

The Role of the General Nephrologist in Evaluating Patients for Kidney Transplantation: Core Curriculum 2020

Sarthak Virmani and William S. Asch



Transplantation is the preferred modality of replacement therapy for most patients with kidney failure. In the United States, more than 3,000 new patients are registered each month on the kidney transplant waiting list for this life-saving therapy. A potential kidney transplant recipient's evaluation typically begins with a referral by the general nephrologist to a transplantation center. In this installment in the *Core Curriculum in Nephrology*, we endeavor to achieve a shared understanding of the patient factors that contribute to optimal patient and allograft outcomes following kidney transplantation. In addition, we provide a primer on the routine listing, evaluation, testing, and candidate selection process in an effort to demystify the current criteria commonly used by transplantation centers. Issues common to a majority of candidates, including cardiovascular health, frailty as a measure of biological age, history of prior malignancy, and high body mass index are reviewed in detail. With this knowledge, we hope to facilitate improved communication between general and transplantation nephrologists.

Complete author and article information appears at end of article text.

Am J Kidney Dis. 76(4):567-579. Published online March 19, 2020.

doi: [10.1053/j.ajkd.2020.01.001](https://doi.org/10.1053/j.ajkd.2020.01.001)

© 2020 by the National Kidney Foundation, Inc.

Introduction

For most patients with kidney failure, kidney transplantation is the preferred modality of kidney replacement therapy (KRT). However, based on medical, surgical, and psychosocial factors, kidney transplantation may not be the best option for an individual patient. Although the primary responsibility of determining which recipient candidates are suitable and will be best served by organ transplantation falls on the transplantation center, the patient's general nephrologist plays a pivotal role in proactively directing patients toward a transplantation evaluation. Accordingly, the general nephrologist should be familiar with the waitlist evaluation process in general and any local candidate selection criteria set by the centers to which their patients are referred.

It is well known that kidney transplantation offers a significant and substantial improvement in quality of life and increases life expectancy in patients with kidney failure treated by KRT, with the relative magnitude of benefit increasing over time. This effect is observed independent of the age and comorbid conditions of patients. In this Core Curriculum, we hope to provide a primer on the routine waitlist evaluation testing and candidate selection criteria standards used by kidney transplantation centers. Many of the selection criteria first used to evaluate candidates were not supported by research. However, the evaluation process has evolved (and continues to evolve) and is increasingly evidence based. Despite this shift toward evidence-based

evaluation, there are inadequate data in some areas, resulting in practice variability between transplantation centers. It is our hope that this knowledge will both demystify the evaluation process and lead to improved communication between general nephrologists and members of the transplantation team to which they refer their patients.

There are multiple reasons why the recipient evaluation process is necessary. First, kidney transplantation is a high-risk medical intervention with associated risks that extend beyond the surgical procedure. Not all candidates are appropriate for an intervention of this magnitude. Second, because the transplantation procedure exposes a healthy living donor to risks without personal medical benefit, it is required that these risks be undertaken only on behalf of a recipient who is expected to do well following transplantation. Third, the gap between the supply and demand of this scarce societal resource is the basis for needing a national kidney allocation system. This obligates the transplantation center to identify recipients who will derive a meaningful duration of benefit from transplantation. The definition of duration of benefit is not specified; however, the evaluation procedures are designed to risk stratify candidates and identify those anticipated to achieve expected posttransplantation outcomes.

Determination of transplantation candidacy is a complex process that involves a multidisciplinary transplantation team assessment, including that of the surgeons, nephrologists, anesthesiologists, case coordinators, pharmacists, psychologists, social workers, dieticians,

FEATURE EDITOR:
Asghar Rastegar

ADVISORY BOARD:
Ursula C. Brewster
Michael Choi
Ann O'Hare
Manoocher Soleimani

The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

and financial coordinators. Needless to say, the referring nephrologist is cardinal to this process. This review not only outlines the characteristics of an ideal candidate for kidney transplantation but also the various factors that make up the comprehensive evaluation process of a prospective kidney transplant recipient (KTR). The majority of this evaluation is designed to identify appropriate candidates, while other aspects help identify risks and conditions that may have a significant bearing on the posttransplantation care of the recipient.

Additional Readings

- ▶ Gordon EJ, Butt Z, Jensen SE, et al. Opportunities for shared decision making in kidney transplantation. *Am J Transplant.* 2013;13(5):1149-1158.
- ▶ Sawinski D, Foley DP. Personalizing the kidney transplant decision. Who doesn't benefit from a kidney transplant? *Clin J Am Soc Nephrol.* 2020;15(2):279-281.
- ▶ Tonelli M, Wiebe N, Knoll G, et al. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. *Am J Transplant.* 2011;11(10):2093-2109. ★ **ESSENTIAL READING**

Timing of Referral

Case: Ms Smith is a 64-year-old woman who presents to the transplantation center for evaluation. She had type 1 diabetes mellitus diagnosed at age 16 years and developed kidney failure from presumed diabetic nephropathy in her mid-40s. Her husband was a compatible match and pre-emptively donated his kidney to her. Despite strict adherence with the immunosuppressive regimen, this first transplant now has advanced-stage chronic kidney disease (CKD) due to chronic calcineurin inhibitor toxicity. Ms Smith also has a history of renal cell carcinoma (RCC) in her native kidneys 7 years ago, requiring a native nephrectomy. She currently has

an estimated glomerular filtration rate (GFR) of 22 mL/min/1.73 m², and her general nephrologist has started planning for the next phase of her KRT.

