, McLaren KM, Morris R, Barr BB, Benton EC, Alloub M, Bunney MH, Smith IW, Smart GE, Bird CC: Detection of human papillomavirus in skin and genital lesions of renal allograft recipients by *in situ* hybridization. *Histopathology* 16: 181–185, 1990
788. Weiss NS: Risk of breast cancer after renal or cardiac transplantation. *Lancet* 346: 1422, 1995
789. National Cancer Institute: *Screening for Breast Cancer* [Pamphlet], Bethesda, MD, National Institutes of Health, 1998
790. United States Preventive Services Task Force: Screening for breast cancer. In: *Guide to Clinical Preventive Services*, 2nd Ed., edited by Di Guiseppi C, Atkins D, Woolf S, Baltimore, Williams & Wilkins, 1996, pp 73–87
791. Stewart T, Tsai S-CJ, Grayson H, Henderson R, Opelz G: Incidence of *de-novo* breast cancer in women chronically immunosuppressed after organ transplantation. *Lancet* 346: 796–798, 1995
792. Hortobagyi GN: Treatment of breast cancer. *N Engl J Med* 339: 974–984, 1998
793. Barrett WL, First MR, Aron BS, Penn I: Clinical course of malignancies in renal transplant recipients. *Cancer* 72: 2186–2189, 1993
794. Leitch AM, Dodd GD, Costanza M, Linver M, Pressman P, McGinnis L, Smith RA: American Cancer Society guidelines for the early detection of breast cancer: Update 1997. *CA Cancer J Clin* 47: 150–153, 1997
795. Elmore JG, Barton MB, Moceri VM, Polk S, Arena PJ, Fletcher SW: Ten-year risk of false positive screening mammograms and clinical breast examinations. *N Engl J Med* 338: 1089–1096, 1998
796. Stewart T, Henderson R, Grayson H, Opelz G: Reduced incidence of rectal cancer, compared to gastric and colonic cancer, in a population of 73,076 men and women chronically immunosuppressed. *Clin Cancer Res* 3: 51–55, 1998
797. United States Preventive Services Task Force: Screening for colorectal cancer. In: *Guide to Clinical Preventive Services*, 2nd Ed., edited by Di Guiseppi C, Atkins D, Woolf S, Baltimore, Williams & Wilkins, 1996, pp 89–103

798. Ratto C, Sofo L, Ippoliti M, Merico M, Doglietto GB, Crucitti F: Prognostic factors in colorectal cancer: Literature review for clinical application. *Dis Colon Rectum* 41: 1033–1049, 1998
799. National Cancer Institute: *Screening for Colorectal Cancer* [Pamphlet], Bethesda, MD, National Institutes of Health, 1998
800. Winawer SJ, Fletcher RH, Miller L, Godlee F, Stolar MH, Mulrow CD, Woolf SH, Glick SN, Ganiats TG, Bond JH, Rosen L, Zapka JG, Olsen SJ, Giardiello FM, Sisk JE, van Antwerp R, Brown-Davis C, Marciniak DA, Mayer RJ: Colorectal cancer screening: Clinical guidelines and rationale. *Gastroenterology* 112: 594–642, 1997
801. Byers T, Levin B, Rothenberger D, Dodd GD, Smith RA: American Cancer Society guidelines for screening and surveillance for early detection of colorectal polyps and cancer: Update 1997. *CA Cancer J Clin* 47: 154–160, 1998
802. Selby JV, Friedman GD, Quesenberry CP Jr, Weiss NS: A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. *N Engl J Med* 326: 653–657, 1992
803. Smith C: Colorectal cancer: Radiologic diagnosis. *Radiol Clin North Am* 35: 439–456, 1997
804. United States Preventive Services Task Force: Screening for prostate cancer. In: *Guide to Clinical Preventive Services*, 2nd Ed., edited by Di Guiseppi C, Atkins D, Woolf S, Baltimore, Williams & Wilkins, 1996, pp 119–134
805. Konety BR, Tewari A, Howard RJ, Barry JM, Hodge EE, Taylor R, Jordon ML: Prostate cancer in the post-transplant population. *Urology* 52: 428–432, 1998
806. National Cancer Institute: *Screening for Prostate Cancer* [Pamphlet], Bethesda, MD, National Institutes of Health, 1998
807. Reppeto L, Granetto C, Hall RR: Prostate cancer. *Crit Rev Oncol Hematol* 27: 145–146, 1998
808. Morton JJ, Howe SF, Lowell JA, Stratta RJ, Taylor RJ: Influence of end-stage renal disease and renal transplantation on serum prostate-specific antigen. *Br J Urol* 75: 498–501, 1995
809. American Urological Association: *Executive Committee Report*, Baltimore, American Urological Association, 1992
810. American College of Physicians: Screening for prostate cancer. *Ann Intern Med* 126: 480–484, 1997
811. Delcambre F, Pruvot FR, Ramon P, Noel C, Pol A, Jaillard-Thery S, Dupont J, Declerck N, Gosselin B, Remy-Jardin M, Wurtz A, Lafitte JJ: Primary bronchogenic carcinoma in transplant recipients. *Transplant Proc* 28: 2884–2885, 1996
812. Danpanich E, Kasiske BL: Risk factors for cancer in renal transplant recipients. *Transplantation* 68: 1859–1864, 1999
813. Brundage MD, Bezjak A, Dixon P, Grimard L, Larochelle M, Warde P, Warr D: The role of palliative thoracic radiotherapy in non-small cell lung cancer. *Can J Oncol* 6: 25–32, 1996
814. United States Preventive Services Task Force: Screening for lung cancer. In: *Guide to Clinical Preventive Services*, 2nd Ed., edited by Di Guiseppi C, Atkins D, Woolf S, Baltimore, Williams & Wilkins, 1996, pp 135–139
815. Henschke CI, McCauley DI, Yankelevitz DF, Naidich DP, McGuinness G, Miettinen OS, Libby DM, Pasmantier MW, Koizumi J, Altorki NK, Smith JP: Early Lung Cancer Action Project: Overall design and findings from baseline screening. *Lancet* 354: 99–105, 1999
816. Henschke CI, Yankelevitz DF: Screening for lung cancer. *J Thorac Imaging* 15: 21–27, 2000
817. Miettinen OS: Screening for lung cancer: Can it be cost-effective? *Can Med Assoc J* 162: 1431–1436, 2000
818. Jassal SV, Roscoe JM, Zaltzman JS, Mazzulli T, Krajden M, Gadawski M, Cattran DC, Cardella CJ, Albert SE, Cole EH: Clinical practice guidelines: Prevention of cytomegalovirus disease after renal transplantation. *J Am Soc Nephrol* 9: 1697–1708, 1998
819. Hibberd PL, Tolkoff-Rubin NE, Cosimi AB, Schooley RT, Isaacson D, Doran M, Delvecchio A, Delmonico FL, Auchincloss HJ, Rubin RH: Symptomatic cytomegalovirus disease in the cytomegalovirus antibody seropositive renal transplant recipient treated with OKT3. *Transplantation* 53: 68–72, 1992
820. Moreso F, Seron D, Morales JM, Cruzado JM, Gil-Vernet S, Perez JL, Fulladosa X, Andres A, Grinyo JM: Incidence of leukopenia and cytomegalovirus disease in kidney transplants treated with mycophenolate mofetil combined with low cyclosporine and steroid doses. *Clin Transplant* 12: 198–205, 1998
