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# Medical Evaluation of the Adult Kidney Transplant Candidate

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Additional information is available at the end of the chapter

## 1. Introduction

### 1.1. Patient education

Prior to the formal evaluation process, all potential transplant candidates are encouraged to attend a "patient education" session. At the meeting, patients are informed about the medical and surgical risks and benefits of renal transplantation, the necessity for frequent outpatient visits in the early postoperative period, the potential adverse effects of immunosuppression, and the importance of compliance with immunosuppressive therapy. The potential advantages and disadvantages of deceased *versus* living donor renal transplantation are discussed with the patients, and when possible, with their family members, significant others, and/or friends. Other issues that are addressed include prolonged waiting time for a deceased donor transplant due to the critical shortage of donor organ and adverse effects of waiting time on patient and graft survival. In addition, patients are forewarned that various medical and psychosocial conditions may preclude a patient from being a transplant candidate. Absolute and relative contraindications to kidney transplantation are outlined in table (1).

### 1.2. General assessment

#### 1.2.1. Medical / urological evaluation

The routine assessment of a renal transplant candidate includes a detailed history and a thorough physical exam. In particular, it is important to search for the etiology of the original kidney disease as it can predict the transplant course and outcome and the risk for disease recurrence. When available, the kidney biopsy report should be reviewed and the risk of

| Absolute contraindications |
| --- |
| Active malignancy |
| Active infection |
| Severe irreversible extrarenal disease |
| Life expectancy < 2 years |
| Liver cirrhosis[1] (unless combined liver and kidney transplant) |
| Primary oxalosis (unless combined liver and kidney transplant) |
| Limited, irremediable rehabilitative potential |
| Poorly controlled psychiatric illnesses |
| Active substance abuse |
| Relative contraindications |
| Active peptic ulcer disease[2] |
| Medical noncompliance |
| Active hepatitis B virus infection[3] |
| Morbid obesity |
| Special considerations |
| ABO incompatibility[4] |
| Positive T cell crossmatch[4] |
| Post-percutaneous coronary intervention (PCI) patients. Transplant surgery not recommended: |
| Within 4 weeks of coronary revascularization with balloon angioplasty |
| Within 3 months of bare metal stent placement |
| Within 12 months of drug eluting stent placement |

[1]Kidney alone transplant may be safe in end-stage kidney disease patients with compemsated HCV cirrhosis and hepatic portal vein gradient < 10 mmHg (see text)
[2]Should be treated prior to transplantation
[3]Liver biopsy and pretransplant antiviral therapy recommended. Hepatology consult.
[4]Pretransplant desensitization protocols may allow successful transplantation across these barriers

**Table 1.** Contraindications for renal transplantation

recurrent disease should be discussed with the transplant candidate. Patients with end-stage kidney disease (ESKD) secondary to congenital or genitourinary abnormalities should undergo a voiding cystourethrogram and appropriate urological evaluation, preferably by the kidney transplant surgeon. Documentation of the patients' residual urine volume from the native kidneys is invaluable in the assessment of graft function in the posttransplant period. A history of familial or hereditary renal disease must be obtained if living related kidney donation is an option. The patients's surgical history should be elicited with special emphasis on previous abdominal operations. The surgical evaluation of the transplant candidate is discussed elsewhere.

A complete physical exam should include a careful assessment for the presence of carotid and peripheral vascular disease. Patients should preferably have a body mass index below 30-35 as obesity is associated with a higher incidence of postoperative complications. In addition to a thorough history and physical exam, patients should also undergo a number of routine laboratory testings and imaging studies as outlined in table 2.

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**Laboratory evaluation**

Serologies: HIV, hepatitis B and C, CMV, EBV, HSV, RPR (FTA-ABS if positive)

Comprehensive metabolic panel, CBC with differential and platelet count, PT/INR, PTT

Urinalysis, urine culture

PSA in men > 50 years of age[1]

Immunofixation electrophoresis in candidates > 60 years of age

**Other evaluation**

ECG

Chest x-ray

Colonoscopy if > 50 years of age[2]

Abdominal ultrasound in diabetics to evaluate for gall stones

Native renal ultrasound to assess for acquired cystic disease or masses

Pap smear (for women)[2]

Mammogram for women > 40 years of age[2] or with family history of breast cancer

Cardiac evaluation (see text)

Urologic evaluation if history of bladder /voiding dysfunction, recurrent urinary tract infections (see text)

**Immunologic studies**

Blood group and HLA typing

HLA antibodies

Crossmatching

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*CMV*: cytomegalovirus; *EBV*: Epstein-Barr virus; *HSV*: herpes simplex virus; *RPR*: rapid plasmin reagin; FTA-ABS: fluores-cin treponemal antibodies; *PSA*: prostate specific antigen; ECG: electrocardiogram

1High-risk patients should be screened at an earlier age (African-Americans, those with two or more first-degree relatives with prostate cancer).

2Part of routine health maintenance, not required for listing unless deemed necessary by the clinician at the time of evaluation.

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**Table 2.** Assessment of renal transplant candidate

### 1.2.2. Psychiatric evaluation

Coexisting psychiatric disorders have been suggested to be associated with poor transplant outcomes due in part to behavioral factors such as nonadherence to medical therapy as well as physiologic factors such as modification of immunologic and stress responses (Danovitch, 2010). Patients should be inquired about mood or anxiety disorders, alterations in perceptions, morbid destructive or violent thoughts directed to self or others, medical adherence, risk taking, substance abuse, and environmental and interpersonal stressors (Danovitch, 2010). Positive prognostic factors include strong family and social support, good insight, sound spirituality, and the ability to cope with various stressors. It should also be noted that neuro-cognitive symptoms may masquerade as depression hence assessment of organic brain dysfunction should not be overlooked. Oftentimes, the psychiatric evaluation for transplant candidacy can be complex and would require referral to subspecialty service for diagnosis and treatment. A comprehensive discussion of psychiatric issues is beyond the scope of this chapter.