821. Schnitzler MA, Woodward RS, Brennan DC, Spitznagel EL, Dunagan WC, Bailey TC: The effects of cytomegalovirus serology on graft and recipient survival in cadaveric renal transplantation: Implications for organ allocation. *Am J Kidney Dis* 29: 428–434, 1997
822. Hirata M, Terasaki PI, Cho YW: Cytomegalovirus antibody status and renal transplantation: 1987–1994. *Transplantation* 62: 34–37, 1996
823. Brennan DC, Garlock KA, Lippmann BA, Buller RS, Gaudreault-Keener M, Lowell JA, Miller SB, Shenoy S, Howard TK, Storch GA: Control of cytomegalovirus-associated morbidity in renal transplant patients using intensive monitoring and either preemptive or deferred therapy. *J Am Soc Nephrol* 8: 118–125, 1997
824. Bienvenu B, Thervet E, Bedrossian J, Scieux C, Mazeron MC, Thouvenot D, Legendre C: Emergence of cytomegalovirus resistance to ganciclovir after oral maintenance treatment in a renal transplant recipient. *Transplant Proc* 32: 407, 2000
825. Bein G, Bitsch A, Hoyer J, Steinhoff J, Fricke L, Machnik H, Dennin R, Kirchner H: A longitudinal prospective study of cytomegalovirus pp65 antigenemia in renal transplant recipients. *Transplant Int* 6: 185–190, 1993
826. Kidd IM, Fox JC, Pillay D, Charman H, Griffiths PD, Emery VC: Provision of prognostic information in immunocompromised patients by routine application of the polymerase chain reaction for cytomegalovirus. *Transplantation* 56: 867–871, 1993
827. Murray BM, Amsterdam D, Gray V, Myers J, Gerbasi J, Venuto RC: Monitoring and diagnosis of cytomegalovirus infection in renal transplantation. *J Am Soc Nephrol* 8: 1448–1457, 1997
828. Essa S, Pacsa AS, Al Attiyah R, El Shazly A, Raghupathy R, Said T: The use of flow cytometry for the detection of CMV-specific antigen (pp65) in leukocytes of kidney recipients. *Clin Transplant* 14: 147–151, 2000
829. Tong CY, Cuevas L, Williams H, Bakran A: Use of laboratory assays to predict cytomegalovirus disease in renal transplant recipients. *J Clin Microbiol* 36: 2681–2685, 1998
830. Aitken C, Barrett-Muir W, Millar C, Templeton K, Thomas J, Sheridan F, Jeffries D, Yaqoob M, Breuer J: Use of molecular assays in diagnosis and monitoring of cytomegalovirus disease following renal transplantation. *J Clin Microbiol* 37: 2804–2807, 1999
831. Hassan-Walker AF, Kidd IM, Sabin C, Sweny P, Griffiths PD, Emery VC: Quantity of human cytomegalovirus (CMV) DNAemia as a risk factor for CMV disease in renal allograft recipients: Relationship with donor/recipient CMV serostatus,

receipt of augmented methylprednisolone and antithymocyte globulin (ATG). *J Med Virol* 58: 182–187, 1999
832. Tong CY, Cuevas LE, Williams H, Bakran A: Prediction and diagnosis of cytomegalovirus disease in renal transplant recipients using qualitative and quantitative polymerase chain reaction. *Transplantation* 69: 985–991, 2000
833. Brando B, Civati G, Grillo C, Busnach G, Colussi G, Broggi ML, Minetti L: Immunological monitoring of viral infections in renal transplant recipients. *Proc Eur Dial Transplant Assoc* 20: 265–270, 1983
834. Mauch TJ, Bratton S, Myers T, Krane E, Gentry SR, Kashtan CE: Influenza B virus infection in pediatric solid organ transplant recipients. *Pediatrics* 94: 225–229, 1994
835. Belshe RB: Influenza prevention and treatment: Current practices and new horizons. *Ann Intern Med* 131: 621–624, 1999
836. Edvardsson VO, Flynn JT, Deforest A, Kaiser BA, Schulman SL, Bradley A, Palmer J, Polinsky MS, Baluarte HJ: Effective immunization against influenza in pediatric renal transplant recipients. *Clin Transplant* 10: 556–560, 1996
837. Furth SL, Neu AM, McColley SA, Case B, Steinhoff M, Fivush B: Immune response to influenza vaccination in children with renal disease. *Pediatr Nephrol* 9: 566–568, 1995
838. Grekas D, Alivanis P, Kiriazopoulou V, Dioudis C, Sioulis A, Derveniotis V, Tourkantonis A: Influenza vaccination of renal transplant patients is safe and serologically effective. *Int J Clin Pharmacol Ther Toxicol* 31: 553–556, 1993
839. Gershon AA: Immunizations for pediatric transplant patients. *Kidney Int* 43[Suppl]: S87–S90, 1993
840. Versluis DJ, Beyer WE, Masurel N, Wenting GJ, Weimar W: Impairment of the immune response to influenza vaccination in renal transplant recipients by cyclosporine, but not azathioprine. *Transplantation* 42: 376–379, 1986
841. Versluis DJ, Beyer WE, Masurel N, Weimar W: Influenza vaccination in dialysis and transplant patients. *Antiviral Res* 1[Suppl]: 289–292, 1985
842. Huang KL, Armstrong JA, Ho M: Antibody response after influenza immunization in renal transplant patients receiving cyclosporin A or azathioprine. *Infect Immun* 40: 421–424, 1983
843. Briggs WA, Rozek RJ, Migdal SD, Shillis JL, Brackett RG, Brandon FB, Mahajan SK, McDonald FD, Kumar SS, Ventura AK, VanderWerf B: Influenza vaccination in kidney transplant recipients: Cellular and humoral immune responses. *Ann Intern Med* 92: 471–477, 1980
844. Kumar SS, Ventura AK, VanderWerf B: Influenza vaccination in renal transplant recipients. *JAMA* 239: 840–842, 1978
845. Stiver HG, Graves P, Meiklejohn G, Schroter G, Eickhoff TC: Impaired serum antibody response to inactivated influenza A and B vaccine in renal transplant recipients. *Infect Immun* 16: 738–741, 1977
846. Pabico RC, Douglas RG, Betts RF, McKenna BA, Freeman RB: Antibody response to influenza vaccination in renal transplant patients: Correlation with allograft function. *Ann Intern Med* 85: 431–436, 1976
847. Sanchez-Fructuoso AI, Prats D, Naranjo P, Fernandez-Perez C, Gonzalez MJ, Mariano A, Gonzalez J, Figueredo MA, Martin JM, Paniagua V, Fereres J, Gomez dlC, Barrientos A: Influenza virus immunization effectivity in kidney transplant patients subjected to two different triple-drug therapy immunosuppression protocols: Mycophenolate versus azathioprine. *Transplantation* 69: 436–439, 2000
848. Blumberg EA, Albano C, Pruett T, Isaacs R, Fitzpatrick J, Bergin J, Crump C, Hayden FG: The immunogenicity of influenza virus vaccine in solid organ transplant recipients. *Clin Infect Dis* 22: 295–302, 1996
849. Blumberg EA, Fitzpatrick J, Stutman PC, Hayden FG, Brozena SC: Safety of influenza vaccine in heart transplant recipients. *J Heart Lung Transplant* 17: 1075–1080, 1998
850. Dengler TJ, Strnad N, Buhring I, Zimmermann R, Girgsdies O, Kubler WE, Zielen S: Differential immune response to influenza and pneumococcal vaccination in immunosuppressed patients after heart transplantation. *Transplantation* 66: 1340–1347, 1998
851. Admon D, Engelhard D, Strauss N, Goldman N, Zakay-Rones Z: Antibody response to influenza immunization in patients after heart transplantation. *Vaccine* 15: 1518–1522, 1997
852. Mack DR, Chartrand SA, Ruby EI, Antonson DL, Shaw BWJ, Heffron TG: Influenza vaccination following liver transplantation in children. *Liver Transplant Surg* 2: 431–437, 1996
853. Mauch TJ, Crouch NA, Freese DK, Braunlin EA, Dunn DL, Kashtan CE: Antibody response of pediatric solid organ transplant recipients to immunization against influenza virus. *J Pediatr* 127: 957–960, 1995
854. Kobashigawa JA, Warner-Stevenson L, Johnson BL, Moriguchi JD, Kawata N, Drinkwater DC, Laks H: Influenza vaccine does not cause rejection after cardiac transplantation. *Transplant Proc* 25: 2738–2739, 1993
855. Furth SL, Neu AM, Sullivan EK, Gensler G, Tejani A, Fivush BA: Immunization practices in children with renal disease: A report of the North American Pediatric Renal Transplant Cooperative Study. *Pediatr Nephrol* 11: 443–446, 1997
856. Park SB, Joo I, Park YI, Suk J, Cho WH, Park CH, Kim HC: Clinical manifestations of tuberculosis in renal transplant patients. *Transplant Proc* 28: 1520–1522, 1996
857. Potter J, Stott DJ, Roberts MA, Elder AG, O'Donnell B, Knight PV, Carman WF: Influenza vaccination of health care workers in long-term-care hospitals reduces the mortality of elderly patients. *J Infect Dis* 175: 1–6, 1997
858. Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 49: 1–38, 2000
859. Monto AS, Robinson DP, Herlocher ML, Hinson JMJ, Elliott MJ, Crisp A: Zanamivir in the prevention of influenza among healthy adults: A randomized controlled trial. *JAMA* 282: 31–35, 1999
860. MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group: Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. *Lancet* 352: 1877–1881, 1998
861. Matsumoto K, Ogawa N, Nerome K, Numazaki Y, Kawakami Y, Shirato K, Arakawa M, Kudoh S, Shimokata K, Nakajima S, Yamakido M, Kashiwagi S, Nagatake T: Safety and efficacy of the neuraminidase inhibitor zanamivir in treating influenza virus infection in adults: Results from Japan: GG167 Group. *Antiviral Ther* 4: 61–68, 1999
862. Boivin G, Goyette N, Hardy I, Aoki F, Wagner A, Trottier S: Rapid antiviral effect of inhaled zanamivir in the treatment of naturally occurring influenza in otherwise healthy adults. *J Infect Dis* 181: 1471–1474, 2000
863. Kaiser L, Henry D, Flack NP, Keene O, Hayden FG: Short-term treatment with zanamivir to prevent influenza: Results of a placebo-controlled study. *Clin Infect Dis* 30: 587–589, 2000
864. Monto AS, Fleming DM, Henry D, de Groot R, Makela M, Klein T, Elliott M, Keene ON, Man CY: Efficacy and safety

of the neuraminidase inhibitor zanamivir in the treatment of influenza A and B virus infections. *J Infect Dis* 180: 254–261, 1999
865. Hayden FG, Osterhaus AD, Treanor JJ, Fleming DM, Aoki FY, Nicholson KG, Bohnen AM, Hirst HM, Keene O, Wightman K: Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenzavirus infections: GG167 Influenza Study Group. *N Engl J Med* 337: 874–880, 1997
866. Hayden FG, Atmar RL, Schilling M, Johnson C, Poretz D, Paar D, Huson L, Ward P, Mills RG: Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *N Engl J Med* 341: 1336–1343, 1999
867. Treanor JJ, Hayden FG, Vrooman PS, Barbarash R, Bettis R, Riff D, Singh S, Kinnersley N, Ward P, Mills RG: Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: A randomized controlled trial: US Oral Neuraminidase Study Group. *JAMA* 283: 1016–1024, 2000
868. Hayden FG, Treanor JJ, Fritz RS, Lobo M, Betts RF, Miller M, Kinnersley N, Mills RG, Ward P, Straus SE: Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: Randomized controlled trials for prevention and treatment. *JAMA* 282: 1240–1246, 1999
869. Englund JA, Champlin RE, Wyde PR, Kantarjian H, Atmar RL, Tarrand J, Yousuf H, Regnery H, Klimov AI, Cox NJ, Whimbey E: Common emergence of amantadine- and rimantadine-resistant influenza A viruses in symptomatic immunocompromised adults. *Clin Infect Dis* 26: 1418–1424, 1998
870. Spence RK, Dafoe DC, Rabin G, Grossman RA, Naji A, Barker CF, Perloff LJ: Mycobacterial infections in renal allograft recipients. *Arch Surg* 118: 356–359, 1983
871. Higgins RM, Cahn AP, Porter D, Richardson AJ, Mitchell RG, Hopkin JM, Morris PJ: Mycobacterial infections after renal transplantation. *Q J Med* 78: 145–153, 1991
872. Coutts II, Jegarajah S, Stark JE: Tuberculosis in renal transplant recipients. *Br J Dis Chest* 73: 141–148, 1979
873. Aguado JM, Herrero JA, Gavalda J, Torre-Cisneros J, Blanes M, Rufi G, Moreno A, Gurgui M, Hayek M, Lumbreras C, Cantarell C: Clinical presentation and outcome of tuberculosis in kidney, liver, and heart transplant recipients in Spain: Spanish Transplantation Infection Study Group, GESITRA. *Transplantation* 63: 1278–1286, 1997
874. Garcia-Leoni ME, Martin-Scapa C, Rodeno P, Valderrabano F, Moreno S, Bouza E: High incidence of tuberculosis in renal patients. *Eur J Clin Microbiol Infect Dis* 9: 283–285, 1990
875. Hall CM, Willcox PA, Swanepoel CR, Kahn D, van Zyl Smit R: Mycobacterial infection in renal transplant recipients. *Chest* 106: 435–439, 1994
876. Sayiner A, Ece T, Duman S, Yildiz A, Ozkahya M, Kilicaslan Z, Tokat Y: Tuberculosis in renal transplant recipients. *Transplantation* 68: 1268–1271, 1999
877. Qunibi WY, al-Sibai MB, Taher S, Harder EJ, de Vol E, Al-Furayh O, Ginn HE: Mycobacterial infection after renal transplantation: Report of 14 cases and review of the literature. *Q J Med* 77: 1039–1060, 1990
878. Jereb JA, Burwen DR, Dooley SW, Haas WH, Crawford JT, Geiter LJ, Edmond MB, Dowling JN, Shapiro R, Pasculle AW: Nosocomial outbreak of tuberculosis in a renal transplant unit: Application of a new technique for restriction fragment length polymorphism analysis of *Mycobacterium tuberculosis* isolates. *J Infect Dis* 168: 1219–1224, 1993