The following section describes specific medical and urological issues that should be addressed during the transplant evaluation process.


## 2. Evaluation of risk factors by specific organ system disease

### 2.1. Recurrence of glomerular disease of the native kidneys

Recurrence of glomerular disease is the third most common cause of graft loss after chronic allograft injury and death with a functioning graft. Currently available data on the incidence of recurrent disease and resultant graft loss are heterogeneous due to different study design, follow-up durations, patient samples, and the variable use of surveillance biopsies among centers. The reported incidence of recurrent renal disease after renal transplantation and the risk of graft loss from disease recurrence are shown in table 3. The clinical course and impact on graft survival vary between different types of glomerulonephritis (Colgert et al., 2008; Kasiske et al., 2009). Nonetheless, with the exception of primary focal segmental glomerulo-sclerosis (FSGS), recurrent glomerular disease is usually a late complication after transplantation. FSGS secondary to reflux nephropathy or obesity does not recur after transplantation. In patients with hypertensive renal disease or other causes of chronic kidney disease, focal segmental sclerosis may be found on histologic evaluation and must be differentiated from the primary disorder. Suggested risk factors for recurrence of primary FSGS include history of recurrence in a previous transplant, younger age at diagnosis, rapid progression to end stage renal disease from the time of initial diagnosis (< 3 years), presence of mesangial proliferation in the native kidneys, older donor kidneys, Caucasian ethnicity, and the collapsing variant. Living donor kidneys (versus deceased donor) have not consistently been demonstrated to be associated with an increased risk of recurrence. Familial and sporadic forms of FSGS with podocin mutation, slow progression to end stage kidney disease (ESKD), and non-nephrotic range proteinuria in the native kidney disease are associated with low risk of recurrence (Ponticelli et al., 2010).

Despite the propensity for certain kidney disease to recur, the risk generally does not preclude transplantation and recurrence rarely results in early graft loss. However, systemic primary amyloidosis (AL amyloidosis) and light chain deposition disease are associated with high rates of disease recurrence and increased morbidity and mortality after transplantation and are considered contraindication to transplantation by most centers. In rare selected patients with sustained complete remission of the hematological disorder kidney transplantation can be performed at the discretion of the transplant nephrologist and hematologist/oncologist (Bridoux et al., 2011; Canaud et al., 2012).

### 2.2. Cardiovascular disease and peripheral vascular disease

Cardiovascular disease (CVD) is the leading cause of death after renal transplantation. Deaths with a functioning graft occurring within 30 days after transplantation are due to ischemic heart disease in nearly half of the cases. Cardiovascular screening is considered by most

|  | Recurrence rates (%) | Graft loss from disease recurrence (%) |
|---|---|---|
| FSGS | 20-50 | 50 |
| Ig A nephropathy | 20-60 | 10-30 |
| MPGN I | 20-50 | 30-35 |
| MPGN II | 80-100 | 10-20 |
| Membranous GN | 3-30 | 30 |
| HUS[2] | 10-40 | 10-40 |
| Anti-GBM disease | 15-50 | < 5 |
| ANCA-associated | 7-25 | < 5 |
|  | Vasculitis |  |
| SLE | 3-10 | < 5 |

*FSGS*: focal segmental glomerulosclerosis; *MPGN*: membranoproliferative glomerulonephritis; *GN*: glomerulonephropathy; *HUS*: hemolytic uremic syndrome; *SLE*: systemic lupus erythematosus.
1Only selected renal disease are listed.
2Diarrhea (+) HUS usually does not recur; Diarrhea (-) or familial may recur in 21-28%; Factor H or I mutation may recur in 80% to 100%; Patients with mutation membrane cofactor protein does not have recurrence (reference Kasiske et al., 2009)

**Table 3.** Rates of recurrent renal disease after transplantation and risk of graft loss from disease recurrence[1]

transplant centers as an essential component of the transplant evaluation process. A detailed cardiovascular history not only predicts the operative risk but also helps in postoperative cardiac management to improve short- and long-term cardiac outcomes. Over the years there has been much controversy over the best strategy for pre-transplant assessment and management of coronary artery disease (CAD) to prevent adverse peri-operative cardiac events. Recently, the American Heart Association / American College of Cardiology (AHA/ACC) have developed the 2012 AHA/ACC guidelines for "Cardiac Disease Evaluation and Management Among Kidney and Liver Transplantation Candidates" based on a comprehensive review of the literature pertinent to perioperative cardiac evaluation of potential kidney or liver transplant recipients (Lentine et al., 2012). These guidelines are endorsed by the American Society of Transplant Surgeons, American Society of Transplantation, and the National Kidney Foundation (discussed below). The AHA/ACC classifications of evidence to perform a test or therapy is shown in table 4.

**a.** Determining whether the transplant candidate has an active cardiac condition

The primary goal of pre-operative evaluation is to determine whether potential transplant candidates have any active cardiac condition both during the initial evaluation and immediately before an anticipated transplantation procedure. "Active" cardiac conditions are defined as unstable coronary syndromes (eg, unstable angina, severe angina, or recent myocardial infarction (MI), decompensated heart failure, significant arrhythmias, and severe valvular disease). The presence of one or more of these conditions is associated with high rates of perioperative cardiovascular morbidity and mortality, hence delay or cancellation of the

| **Evidence Class: Magnitude of procedure/treatment effect** |
|---|
| I Conditions for which there is evidence for and/or general agreement that the procedure/therapy is useful and effective |
| II Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of performing the procedure/therapy |
| IIa Weight of evidence/opinion is in favor of usefulness/efficacy |
| IIb Usefulness/efficacy is less well established by evidence/opinion |
| III Conditions for which there is evidence and/or general agreement that the procedure/therapy is not useful/effective and in some cases may be harmful |
| **Evidence Level: Estimate of certainty (precision) of procedure/treatment effect** |
| A Consistent direction and magnitude of effect from multiple randomized controlled trials |
| B Consistent retrospective cohort, exploratory cohort, ecological, outcome research, or case-control studies, or extrapolation from level A studies |
| C Case-series studies or extrapolations from level B studies |

**Table 4.** Evidence Grading

surgical procedure may be required. The 2012 AHA/ACC guidelines recommend that a thorough history and physical examination be performed in all patients preoperatively to identify any active cardiac conditions (Class I; Level of Evidence C). In prospective transplant candidates with chronic cardiac conditions, re-assessment of their cardiac status before surgery may be necessary. The former is defined as chronic limiting angina, an MI that is < 30 days old but without symptoms of unstable angina, prior history of coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI), decompensated heart failure, moderate valvular disease or prior valve surgey, or stable arrhythmias.

**b.** Noninvasive stress testing in kidney transplant candidates without active cardiac conditions

The AHA/ACC recommend noninvasive stress testing in kidney transplant candidates with no active cardiac conditions based on the presence of multiple CAD risk factors regardless of functional status. Eight relevant risk factors among transplant candidates –as defined in the Lisbon Conference report include: diabetes, prior cardiovascular disease, dialysis duration of greater than 12 months, left ventricular hypertrophy, age > 60 years, smoking, hypertension, and dyslipidemia (Abbud-Filho et al., 2007). Although the exact number of risk factors required to initiate noninvasive stress testing has not been well defined, the AHA/ACC Committee suggests that the presence of 3 or more risk factors should prompt further evaluation with noninvasive stress testing (Class IIb; Level of Evidence C) (Lentine et al., 2012)

Noninvasive stress testing for CAD may be performed with exercise or with a pharmacological agent, and gauged by electrocardiography (EKG) changes (exercise stress test), myocardial perfusion distribution (myocardial perfusion imaging), or left ventricular wall motion (stress echocardiogram). Myocardial perfusion studies (MPS) and dobutamine stress echocardiogram (DSE) are more commonly used due to the frequent abnormalities detected on baseline EKGs in patients with ESKD. In addition, dialysis patients may not be able to achieve an adequate level of exercise during an exercise stress test because of their sedentary lifestyles. However,

it should also be noted that in ESKD patients both myocardial perfusion study (MPS) and DSE have reduced sensitivity and specificity compared with that of the general population. In the general population, abnormalities on myocardial perfusion study has been suggested to correlate well with the presence of coronary artery disease (CAD) with mean weighted sensitivity of 88% and specificity of 74% (Klocke et al., 2003). In patients with stage 5 CKD (GFR < 15 ml/min or dialysis dependent) DSE and MPS have been reported to have sensitivities ranging from 44% to 89%, and 29% to 92%, respectively, and specificities ranging from 71% to 94% and 67% to 89%, respectively, for identifying ≥ 1 coronary stenosis > 70% (Lentine et al. 2009, Lentine et al, 2012). Furthermore, abnormal MPS and DSE test results have not been consistently shown to be associated with prognostic value for cardiac events and mortality in ESKD patients. In a meta-analysis of 12 studies involving either thallium-201 scintigraphy or DSE, Rabbat *et al*. demonstrated that ESKD patients with inducible ischemia had 6 times higher risk of MI and 4 times higher risk of cardiac death than patients without inducible ischemia (Rabbat et al., 2003). In contrast, in a small prospective study of 106 kidney transplant candidates clinically classified as moderate (age ≥50 years) or high (diabetes mellitus, extra-cardiac vascular disease, or known CAD) coronary risk who underwent MPS, DSE, and coronary angiography, De Lima *et al.* found that clinical risk stratification and coronary angiographic findings of CAD (defined as ≥70% stenosis in ≥1 epicardial arteries by visual estimation by 2 observers) predicted major adverse cardiac events (MACEs) [defined as sudden death, myocardial infarction, arrhythmia, heart failure, unstable angina, or revascularization] after a median follow-up of 46 months but results of MPS and DSE did not predict MACEs (De Lima et al., 2003).

Given the wide ranges of sensitivities and specificities of the MPS and DSE and the inconsistent associations of angiographically defined CAD with subsequent survival in ESKD patients, the AHA/ACC Writing Committee acknowledges that there are currently no definitive data to support or refute screening for myocardial ischemia among potential kidney transplant candidates without active cardiac conditions. However, it is recommended that until further data are available, it may be useful to use aggregate CAD risk factors to target screening of patients with the highest pretest probability of having significant CAD. Suggested algorithm for pretransplant cardiac evaluation based on the 2012 AHA/ACC guidelines is shown in figure 1.

In general, high cardiac risk candidates should undergo a formal evaluation by cardiology. If necessary, percutaneous coronary intervention or coronary bypass surgery and cardiac rehabilitation should be performed prior to transplantation. If coronary intervention is indicated, caution should be made especially if stenting is planned. The 2012 AHA/ACC guidelines do not recommend transplant surgery within 3 months of bare metal stent (BMS) and within 12 months of DES placement, particularly if the anticipated time of poststent dual antiplatelet therapy will be shortened (Class III; level of Evidence B). Transplant surgery is also not advisable in patients within 4 weeks of coronary revascularization with balloon angioplasty (Clas III; Level of Evidence B) (Lentine et al., 2012).