879. Mourad G, Soulillou JP, Chong G, Pouliquen M, Hourmant M, Mion C: Transmission of *Mycobacterium tuberculosis* with renal allografts. *Nephron* 41: 82–85, 1985
880. Peters TG, Reiter CG, Boswell RL: Transmission of tuberculosis by kidney transplantation. *Transplantation* 38: 514–516, 1984
881. John GT, Thomas PP, Thomas M, Jeyaseelan L, Jacob CK, Shastry JC: A double-blind randomized controlled trial of primary isoniazid prophylaxis in dialysis and transplant patients. *Transplantation* 57: 1683–1684, 1994
882. Thomas PA, Mozes MF, Jonasson O: Hepatic dysfunction during isoniazid chemoprophylaxis in renal allograft recipients. *Arch Surg* 114: 579–599, 1979
883. Gordin FM, Matts JP, Miller C, Brown LS, Hafner R, John SL, Klein M, Vaughn A, Besch CL, Perez G, Szabo S, El-Sadr W: A controlled trial of isoniazid in persons with anergy and human immunodeficiency virus infection who are at high risk for tuberculosis: Terry Beirn Community Programs for Clinical Research on AIDS. *N Engl J Med* 337: 315–320, 1997
884. Hawken MP, Meme HK, Elliott LC, Chakaya JM, Morris JS, Githui WA, Juma ES, Odhiambo JA, Thiong'o LN, Kimari JN, Ngugi EN, Bwayo JJ, Gilks CF, Plummer FA, Porter JD, Nunn PP, McAdam KP: Isoniazid preventive therapy for tuberculosis in HIV-1-infected adults: Results of a randomized controlled trial. *AIDS* 11: 875–882, 1997
885. Pape JW, Jean SS, Ho JL, Hafner A, Johnson WDJ: Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. *Lancet* 342: 268–272, 1993
886. Halsey NA, Coberly JS, Desormeaux J, Losikoff P, Atkinson J, Moulton LH, Contave M, Johnson M, Davis H, Geiter L, Johnson E, Huebner R, Boulos R, Chaisson RE: Randomised trial of isoniazid versus rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1 infection. *Lancet* 351: 786–792, 1998
887. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong: Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. *Am Rev Respir Dis* 145: 36–41, 1992
888. Falk A, Fuchs GF: Prophylaxis with isoniazid in inactive tuberculosis: Veterans Administration Cooperative Study XII. *Chest* 73: 44–48, 1978
889. John GT, Mukundan U, Vincent L, Jacob CK, Shastry JC: Primary drug resistance to *Mycobacterium tuberculosis* in renal transplant recipients. *Natl Med J India* 8: 211–212, 1995
890. American Thoracic Society and Centers for Disease Control and Prevention: Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 49[RR-6]: 1–54, 2000
891. Morphological characteristics of renal allografts showing renal dysfunction under FK 506 therapy: Is graft biopsy available to reveal the morphological findings corresponding with FK 506 nephropathy? Japanese FK 506 Study Group. *Transplant Proc* 25: 624–627, 1993
892. Linnemann CC Jr, First MR: Risk of pneumococcal infections in renal transplant patients. *JAMA* 241: 2619–2621, 1979
893. Arnold WC, Steele RW, Rastogi SP, Flanigan WJ: Response to pneumococcal vaccine in renal allograft recipients. *Am J Nephrol* 5: 30–34, 1985
894. Rytel MW, Dailey MP, Schiffman G, Hoffmann RG, Piering WF: Pneumococcal vaccine immunization of patients with renal impairment. *Proc Soc Exp Biol Med* 182: 468–473, 1986
895. Linnemann CC Jr, First MR, Schiffman G: Revaccination of

renal transplant and hemodialysis recipients with pneumococcal vaccine. *Arch Intern Med* 146: 1554–1556, 1986
896. Kazancioglu R, Sever MS, Yuksel-Onel D, Eraksoy H, Yildiz A, Celik AV, Kayacan SM, Badur S: Immunization of renal transplant recipients with pneumococcal polysaccharide vaccine. *Clin Transplant* 14: 61–65, 2000
897. Dengler TJ, Strnad N, Zimmermann R, Allers C, Markus BH, Nessen SV, Kubler W, Zielen S: Pneumococcal vaccination after heart and liver transplantation: Immune responses in immunosuppressed patients and in healthy controls [German]. *Dtsch Med Wochenschr* 121: 1519–1525, 1996
898. Gennery AR, Cant AJ, Spickett GP, Walshaw D, Hunter S, Hasan A, Hamilton JR, Dark J: Effect of immunosuppression after cardiac transplantation in early childhood on antibody response to polysaccharide antigen. *Lancet* 351: 1778–1781, 1998
899. Lufft V, Kliem V, Behrend M, Pichlmayr R, Koch KM, Brunkhorst R: Incidence of *Pneumocystis carinii* pneumonia after renal transplantation: Impact of immunosuppression. *Transplantation* 62: 421–423, 1996
900. Branten AJ, Beckers PJ, Tiggeler RG, Hoitsma AJ: *Pneumocystis carinii* pneumonia in renal transplant recipients. *Nephrol Dial Transplant* 10: 1194–1197, 1995
901. Hardy AM, Wajszczuk CP, Suffredini AF, Hakala TR, Ho M: *Pneumocystis carinii* pneumonia in renal-transplant recipients treated with cyclosporine and steroids. *J Infect Dis* 149: 143–147, 1984
902. Arend SM, Westendorp RG, Kroon FP, van't Wout JW, Vandenbroucke JP, Van Es LA, van der Woude FJ: Rejection treatment and cytomegalovirus infection as risk factors for *Pneumocystis carinii* pneumonia in renal transplant recipients. *Clin Infect Dis* 22: 920–925, 1996
903. Hennequin C, Page B, Roux P, Legendre C, Kreis H: Outbreak of *Pneumocystis carinii* pneumonia in a renal transplant unit. *Eur J Clin Microbiol Infect Dis* 14: 122–126, 1995
904. Hibberd PL, Tolkoff-Rubin NE, Doran M, Delvecchio A, Cosimi AB, Delmonico FL, Auchincloss HJ, Rubin RH: Trimethoprim-sulfamethoxazole compared with ciprofloxacin for the prevention of urinary tract infection in renal transplant recipients: A double-blind, randomized controlled trial (Doc. No. 15). *Online J Curr Clin Trials* 1992
905. Gordon SM, LaRosa SP, Kalmadi S, Arroliga AC, Avery RK, Truesdell-LaRosa L, Longworth DL: Should prophylaxis for *Pneumocystis carinii* pneumonia in solid organ transplant recipients ever be discontinued? *Clin Infect Dis* 28: 240–246, 1999
906. Elinder CG, Andersson J, Bolinder G, Tyden G: Effectiveness of low-dose cotrimoxazole prophylaxis against *Pneumocystis carinii* pneumonia after renal and/or pancreas transplantation. *Transplant Int* 5: 81–84, 1992
907. Fox BC, Sollinger HW, Belzer FO, Maki DG: A prospective, randomized, double-blind study of trimethoprim-sulfamethoxazole for prophylaxis of infection in renal transplantation: Clinical efficacy, absorption of trimethoprim-sulfamethoxazole, effects on the microflora, and the cost-benefit of prophylaxis. *Am J Med* 89: 255–274, 1990