In patients with established CVD or in those at risk for CV events, aggressive risk factor modification and treatment *per* ACC/AHA guidelines (Pearson et al., 2002) are recommended. The cardioprotective effects of statins, aspirin, ACE inhibitors, and/or β blockers have been

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┌─────────────────────────────────────────────────────────┐
│           All prospective transplant candidates          │
└─────────────────────────────────────────────────────────┘
                            │
                            ▼
┌─────────────────────────────────────────────────────────┐
│ Thorough history and physical exam to identify active    │
│ cardiac conditions                                       │
└─────────────────────────────────────────────────────────┘
                            │
                            ▼
┌─────────────────────────────────────────────────────────┐
│ Active cardiac condition(s) present?                     │
│   •  Unstable coronary syndromes[1]                      │
│   •  Decompensated heart failure                         │
│   •  Significant arrhythmias                             │
│   •  Severe valvular disease                             │
└─────────────────────────────────────────────────────────┘
          │                                  │
          ▼                                  ▼
     ┌────────┐                         ┌────────┐
     │  Yes   │                         │   No   │
     └────────┘                         └────────┘
          │                                  │
          ▼                                  ▼
┌──────────────────┐     ┌─────────────────────────────────────────┐
│ Delay or cancel  │     │ Non-invasive stress test[2] if ≥ 3      │
│ transplant       │     │ risk factors:                            │
└──────────────────┘     │   •  Diabetes                            │
                         │   •  Prior cardiovascular disease        │
                         │   •  Dialysis duration > 12 months       │
                         │   •  Left ventricular hypertrophy (LVH)  │
                         │   •  Age > 60                            │
                         │   •  Smoking                             │
                         │   •  Hypertension                        │
                         │   •  Dyslipidemia                        │
                         └─────────────────────────────────────────┘
                                           │
                                           ▼
                              ┌─────────────────────────┐
                              │    Normal stress test    │
                              └─────────────────────────┘
                                    │             │
                                    ▼             ▼
                               ┌────────┐    ┌────────┐
                               │   No   │    │  Yes   │
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                                    │             │
                                    ▼             ▼
              ┌──────────────────┐  →  ┌────────┐  →  ┌────────────────┐
              │ Coronary         │     │ Normal │     │ List/Transplant│
              │ angiogram        │     └────────┘     └────────────────┘
              └──────────────────┘
                       │
                       ▼
                 ┌──────────┐
                 │ Abnormal │
                 └──────────┘
                       │
                       ▼
┌─────────────────────────────────────────────────────────┐
│ Management per AHA/ACC guidelines; Cardiology referral   │
└─────────────────────────────────────────────────────────┘
```

[1]Unstable coronary syndromes: unstable angina, severe angina, recent myocardial infarction
[2]Myocardial perfusion study or dobutamine stress echocardiogram (center specific).

**Figure 1.** Suggested algorithm for pretransplant cardiac evaluation

well-described. Omega-3 fatty acid consumption from fish or fish oil has also been suggested to confer a cardioprotective effect. If feasible, β1 cardioselective agents should be given several weeks prior to a planned living donor renal transplant. This allows time to maximize the efficacy of beta blockers and time to slowly titrate beta blockers, avoiding bradycardia and hypotension. Avoidance of these adverse effects may decrease the risk of stroke and all-cause mortality, leading to a positive net clinical benefit (Deveraeaux et al., 2008, Harte et al. 2008).

### 2.2.1. Biomarkers for cardiac risk assessment

In recent years, cardiac troponin T (cTnT) has been suggested to provide prognostic informa‐tion in the cardiac evaluation of patients with ESKD. Independent investigators have demon‐strated an association between increased levels of cardiac toponin T isoforms and all-cause and cardiac death risk in asymptomatic patients with ESKD (Lentine et al., 2009, Khan et al., 2005). In a study consisting of 644 wait-listed renal transplant candidates, Hickson *et al.* demonstrated that increasing cTnT levels were associated with progressively reduced survival independent of low serum albumin and history of stroke. The survival of patients with cTnT levels between 0.01 and 0.03 ng/mL did not differ from that of patients with levels < 0.01 ng/mL. In contrast, cTnT levels between 0.03 and 0.09 ng/mL were associated with significantly increased mortality (hazard ratio, HR=3.01, p=0.040). Notably, mortality was further increased in patients with cTnT levels >0.1 ng/mL (HR=4.085, p=0.009) whereas in patients with normal cTnT, excellent survival was achieved independent of other risk factors (Hickson et al., 2008). The 2012 AHA/ACA guidelines support the use of cTnT level at the time of evaluation for kidney transplantation as an additional prognostic marker (Class IIb; Level of Evidence B) (Lentine et al., 2012). However, the routine use of cTnT as adjunctive tools in cardiac risk assessment in renal transplant candidates remains to be studied.

## 2.3. Nonischemic cardiomyopathy

Patients with CKD frequently suffer from nonischemic cardiac abnormalities including left ventricular hypertrophy (LVH), left ventricular dilatation, left ventricular systolic and/or diastolic dysfunction. Renal transplantation has variably been shown to improve left ventric‐ular dysfunction and ameliorate LVH (Zolty et al., 2008). Hence, the presence of such abnor‐malities does not necessarily preclude transplantation. Nonetheless, patients with an ejection fraction of 40% are considered moderate to high risk candidates and warrant a formal Cardiology consultation. An ejection fraction below 40% generally precludes transplantation. It is our practice to refer these patients to Cardiomyopathy Center for further diagnostic and therapeutic interventions. The presence of advanced irreversible cardiomyopathy is a contra‐indication to solitary kidney transplantation and patients should be referred for possible combined kidney-heart transplantation.

## 2.4. Peripheral vascular disease

Patients with a history of transient ischemic attacks or cerebrovascular accidents should under‐go carotid Doppler studies. Duplex ultrasonography may be considered in asymptomatic pa‐tients with symptomatic peripheral arterial disease (PAD), CAD, or atherosclerotic aortic

aneurysm (Class IIb). Patients without clinical evidence of atherosclerosis may also be screened if they have 2 or more risk factors including hypertension, hyperlipidemia, cigarette smoking, family history of atherosclerosis manifested before age 60 in a first-degree relative, or family history of ischemic stroke (Class IIb). It is also reasonable to screen asymptomatic patients with a carotid bruit (Class IIa). Lastly, asymptomatic patients with known or suspected carotid artery disease are recommended to undergo duplex ultrasonography studies (Class I) (Lentine et al., 2012). Evidence of significant stenosis requires vascular surgery consultation. If necessary, carotid endarterectomy should be performed prior to transplantation and patients should be symptom free for at least six months prior to transplantation. For those with milder carotid disease, neurology consultation and optimal medical management may be sufficient.

Peripheral vascular disease is present in a significant number of renal transplant recipients and is associated with increased morbidity and mortality. Vascular imaging with either a Doppler ultrasound, computed tomography (CT) scan or magnetic resonance angiography (MRA) of the pelvic vasculature is indicated in patients with a history of claudication and/or signs of diminished peripheral arterial pulses (particularly in diabetics) on physical exam. Our single-center experience reveals that in asymptomatic patients with diminished pedal pulses but good femoral pulses, screening has not resulted in intervention in any cases. Angiogram should be considered if noninvasive studies suggest the presence of large-vessel disease. Significant aortoiliac disease requires evaluation by the surgical transplant team and may preclude transplantation.

In transplant candidates with autosomal dominant polycystic kidney disease, screening for intracranial aneurysm with either CT scan or MRA is probably warranted in all patients with a history of headaches, stroke and/or family history of intracranial aneurysm or cerebrovascular accident.

## 2.5. Infections

All patients should be assessed for common latent or active infections and questioned for a history of infectious exposures. Active infections including diabetic foot ulcers and osteomyelitis must be fully treated prior to transplantation. A prior history of tuberculosis or untreated tuberculosis exposure requires appropriate posttransplant prophylactic therapy. Patients with an established history of systemic coccidioidomycosis or histoplasmosis or those from an endemic area should undergo appropriate antibody testing. In addition, these patients should be informed of possible disease reactivation with immunosuppressive therapy and indefinite posttransplant azole prophylactic therapy. A history of immunization should also be obtained to assure adequate immunizations for common infections prior to transplantation (e.g. hepatitis B, pneumovax, and other standard immunization appropriate for age). Immunization update is mandatory for those who have undergone surgical splenectomy. Up-to-date recommendations for routine adult immunizations are available through the Centers for Disease Control and Prevention website www.cdc.gov/vaccines/schedules/downloads/adult/adult-schedule.pdf. Ideally, all potential transplant candidates should complete all recommended immunizations at least 4 to 6 weeks before transplantation to achieve optimal immune response and to minimize the possibility of live vaccine-derived infection in the posttransplant period. Household members, close contacts, and health care workers should also be fully immunized.

Infection with influenza A (H1N1) virus has emerged as an important cause of morbidity and mortality in the general and dialysis population worldwide. More importantly, infected patients on chronic dialysis treatment were found to have a 10-fold higher mortality rate compared to the general population (Marcelli et al., 2009). Recipients of solid organ transplants have also been suggested to be at risk for more severe disease (Kumar et al., 2010). In a multicenter cohort study consisting of 237 adult and pediatric solid organ transplant recipients with microbiological-confirmed influenza A H1N1 infection, 71% required hospitalization. Among 230 patients for whom data on complications were available, 32% had pneumonia, 16% were admitted to the intensive care units, and ten (4%) died.(Kumar et al., 2010) Hence, unless contraindicated, influenza A (H1N1) vaccine should be considered in all prospective transplant candidates.

Hepatitis B antigenemia does not preclude transplant candidacy. However, patients should be referred for a liver biopsy to assess the severity of liver disease because liver enzymes may be spuriously normal despite necroinflammatory changes on biopsy (Fabrizi et al., 2010). Transplant candidacy should be based on both liver histology and serologic evidence of HBV replication (i.e. HBV DNA and HBeAg positivity). In transplant candidates with active HBV replication, antiviral therapy should be initiated pretransplantation. The presence of histolog-ically mild liver disease does not preclude transplantation. However, patients should be forewarned that the introduction of immunosuppressive therapy in the posttransplant period can lead to progression of liver disease even in patients with histologically mild disease before transplantation. All patients with HBV should be placed on antiviral therapy after transplan-tation to prevent HBV reactivation and replication and progression of liver disease. Similar to HBV infection, liver biopsy is essential in the evaluation of transplant candidate with HCV because clinical and biochemical findings are unreliable indicators of the severity of liver disease in the dialysis population. The presence of minimal to mild chronic hepatitis (stages I and II) does not preclude transplantation. Pretransplantation antiviral treatment should be considered to prevent the progression of liver disease and protect the graft against HCV-related glomerulonephritis (Fabrizi et al., 2010). It should be noted that there is currently no effective treatment for chronic hepatitis C in renal transplant recipients. Although treatment with interferon-$\alpha$ may result in clearance of HCV RNA in 25-50% of cases, rapid relapse following drug withdrawal is nearly universal. More importantly, interferon-$\alpha$ treatment has been shown to precipitate acute allograft rejection and graft loss and is currently not routinely recommended for renal transplant recipients with HCV infection. The use of interferon-$\alpha$ should be individualized at the discretion of the transplant nephrologist and hepatologist. Studies evaluating interferon-free regimens are currently underway (Yee et al., 2012). Hepatitis C positive transplant candidates should be given the option of receiving a HCV-positive donor kidney which may reduce deceased donor kidney waiting time considerably.