908. Maki DG, Fox BC, Kuntz J, Sollinger HW, Belzer FO: A prospective, randomized, double-blind study of trimethoprim-sufamethoxazole for prophylaxis of infection in renal transplantation: Side effects of trimethoprim-sulfamethoxazole, interaction with cyclosporine. *J Lab Clin Med* 119: 11–24, 1992
909. Ioannidis JPA, Cappelleri JC, Skolnik PR, Lau J, Sacks HS: A meta-analysis of the relative efficacy and toxicity of *Pneumocystis carinii* prophylactic regimens. *Arch Intern Med* 156: 177–188, 1996
910. Hughes WT: Use of dapsone in the prevention and treatment of *Pneumocystis carinii* pneumonia: A review. *Clin Infect Dis* 27: 191–204, 1998
911. Rifkind D: *Pneumocystis carinii* pneumonia in renal transplant recipients. *Natl Cancer Inst Monogr* 43: 49–54, 1976
912. Plotkin JS, Buell JF, Njoku MJ, Wilson S, Kuo PC, Bartlett ST, Howell C, Johnson LB: Methemoglobinemia associated with dapsone treatment in solid organ transplant recipients: A two-case report and review. *Liver Transplant Surg* 3: 149–152, 1997
913. Saukkonen K, Garland R, Koziel H: Aerosolized pentamidine as alternative primary prophylaxis against *Pneumocystis carinii* pneumonia in adult hepatic and renal transplant recipients. *Chest* 109: 1250–1255, 1996
914. Spieker C, Barenbrock M, Tepel M, Buchholz B, Rahn KH, Zidek W: Pentamidine inhalation as a prophylaxis against *Pneumocystis carinii* pneumonia after therapy of acute renal allograft rejection with Orthoclone (OKT3). *Transplant Proc* 24: 2602–2603, 1992
915. El-Sadr WM, Murphy RL, Yurik TM, Luskin-Hawk R, Cheung TW, Balfour HHJ, Eng R, Hooton TM, Kerkering TM, Schutz M, van der Horst C, Hafner R: Atovaquone compared with dapsone for the prevention of *Pneumocystis carinii* pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both: Community Program for Clinical Research on AIDS and the AIDS Clinical Trials Group. *N Engl J Med* 339: 1889–1895, 1998
916. Green PT, Reents S, Harman E, Curtis AB: Pentamidine-induced *torsades de pointes* in a renal transplant recipient with *Pneumocystis carinii* pneumonia. *South Med J* 83: 481–484, 1990
917. Nagington J: Reactivation of hepatitis B after transplantation operations. *Lancet* 1: 558–560, 1977
918. Dusheiko G, Song E, Bowyer S, Whitcutt M, Maier G, Meyers A, Kew MC: Natural history of hepatitis B virus infection in renal transplant recipients: A fifteen year follow-up. *Hepatology* 3: 330–336, 1983
919. Pirson Y, Alexandre GPJ, van Ypersele de Strihou C: Long-term effect of HBs antigenemia on patient survival after renal transplantation. *N Engl J Med* 296: 194–196, 1977
920. Weir MR, Kirkman RL, Strom TB, Tilney NL: Liver disease in recipients of long-functioning renal allografts. *Kidney Int* 28: 839–844, 1985
921. Harnett JD, Zeldis JB, Parfrey PS, Kennedy M, Sircer R, Steinman TI, Guttman RD: Hepatits B disease in dialysis and transplant patients. *Transplantation* 44: 369–376, 1987
922. Parfrey PS, Forbes RDC, Hutchinson TA, Beaudoin JG, Dauphinee WD, Hollomby DJ, Guttmann RD: The clinical and pathological course of hepatitis B liver disease in renal transplant recipients. *Transplantation* 37: 461–466, 1984
923. Grekas D, Dioudis C, Mandraveli K, Alivanis P, Alexiou S, Derveniotis V, Hatzibaloglou A, Tourkantonis A: Renal transplantation in asymptomatic carriers of hepatitis B surface antigen. *Nephron* 69: 267–272, 1995
924. Rao KV, Kasiske BL, Anderson WR: Variability in the morphological spectrum and clinical outcome of chronic liver disease in hepatitis B-positive and B-negative renal transplant recipients. *Transplantation* 51: 391–396, 1991
925. Parfrey PS, Farge D, Forbes C, Dandavino R, Kenick S,

Guttman RD: Chronic hepatitis in end-stage renal disease: Comparison of HbsAg-negative and HbsAg-positive patients. *Kidney Int* 28: 959–967, 1985
926. Mathurin P, Mouquet C, Poynard T, Sylla C, Benalia H, Fretz C, Thibault V, Cadranel JF, Bernard B, Opolon P, Coriat P, Bitker MO: Impact of hepatitis B and C virus on kidney transplantation outcome. *Hepatology* 29: 257–263, 1999
927. London WT, Drew JS, Blumberg BS, Grossman RA, Lyons PJ: Association of graft survival with host response to hepatitis B infection in patients with kidney transplants. *N Engl J Med* 296: 241–244, 1977
928. Agarwal SK, Dash SC, Tiwari SC, Mehta SN, Saxena S, Malhotra KK: Clinicopathologic course of hepatitis B infection in surface antigen carriers following living-related renal transplantation. *Am J Kidney Dis* 24: 78–82, 1994
929. Nelson SR, Snowden SA, Sutherland S, Smith HM, Parsons V, Bewick J: Outcome of renal transplantation in hepatitis BsAg-positive patients. *Nephrol Dial Transplant* 9: 1320–1323, 1994
930. Chan PCK, Lok ASF, Cheng IKP, Chan MK: The impact of donor and recipient hepatitis B surface antigen status on liver disease and survival in renal transplant recipients. *Transplantation* 53: 128–131, 1992
931. Huang CC, Lai MK, Fong MT: Hepatitis B liver disease in cyclosporine-treated renal allograft recipients. *Transplantation* 49: 540–544, 1990
932. Pol S, Debure A, Degott C, Carnot F, Legendre C, Brechot C, Kreis H: Chronic hepatitis in kidney allograft recipients. *Lancet* 335: 878–880, 1990
933. Degos F, Lugussy C, Degott C, Debure A, Carnot F, Thiers V, Tiollais PKH, Brechot C: Hepatitis B virus and hepatitis B related viral infection in renal transplant recipients. *Gastroenterology* 94: 151–156, 1988
934. Fornairon S, Pol S, Legendre C, Carnot F, Manzer-Bruneel MF, Brechot C, Kreis H: The long-term virologic and pathologic impact of renal transplantaion on chronic hepatitis B virus infection. *Transplantation* 62: 297–299, 1996
935. Rostaing L, Izopet J, Cisterne J-M, Arnaud C, Duffaut M, Rumaeau J-L, Puel J, Durand D: Impact of hepatitis C virus duration and hepatitis C virus genotypes on renal transplant patients. *Transplantation* 65: 930–936, 1998
936. Grob P: Hepatitis B vaccination of renal transplant and hemodialysis patients. *Scand J Infect Dis Suppl* 38: 28–32, 1983
937. Feuerhake A, Muller R, Lauchart W, Pichlmayr R, Schmidt FW: HBV-vaccination in recipients of kidney allografts. *Vaccine* 2: 255–256, 1984