Histological evidence of liver cirrhosis has been regarded as a contraindication to solitary kidney transplantation due to the risk of frank hepatic decompensation after transplantation as a consequence of immunosuppression. However, recent studies suggest that kidney alone transplant may be safe in end stage kidney disease (ESKD) patients with compensated hepatitis C (HCV) cirrhosis and hepatic portal venous gradient (HPVG) of less than 10 mmHg. In a

single center study consisting of 37 kidney alone HCV positive transplant recipients (n=9 with cirrhosis and n= 28 with no cirrhosis), none developed decompensation of their liver disease at 3-year follow-up although one patient in the non-cirrhosis group developed metastatic hepatocellular carcinoma 16 months after transplantation. One- and three-year graft survival rates were 75% and 75% *vs.* 92.1% and 75.1% for the cirrhosis and non-cirrhosis groups, respectively (P=0.72). The corresponding one- and three-year patient survival rates were 88.9% and 88.9% *vs.* 96.3% and 77.9%, respectively (P=0.76). Only recipient age and decreasing albumin levels were significantly associated with worse graft and patient survival. The authors concluded that kidney alone transplant may be safe in ESKD patients with compensated HCV cirrhosis and HPVG of less than 10 mmHg. (Paramesh et al., 2012). While limited studies suggest that combined liver-kidney transplant may be unnecessary in ESKD patients with compensated HCV cirrhosis and HPVG of less than 10 mmHg, patients with decompensated liver cirrhosis should be referred for combined liver-kidney transplant.

Infections with the human immunodeficiency virus (HIV) was once considered a contraindication to transplantation due to early report of serious infectious complications and death following HIV infection transmitted from a transplanted organ or inadvertent transplantation of HIV-infected patients. However, with the advent of highly effective highly active antiretroviral agents (HAART) regimen, there have been changing views regarding transplantation in HIV positive patients. Currently, a number of transplant centers would consider transplantation in stable HIV patients, defined as those with an undetectable HIV viral load, CD4 lymphocyte count greater than 300/mm$^3$, and absence of opportunistic infections in the previous year. Specific recommendations may vary from center to center and a formal consultation with infectious disease is recommended.

### 2.6. Malignancy

Transplant recipients are at greater risk of developing both *de novo* and recurrent malignancy due to the use of immunosuppressants. As the incidence of malignancy increases with the intensity and duration of immunosuppression, a history of immunosuppressive therapy for the native kidneys represents an added risk for posttransplant malignancy. For patients who have had a history of malignancy, consultation with oncology is advisable. Table 5 provides the general guidelines for minimum tumor-free waiting periods for common malignancies. Among the pre-transplant treated cancers, the highest recurrence rates have been observed with multiple myeloma (67%), non-melanoma skin cancers (53%), bladder carcinomas (29%), sarcomas (29%), symptomatic renal cell carcinomas (27%), and breast carcinomas (23%) (Penn I, 1997). In an analysis of the Israel Penn International Transplant Tumor Registry involving 90 patients with a history of pretransplant prostate adenocarcinoma (77 renal, 10 heart, and 3 liver transplant recipients), prostate cancer recurrences were shown to be related to the stage of disease at initial diagnosis (Woodle et al., 2005). Tumor recurrence rates were 14%, 16%, and 33% for stage I, II, and III diseases, respectively. Hence, a longer waiting time may be necessary for more advanced disease. Most transplant centers adhere to standard cancer surveillance appropriate for age for all transplant candidates although the utility of such screening has been challenged by experts in the field (Danovitch GM, 2003).

Of note, studies in end-stage kidney disease (ESKD) patients treated by dialysis or transplantation, and in patients with HIV/AIDS suggest that cancers can be categorized into ESKD-related, immune deficiency-related, not related to immune deficiency or of uncertain status. ESKD-related cancers include kidney, urinary tract, thyroid and multiple myeloma (Steward et al., 2008). Hence screening for malignancy in adult kidney transplant candidates should focus on kidney and urinary tract particularly in dialysis-dependent ESKD patients. Serum immunofixation electrophoresis should be performed in all transplant candidates older than 60 years of age. Chronic hepatitis B and C infected individuals should be screened for liver cancer. Although thyroid carcinoma has been observed at increased frequency in dialysis patients compared with the general population, thyroid ultrasound is not part of routine pretransplant screening. It has been suggested that regular thyroid ultrasound is justified in dialysis patients although there have been no studies to confirm or refute this recommendation. Therefore, screening prospective renal transplant candidates for thyroid cancer should be done at the discretion of the clinicians. All suitable renal transplant candidate should have a baseline renal ultrasound to screen for renal neoplasm (discussed further under urologic evaluation).

| | |
|---|---|
| **Most tumors: wait time ≥2 years** | |
| **No waiting time if cure at the time of transplantation** | |
| Incidental renal cell carcinoma | |
| *In situ* carcinoma of bladder | |
| *In situ* carcinoma of cervix | |
| Basal cell carcinoma | |
| Squamous cell carcinoma (skin) [2,3] | |
| **Waiting time ≥2-5 years[2]** | |
| Melanoma[2,4] | 5 yrs |
| Wilms tumor | 2 yrs |
| Renal cell carcinoma | 2 yrs if < 5cm |
| | 5 yrs if > 5 cm |
| Breast carcinoma[5] | 2-5 yrs |
| Lymphoma | 2-5 yrs |
| Colorectal carcinoma | 2-5 yrs |
| Invasive bladder | 2 yrs |
| Uterine body | 2 yrs |
| Invasive cervical carcinoma | 2-5 yrs |

[1]Certain cancers may recur despite a tumor-free waiting period.

[2]Oncology evaluation or consultation with the Israel Penn International Transplant Tumor Registry at www.ipittr.org may be invaluable

[3]Surveillance

[4]In situ melanoma may require a shorter waiting period of 2 years (dermatology consultation is probably warranted)

[5]Early in situ (eg ductal carcinoma in situ) may only require 2-year wait. Individuals with advanced breast cancer (stage III or IV) should be advised against transplantation