938. Jacobson IM, Jaffers G, Dienstag JL, Tolkoff-Rubin NE, Cosimi AB, Delmonico F, Watkins E, Hinkle C, O'Rourke S, Russell PS: Immunogenicity of hepatitis B vaccine in renal transplant recipients. *Transplantation* 39: 393–395, 1985
939. Lefebure AF, Verpooten GA, Couttenye MM, De Broe ME: Immunogenicity of a recombinant DNA hepatitis B vaccine in renal transplant patients. *Vaccine* 11: 397–399, 1993
940. Protection against viral hepatitis. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 39(RR-2): 1–26, 1990
941. Grob PJ, Dufek A, Joller-Jemelka HI: Hepatitis B immunization: When is a booster injection necessary [German]? *Schweiz Med Wochenschr* 115: 394–402, 1985
942. European Consensus Group on Hepatitis: Are booster immunisations needed for lifelong hepatitis B immunity? *Lancet* 355: 561–565, 2000
943. Krugman S, Overby LR, Mushahwar IK, Ling CM, Frosner CG, Deinhardt F: Viral hepatitis type B: Studies on natural history and prevention re-examined. *N Engl J Med* 300: 101–106, 1979
944. Perrillo RP, Chau KH, Overby LR, Decker RH: Anti-hepatitis B core immunoglobulin M in the serologic evaluation of hepatitis B virus infection and simultaneous infection with type B, delta agent, and non-A and non-B viruses. *Gastroenterology* 85: 163–167, 1983
945. Hoofnagle JH, Dusheiko GM, Seeff LB, Jones EA, Waggoner JG, Bales ZB: Seroconversion from hepatitis B e-antigen to antibody in chronic type B hepatitis. *Ann Intern Med* 94: 744–748, 1981
946. Realdi G, Alberti A, Rugge M, Bortolotti F, Rigoli AMTF, Ruol A: Seroconversion from hepatitis B e-antigen to anti-HBe in chronic hepatitis B virus infection. *Gastroenterology* 79: 195–199, 1980
947. Hendricks DA, Stowe BJ, Hoo BS, Kolberg J, Irvine BD, Neuwald PD, Urdea MS, Perillo RP: Quantitation of HBV DNA in human serum using a branched DNA (bDNA) signal amplification assay. *Am J Clin Pathol* 104: 537–546, 1995
948. Hu KQ, Vierling JM: Molecular diagnostic techniques for viral hepatitis. *Gastroenterol Clin North Am* 23: 479–498, 1994
949. Dienstag J, Perillo R, Schiff E, Bartholomew M, Vicary C, Rubin M: A preliminary trial of lamivudine for chronic hepatitis B infection. *N Engl J Med* 333: 1657–1661, 1995
950. Tassopoulos NC, Volpes R, Pastore G, Heathcote J, Buti M, Goldin RD, Hawley S, Barber J, Condreay L, Gray DF: Efficacy of lamivudine in patients with hepatitis B e-antigen-negative/hepatitis B virus DNA-positive (precore mutant) chronic hepatitis B: Lamivudine Precore Mutant Study Group. *Hepatology* 29: 889–896, 1999
951. Lai CL, Chien RN, Leung NW, Chang TT, Guan R, Tai DI, Ng KY, Wu PC, Dent JC, Barber J, Stephenson SL, Gray DF: A one-year trial of lamivudine for chronic hepatitis B: Asia Hepatitis Lamivudine Study Group. *N Engl J Med* 339: 61–68, 1998
952. Rostaing L, Henry S, Cirterne J-M, Icart J, Durnand D: Efficacy and safety of lamivudine on replication of recurrent hepatitis B after cadaver renal transplantation. *Transplantation* 64: 1624–1627, 1997
953. Goffin E, Horsmans Y, Cornu C, Squifflet J-P, Pirson Y: Lamivudine inhibits hepatitis B virus replication in kidney graft recipients. *Transplantation* 66: 407–409, 1998
954. Chan TM, Lok AS, Cheng IK, Chan RT: A prospective study of hepatitis C virus infection among renal transplant recipients. *Gastroenterology* 104: 862–868, 1993
955. Lau JY, Davis GL, Brunson ME, Qian KP, Lin HJ, Quan S, DiNello R, Polito AJ, Scornik JC: Hepatitis C virus infection in kidney transplant recipients. *Hepatology* 18: 1027–1031, 1993
956. Marcen R, Gamez C, Mateos ML, Orofino L, Teruel JL, Serrano P, Pascual J, Quereda C, Nash R, Ortuno J: Hepatitis C antibody after kidney transplantation: Clinical significance. *Am J Nephrol* 13: 184–189, 1993
957. Lampertico P, Ardoldi A, Rumi MG, Paparella M, Tarantino A, Ponticelli C, Colombo M: Relationship between HCV infection and chronic hepatitis in renal transplantation. *Gastroenterology* 104: A934, 1993
958. Roth D, Fernandez JA, Burke GW, Esquenazi V, Miller J:

Detection of antibody to hepatitis C virus in renal transplant recipients. *Transplantation* 51: 396–400, 1991
959. Roth D, Zucker K, Cirocco R, DeMattos A, Burke GW, Nery J, Esquenazi V, Babischkin S, Miller J: The impact of hepatitis C virus infection on renal allograft recipients. *Kidney Int* 45: 238–244, 1994
960. Fritsche C, Brandes JC, Delaney SR, Gallagher-Lepak S, Menitove JE, Rich L, Scannell C, Swanson P, Lee HH: Hepatitis C is a poor prognostic indicator in black kidney transplant recipients. *Transplantation* 55: 1283–1287, 1993
961. Hanafusa T, Ichikawa Y, Kishikawa H, Kyo M, Fukunishi T, Kokado Y, Okuyama A, Shinji Y, Nagano S: Retrospective study on the impact of hepatitis C virus infection on kidney transplant patients over 20 years. *Transplantation* 66: 471–476, 1998
962. Legendre C, Garrigue V, Le Bihan C, Mamzer-Bruneel MF, Chaix ML, Landais P, Kreis H, Pol S: Harmful long-term impact of hepatitis C virus infection in kidney transplant recipients. *Transplantation* 65: 667–670, 1998
963. Periera BJ, Wright TL, Schmid CH, Levey AS: The impact of pretransplantation hepatitis C infection on the outcome of renal transplantation. *Transplantation* 60: 799–805, 1995
964. Haem J, Berthoux P, Mosnier JF, Grattard F, Cecillon S, Pozzetto B, Alamartine E, Berthoux F: Clear evidence of the existence of healthy carriers of hepatitis C virus among renal transplant recipients. *Transplantation* 62: 699–700, 1996
965. Ponz E, Campistol JM, Bruguera M, Barrera JM, Gil C, Pinto JB, Andreu J: Hepatitis C virus infection among kidney transplant recipients. *Kidney Int* 40: 748–751, 1991
966. Pereira BJ, Natov SN, Bouthot BA, Murthy BV, Ruthazer R, Schmid CH, Levey AS, New England Organ Bank Hepatitis C Study Group: Effects of hepatitis C infection and renal transplantation on survival in end-stage renal disease. *Kidney Int* 53: 1374–1381, 1998
967. Knoll GA, Tankersley MR, Lee JY, Julian BA, Curtis JJ: The impact of renal transplantation on survival in hepatitis C-positive end-stage renal disease patients. *Am J Kidney Dis* 29: 608–614, 1997
968. Rao KV, Anderson WR, Kasiske BL, Dahl DC: Value of liver biopsy in the evaluation and management of chronic liver disease in renal transplant recipients. *Am J Med* 94: 241–250, 1993
969. Roth D, Cirocco R, Zucker K, Ruiz P, Viciana A, Burke G, Carreno M, Esquenazi V, Miller J: *De novo* membranoproliferative glomerulonephritis in hepatitis C virus-infected renal allograft recipients. *Transplantation* 59: 1676–1682, 1995
970. Cruzado JM, Gil-Vernet S, Ercilla G, Seron D, Carrera M, Bas J, Torras J, Alsina J, Grinyo JM: Hepatitis C virus-associated membranoproliferative glomerulonephritis in renal allografts. *J Am Soc Nephrol* 7: 2469–2475, 1996
971. Gallay BJ, Alpers CE, Davis CL, Schultz MF, Johnson RJ: Glomerulonephritis in renal allografts associated with hepatitis C infection: A possible relationship with transplant glomerulopathy in two cases. *Am J Kidney Dis* 26: 662–667, 1995
972. Morales JM, Pascual-Capdevila J, Campistol JM, Fernandez-Zatarain G, Munoz MA, Andres A, Praga M, Martinez MA, Usera G, Fuertes A, Oppenheimer F, Artal P, Darnell A, Rodicio JL: Membranous glomerulonephritis associated with hepatitis C virus infection in renal transplant patients. *Transplantation* 63: 1634–1639, 1997
973. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M: Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science (Washington DC)* 244: 359–362, 1989
974. Kuo G, Choo QL, Alter HJ, Gitnick GL, Redeker AG, Purcell RH, Miyamura T, Dienstag JL, Alter MJ, Stevens CE: An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. *Science (Washington DC)* 244: 362–364, 1989
975. Sampietro M, Badalamenti S, Salvadori S, Corbetta N, Graziani G, Como G, Fiorelli G, Ponticelli C: High prevalence of a rare hepatitis C virus in patients treated in the same hemodialysis unit: Evidence for nosocomial transmission of HCV. *Kidney Int* 47: 911–917, 1995
976. Pereira BJ, Milford EL, Kirkman RL, Levey AS: Transmission of hepatitis C virus by organ transplantation. *N Engl J Med* 325: 454–460, 1991
977. Pereira BJ, Wright TL, Schmid CH, Levey AS, New England Organ Bank Hepatitis C Study Group: A controlled study of hepatitis C transmission by organ transplantation. *Lancet* 345: 484–487, 1995
978. Roth D, Fernandez JA, Babischkin S, De Mattos A, Buck BE, Quan S, Olson L, Burke GW, Nery JR, Esquenazi V: Detection of hepatitis C virus infection among cadaver organ donors: Evidence for low transmission of disease. *Ann Intern Med* 117: 470–475, 1992
979. Rostaing L, Izopet J, Baron E, Duffaut M, Puel J, Durand D, Suc JM: Preliminary results of treatment of chronic hepatitis C with recombinant interferon alpha in renal transplant patients. *Nephrol Dial Transplant* 10[Suppl 6]: 93–96, 1995
980. Harihara Y, Kurooka Y, Yanagisawa T, Kuzuhara K, Otsubo O, Kumada H: Interferon therapy in renal allograft recipients with chronic hepatitis C. *Transplant Proc* 26: 2075, 1994
981. Ozgur O, Boyacioglu S, Telatar H, Haberal M: Recombinant alpha-interferon in renal allograft recipients with chronic hepatitis C. *Nephrol Dial Transplant* 10: 2104–2106, 1995
982. Chan TM, Lok AS, Cheng IK, Ng IO: Chronic hepatitis C after renal transplantation: Treatment with alpha-interferon. *Transplantation* 56: 1095–1098, 1993
983. Casanovas TT, Baliellas C, Sese E, Iborra MJ, Benasco C, Andres E, Gonzalez MT, Gil-Vernet S, Casanova A, Casais LA: Interferon may be useful in hemodialysis patients with hepatitis C virus chronic infection who are candidates for kidney transplant. *Transplant Proc* 27: 2229–2230, 1995
984. Duarte R, Huraib S, Said R, Abdel-Khadir A, Sullivan S, Chaballout A, Sbeih F, Mughal T: Interferon-alpha facilitates renal transplantation in hemodialysis patients with chronic viral hepatitis. *Am J Kidney Dis* 25: 40–45, 1995
985. Van Ness MM, Diehl AM: Is liver biopsy useful in the evaluation of patients with chronically elevated liver enzymes? *Ann Intern Med* 111: 473–478, 1989
986. Wolf PL, Williams D, Coplon N, Coulson AS: Low aspartate transaminase activity in serum of patients undergoing chronic hemodialysis. *Clin Chem* 18: 567–568, 1972
987. Goffin E, Pirson Y, Cornu C, Geubel A, Squifflet JP, van Ypersele de Strihou C: Outcome of HCV infection after renal transplantation. *Kidney Int* 45: 551–555, 1994
988. Pereira BJ, Milford EL, Kirkman RL, Quan S, Sayre KR, Johnson PJ, Wilber JC, Levey AS: Prevalence of hepatitis C virus RNA in organ donors positive for hepatitis C antibody and in the recipients of their organs. *N Engl J Med* 327: 910–915, 1992
989. Aeder MI, Shield CF, Tegtmeier GE, Bayer W, Luger AM, Nelson PW, Pierce GE, Polito A, Wilber JC, Johnson P:

Incidence and clinical impact of hepatitis C virus-positive donors in cadaveric transplantation. *Transplant Proc* 25: 1469–1471, 1993
990. Aach RD, Stevens CE, Hollinger FB, Mosley JW, Peterson DA, Taylor PE, Johnson RG, Barbosa LH, Nemo GJ: Hepatitis C virus infection in post-transfusion hepatitis: An analysis with first- and second-generation assays. *N Engl J Med* 325: 1325–1329, 1991
991. Soffredini R, Rumi M, Lampertico P, Aroldi A, Tarantino A, Ponticelli C, Colombo M: Increased detection of antibody to hepatitis C virus in renal transplant patients by third-generation assays. *Am J Kidney Dis* 28: 437–440, 1996
992. Weiner AJ, Kuo G, Bradley DW, Bonino F, Saracco G, Lee C, Rosenblatt J, Choo QL, Houghton M: Detection of hepatitis C viral sequences in non-A, non-B hepatitis. *Lancet* 335: 1–3, 1990
993. Simmonds P, Zhang LQ, Watson HG, Rebus S, Ferguson ED, Balfe P, Leadbetter GH, Yap PL, Peutherer JF, Ludlam CA: Hepatitis C quantification and sequencing in blood products, haemophiliacs, and drug users. *Lancet* 336: 1469–1472, 1990
994. Ulrich PP, Romeo JM, Lane PK, Kelly I, Daniel LJ, Vyas GN: Detection, semiquantitation, and genetic variation in hepatitis C virus sequences amplified from the plasma of blood donors with elevated alanine aminotransferase. *J Clin Investig* 86: 1609–1614, 1990
995. Busch MP, Wilber JC, Johnson P, Tobler L, Evans CS: Impact of specimen handling and storage on detection of hepatitis C virus RNA. *Transfusion* 32: 420–425, 1992