**Table 5.** Malignancy and renal transplantation[1,2]

### 2.7. Specific gastrointestinal evaluation

There has been no consensus on whether all asymptomatic renal transplant candidates should be screened for cholelithiasis. Screening is warranted, however, in diabetics and patients with a history of cholecystitis. Pretransplant cholecystectomy is recommended for these patients if there is evidence of cholelithiasis due to the increased risk of life-threatening cholecystitis after transplantation.

### 2.8. Hypercoagulable states

Thrombophilia generally does not preclude transplantation but does mandate the initiation of preventive strategies to reduce thrombotic complications and early graft loss. All transplant candidates should have routine coagulation studies performed. In high-risk candidates such as those with a previous history of thrombotic events including recurrent thrombosis of arteriovenous grafts and fistulas, positive family history of thrombosis, or history of recurrent miscarriage in female transplant candidates, a more extensive hypercoagulability profile should be performed. These may include screening for activated protein C resistance ratio or factor V Leiden mutation, factor II 20210 gene mutation, antiphospholipid antibody, lupus anticoagulation, protein C or protein S deficiency, antithrombin III deficiency, and homocysteine levels. It is our center practice to screen for lupus anticoagulant and antiphospholipid antibodies in all renal transplant candidates with systemic lupus erythematosous (Pham et al., 2010). It should be noted that although a prior history of thromboembolism does not preclude transplantation, a history of extensive venous thrombosis that involve the inferior vena cava, iliac vein or both may contraindicate transplantation and warrants evaluation by the surgical transplant team.

There has been no consensus on the optimal management of recipients with abnormal hypercoagulability profile. However, unless contraindicated, perioperative and/or postoperative prophylactic anticoagulation should be considered, particularly in patients with a prior history of recurrent thrombotic events. Transplant of pediatric *en bloc* kidneys into adult recipient with a history of thrombosis should probably be avoided. The duration of anticoagulation has not been well defined, but lifelong anticoagulation should be considered in high-risk candidates (Pham et al., 2010).

### 2.9. Urologic evaluation

All renal transplant candidates on dialysis should be imaged with a renal ultrasound, CT, or MRI to evaluate for acquired cystic kidney disease and associated renal cell carcinoma. Although there has been no consensus on the frequency of screening for renal neoplasms in wait-listed patients, the frequency of screening should follow the guidelines set forth for dialysis patients. If there is no evidence of acquired cystic kidney disease at initial screening, repeat ultrasound can be done annually or biannually (Eitner et al., 2010). Annual screening in patients who have been on dialysis for three to five years has been advocated (Chapman et al. 2011).. Urinalysis and urine cultures should be performed in all patients with significant residual urine volume. Transplant candidates with a history of recurrent urinary tract

infections, voiding symptoms, or end stage renal disease secondary to congenital or genito-urinary abnormalities should undergo a voiding cystourethrogram (VCUG). Persistent hematuria or sterile pyuria may warrant endoscopic evaluation and/or retrograde pyelography. Urodynamic studies may be helpful in patients with a history of lower urinary tract dysfunction and/or urinary incontinence. Patients with bladder dysfunction secondary to neurogenic bladder or chronic infections can often be managed without urinary diversion. In continent patients with lower urinary tract dysfunction, intermittent self-catheterization is a safe and effective alternative to urinary diversion. However, a formal urologic evaluation and patient education during the initial transplant evaluation process is mandatory. Augmentation cystoplasty or urinary diversion procedures may be necessary in patients in whom simple reimplantation into a dysfunctional bladder is not an option. Male transplant candidates with sufficient urine volume and symptoms of outflow tract obstruction due to benign prostatic hypertrophy should undergo prostate resection before transplantation, whereas in anuric patients, the procedure should be postponed until after a successful renal transplant.

## 2.10. Specific urologic considerations: Pretransplant nephrectomy

For most patients with autosomal dominant polycystic kidney disease (ADPKD) pretransplant nephrectomy is not routinely recommended. However, unilateral or bilateral pretransplant nephrectomy(ies) may be necessary for those with massively enlarged kidneys, recurrent infection, bleeding, and/or intractable pain. Table 6 lists the special indications for pretransplant native nephrectomy. Generally, a minimum of six weeks after nephrectomy is recommended prior to transplantation. For transplant candidates who undergo preemptive transplantation from a living donor, simultaneous native nephrectomy and transplantation may be performed.
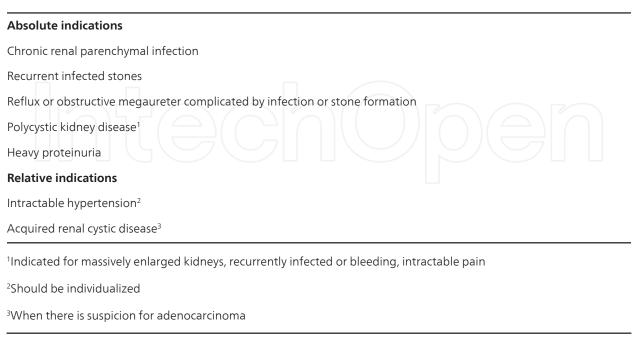
**Absolute indications**

Chronic renal parenchymal infection

Recurrent infected stones

Reflux or obstructive megaureter complicated by infection or stone formation

Polycystic kidney disease[1]

Heavy proteinuria

**Relative indications**

Intractable hypertension[2]

Acquired renal cystic disease[3]

[1]Indicated for massively enlarged kidneys, recurrently infected or bleeding, intractable pain

[2]Should be individualized

[3]When there is suspicion for adenocarcinoma

**Table 6.** Indications for pretransplant native nephrectomy

## 3. Evaluation of risk factors related to specific patients' characteristics

### 3.1. Advanced age

There is no arbitrary age limit for transplantation. The United Network for Organ Sharing/ Organ Procurement Transplantation (UNOS OPTN) database revealed that the number of kidney transplants performed in patients ≥ 65 has more than tripled over the last decade (ww.unos.org). Similar to the younger population, transplantation in the older age group of 60 to 74 years has been shown to improve survival compared to their wait-listed counterparts. Graft loss from rejection is lower in older compared to younger recipients presumably due to the decreased immune responsiveness in the aged population. It must be noted, however, that older transplant recipients are at increased risks for infectious complications, malignancy related to immunosuppression, and deaths in the early posttransplant period, most often as a consequence of cardiovascular disease.