996. Lau JY, Davis GL, Orito E, Qian KP, Mizokami M: Significance of antibody to the host cellular gene derived epitope GOR in chronic hepatitis C virus infection. *J Hepatol* 17: 253–257, 1993
997. Kwok S, Higuchi R: Avoiding false positives with PCR. *Nature (Lond)* 339: 237–238, 1989
998. Urdea MS, Horn T, Fultz TJ, Anderson M, Running JA, Hamren S, Ahle D, Chang CA: Branched DNA amplification multimers for the sensitive, direct detection of human hepatitis viruses. *Nucleic Acids Symp Ser* 24: 197–200, 1991
999. Lau JY, Davis GL, Kniffen J, Qian KP, Urdea MS, Chan CS, Mizokami M, Neuwald PD, Wilber JC: Significance of serum hepatitis C virus RNA levels in chronic hepatitis C. *Lancet* 341: 1501–1504, 1993
1000. Okamoto H, Sugiyama Y, Okada S, Kurai K, Akahane Y, Sugai Y, Tanaka T, Sato K, Tsuda F, Miyakawa Y: Typing hepatitis C virus by polymerase chain reaction with type-specific primers: Application to clinical surveys and tracing infectious sources. *J Gen Virol* 73: 673–679, 1992
1001. Feray C, Samuel D, Thiers V, Gigou M, Pichon F, Bismuth A, Reynes M, Maisonneuve P, Bismuth H, Brechot C: Reinfection of liver graft by hepatitis C virus after liver transplantation. *J Clin Investig* 89: 1361–1365, 1992
1002. Widell A, Shev S, Mansson S, Zhang YY, Foberg U, Norkrans G, Fryden A, Weiland O, Kurkus J, Nordenfelt E: Genotyping of hepatitis C virus isolates by a modified polymerase chain reaction assay using type specific primers: Epidemiological applications. *J Med Virol* 44: 272–279, 1994
1003. Weiner AJ, Geysen HM, Christopherson C, Hall JE, Mason TJ, Saracco G, Bonino F, Crawford K, Marion CD, Crawford KA: Evidence for immune selection of hepatitis C virus (HCV) putative envelope glycoprotein variants: Potential role in chronic HCV infections. *Proc Natl Acad Sci USA* 89: 3468–3472, 1992
1004. Farci P, Alter HJ, Govindarajan S, Wong DC, Engle R, Lesniewski RR, Mushahwar IK, Desai SM, Miller RH, Ogata N: Lack of protective immunity against reinfection with hepatitis C virus. *Science (Washington DC)* 258: 135–140, 1992
1005. Nakao T, Enomoto N, Takada N, Takada A, Date T: Typing of hepatitis C virus genomes by restriction fragment length polymorphism. *J Gen Virol* 72: 2105–2112, 1991
1006. Stuyver L, Rossau R, Wyseur A, Duhamel M, Vanderborght B, Van Heuverswyn H, Maertens G: Typing of hepatitis C virus isolates and characterization of new subtypes using a line probe assay. *J Gen Virol* 74: 1093–1102, 1993
1007. Mahmoud IM, Sobh MA, Amer GM, El Chenawy FA, Gazareen SH, El Sherif A, El Sawy E, Ghoneim MA: A prospective study of hepatitis C viremia in renal allograft recipients. *Am J Nephrol* 19: 576–585, 1999
1008. Izopet J, Rostaing L, Sandres K, Cisterne JM, Pasquier C, Rumeau JL, Duffaut M, Durand D, Puel J: Longitudinal analysis of hepatitis C virus replication and liver fibrosis progression in renal transplant recipients. *J Infect Dis* 181: 852–858, 2000
1009. Agamanolis DP, Tan JS, Parker DL: Immunosuppressive measles encephalitis in a patient with a renal transplant. *Arch Neurol* 36: 686–690, 1979
1010. Nakano T, Shimono Y, Sugiyama K, Nishihara H, Higashigawa M, Komada Y, Ito M, Sakurai M, Yoshida A, Kitamura K, Ihara T, Kamiya H, Hamazaki M, Sata T: Clinical features of measles in immunocompromised children. *Acta Paediatr Jpn* 38: 212–217, 1996
1011. Mazariegos GV, Green M, Reyes J, Nour B, Tzakis A, Starzl TE: Rubella infection after orthotopic liver transplantation. *Pediatr Infect Dis J* 13: 161–162, 1994
1012. Broyer M, Tete MJ, Guest G, Gagnadoux MF, Rouzioux C: Varicella and zoster in children after kidney transplantation: Long-term results of vaccination. *Pediatrics* 99: 35–39, 1997
1013. Watson JC, Hadler SC, Dykewicz CA, Reef S, Phillips L: Measles, mumps, and rubella: Vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 47: 1–57, 1998
1014. Pertussis vaccination: Use of acellular pertussis vaccines among infants and young children: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 46: 1–25, 1997
1015. Prevots DR, Sutter RW, Strebel PM, Wharton M, Hadler SC: Poliomyelitis prevention in the United States: Introduction of a sequential vaccination schedule of inactivated poliovirus vaccine followed by oral poliovirus vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 46: 1–25, 1997
1016. Centers for Disease Control and Prevention: Recommended childhood immunization schedule: United States, July–December 1996. *JAMA* 276: 775–776, 1996
1017. Update: Vaccine side effects, adverse reactions, contraindications, and precautions: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 45: 1–35, 1996
1018. Recommended childhood immunization schedule: United States, July–December 1996: Advisory Committee on Immunization Practices, the American Academy of Pediatrics, the American Academy of Family Physicians, and the Food and Drug Administration (FDA). *MMWR* 45: 635–638, 1996

1019. Enke BU, Bokenkamp A, Offner G, Bartmann P, Brodehl J: Response to diphtheria and tetanus booster vaccination in pediatric renal transplant recipients. *Transplantation* 64: 237–241, 1997
1020. Huzly D, Neifer S, Reinke P, Schroder K, Schonfeld C, Hofmann T, Bienzle U: Routine immunizations in adult renal transplant recipients. *Transplantation* 63: 839–845, 1997
1021. Sever MS, Yildiz A, Eraksoy H, Badur S, Yuksel-Onel D, Gorcin B, Turk S, Erkoc R: Immune response to *Haemophilus influenzae* type B vaccination in renal transplant recipients with well-functioning allografts. *Nephron* 81: 55–59, 1999
1022. Giacchino R, Marcellini M, Timitilli A, Degli IL, Losurdo G, Palumbo M, Sartorelli M, Comparcola D, Mauro LM, Gusmano R: Varicella vaccine in children requiring renal or hepatic transplantation. *Transplantation* 60: 1055–1056, 1995
1023. Zamora I, Simon JM, Da Silva ME, Piqueras AI: Attenuated varicella virus vaccine in children with renal transplants. *Pediatr Nephrol* 8: 190–192, 1994
1024. Measles pneumonitis following measles-mumps-rubella vaccination of a patient with HIV infection, 1993. *MMWR* 45: 603–606, 1996
1025. Institute of Medicine: Measles and mumps vaccines. In: *Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality*, edited by Stratton KR, Howe CJ, Johnston RB, Washington DC, National Academy Press, 1994, pp 118–186