Although advanced age *per se* has not been regarded as contraindication to transplantation, kidney transplantation among recipients over 80 years of age is uncommonly performed. Analysis of the UNOS/OPTN database revealed that of the transplants performed between 2000 and 2007 in recipients ≥ 60 years of age, only 0.6% were older than 80 years of age. For statistical analysis purposes, patients were divided into three age groups, 60-69, 70-79, and > 80 years with recipients aged 60-69 years used as reference. Median ages for recipients aged 60-69, 70-79, and > 80 years were 64, 72, and 81 years, respectively. Most of the differences were seen between recipients aged 60-69 and > 80 years. The rates of living donor transplants were lower in recipients > 80 years compared to 60-69 years (18% vs. 32%, respectively). The acute rejection rate at 1-year among recipients > 80 years was comparable to that of recipients 60-69 years of age. Three-year patient survival was significantly lower in recipients older than 80 years compared to recipients aged 60-69 years (64% vs. 84%, respectively) with an unadjusted relative risk of death of 2.35 (95% CI 1.83-3.03). However, graft survival was excellent and did not differ significantly between the two groups (88% vs. 90%) (Poommipanit et al., 2010). Hence, the assessment of transplant candidacy for patients over 80 years of age remains a challenge for transplant physicians. Screening for covert cardiovascular disease and occult malignancy, and careful assessment of infectious risk in older prospective transplant candidates are crucial and mandatory.

Currently, the waiting time for a deceased donor transplant in the United States is such that many wait-listed older transplant candidates die while awaiting transplantation from a standard deceased donor kidney. Furthermore, the duration of pretransplant dialysis has been shown to confer a significant and progressive increase in the risk of death-censored graft loss and the risk for patient death after transplantation. Compared with preemptive renal transplantation, waiting time of 0-6 months, 6-12 months, 12-24 months, and over 24 months conferred a 17%, 37%, 55%, and 68% increase risk for death-censored graft loss after transplantation, respectively (Meier-Kriesche et al., 2000). Similarly, mortality risk after transplantation was significantly increased with increasing waiting time on dialysis. It is our center practice to offer the expanded criteria donor (ECD) program to all candidates 50 years of age or older. Patients should be informed that candidates for ECD kidneys are simultaneously

listed for a standard and ECD kidney. Although living donor kidneys offer older transplant candidates the best chance of meaningful improved survival and quality of life, older patients are often reluctant to accept living donor kidneys from their children or grandchildren. These issues must be discussed with patients and their families with particular care and compassion to optimize the chance of a satisfactory outcome. Nonetheless, it should be noted that extreme recipient-donor age pair (e.g recipient > 80 years and donor aged 20-30 years) may represent a great challenge for the clinicians as well as patients and their families.

### 3.2. Obesity

Obesity is considered a contraindication to transplantation by some centers as it is associated with increased risks of posttransplant complications including delayed graft function, surgical wound infection, and death, particularly from cardiovascular disease. Although there has been no consensus on an acceptable upper limit body mass index (BMI), weight reduction to a BMI of 30-35kg/m$^2$ or less prior to transplantation is recommended. Morbidly obese candidates may benefit from surgery referral for gastric bypass surgery or gastric banding procedure, or more recently, laparoscopic sleeve gastrectomy. However, it should be noted that there has been limited data on the safety and efficacy of bariatric surgery (BS) in renal transplant candidates. The USRDS registry data (1991-2004) demonstrated a median excess body weight loss of 31%-61% after bariatric surgery, with thirty-day mortality rate of 3.5% (72 were performed on pre-listed, 29 on waitlisted, and 87 on posttransplant patients). One graft was lost within 30 days after BS. (Modanlou et al. 2009). The authors concluded that although peri-operative mortality was not negligible, the rate may be lower with experienced surgeons and comparable to trials involving patients without kidney disease.

Data on patient and graft survival in obese *versus* non-obese transplant recipients are variable and contradictory. Determination of transplant candidacy in obese patients should, therefore, be assessed on an individual basis rather than reliance on an absolute BMI index. Obese candidates with comorbid conditions such as known coronary artery disease and advanced age are at particularly high risk and may fare better receiving dialysis.

### 3.3. Managing the wait-list candidates

Whereas the number of patients on the transplant waiting list has steadily increased, the number of deceased donor kidneys has remained far below the growing need, leading to longer waiting time and increased wait-list deaths. Hence, managing the wait-list has been one of the greatest problems facing transplant centers. Periodic reassessment of transplant candidates' medical and psychosocial issues entails ongoing communication between the dialysis units, patients, and transplant coordinators and transplant programs. In the event of a significant intercurrent illness that may necessitate delisting or placing candidates on hold, pertinent medical records should be obtained and reviewed by a transplant physician. If necessary, patients must be seen to reassess their candidacy. Most transplant programs attempt to see transplant candidates on an annual basis to update their overall heatlh and demographic issues although older candidates may require more frequent visits at the discretion of the transplant physician. During the follow-up visit, routine health maintenance status and cancer screening

appropriate for age and gender such as prostate specific antigen, mammography, pap smear, and colonoscopy are also reviewed. Although recommendations for cardiac surveillance of waitlisted patients varies among transplant centers, most transplant programs advocate annual cardiac screening in diabetic transplant candidates. In addition to reassessing patients' medical status, the availability of living donors should be re-addressed. Currently, in an effort to maximize the utilization of living kidney donors, our program has implemented an algorithm to evaluate crossmatch positive and ABO-incompatible donor-recipient pairs. Patients are advised of living donor options including paired exchange transplantation, positive crossmatch and ABO incompatible transplantation through desensitization protocols, and living donor kidney exchange for both ABO-incompatible and crossmatch positive donor-recipient combinations. Discussion of this topic is beyond the scope of this chapter. For older transplant candidates, the advantages and disadvantages of expanded criteria donor kidney transplantation should be addressed. Finally, effective communication between patients' primary nephrologists and transplant centers is invaluable in permitting wait-listed transplant candidates to be at their optimal medical health when a deceased donor kidney becomes available.

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