Question 1: Given her positive transplantation experience and high quality of life during the past 20 years, Mrs Smith wants to be considered for repeat kidney transplantation. What is the next best course of action?

- Wait until she starts on dialysis to refer her back to the transplantation center.
- Proceed with dialysis planning because she is too old for consideration of repeat transplantation.
- History of RCC precludes her from repeat transplantation consideration.
- Prompt referral back to the transplantation center.

For the answer to the question, see the following text.

Current Organ Procurement and Transplantation Network (OPTN) policy allows for an approved candidate to gather waiting time from the time their GFR (or equivalent measure) is ≤ 20 mL/min. However, this period of advanced-stage CKD before commencement of dialysis only counts toward waiting time for approved and registered candidates. That is to say, unlike the back crediting of waiting time to the inaugural dialysis treatment date for patients already receiving dialysis, back crediting of time does not occur for patients not yet on KRT. The most strategic approach is to refer pre-kidney failure patients to the transplantation center early (Fig 1). Although potential candidates can be evaluated at a GFR > 20 mL/min, they can only be actively listed when GFR is ≤ 20 mL/min. Moreover, because an intercurrent illness can unexpectedly reduce the patient's GFR into the listable range, referral

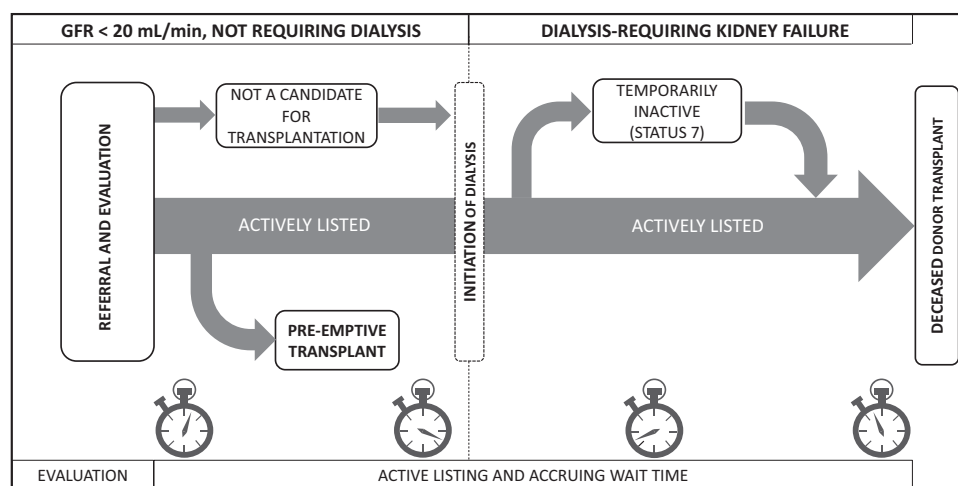


Figure 1. Transplantation evaluation timeline. Flow diagram shows the sequence of events encountered from the time of candidate evaluation to the time of kidney transplantation. Note that candidates can start accruing wait time before starting on dialysis and waiting time continues to accumulate when the patient is status 7 (temporarily unavailable). Abbreviation: GFR, glomerular filtration rate.

Box 1. Start of Wait Time on Kidney Transplant Wait List

- Date of ESKD/start of dialysis as recorded on the Federal 2728 form
- Date of UNOS registration if GFR is ≤ 20 mL/min and not yet on dialysis
- Date the GFR was ≤ 20 mL/min if evaluated and registered at GFR > 20 mL/min

Abbreviations: ESKD, end-stage renal disease; GFR, glomerular filtration rate; UNOS, United Network for Organ Sharing.

when the GFR is in the 20- to 25-mL/min range is appropriate (Box 1).

Rarely, when continued dialysis is threatened by exhausted vascular access and peritoneal dialysis is not feasible, special consideration is given. The OPTN policies allow a candidate's transplantation physician to use reasonable medical judgment to request that a candidate undergo transplantation out of sequence due to medical urgency.

Transplantation centers recognize that it is important for the referring nephrologist to maintain a good rapport with their patients. Because failing to provide a transplantation endorsement for poor and marginal candidates can threaten an established therapeutic relationship, transplantation centers generally welcome all referred candidates for evaluation. Negative feelings associated with being declined are then more focused on the transplantation center, leaving the patient and nephrologist with a preserved alliance. Note that when referring a marginal candidate, it is helpful for the nephrologist to communicate the patient's status in advance with the transplantation center. Often, some patients are either very frustrated or disappointed to learn that they are not a candidate and explaining the justification behind the decline can require an extended encounter with the transplantation center. To accommodate this, some programs have a separate clinic dedicated to the evaluation of these patients. Alternatively, this may lay the groundwork for an open discussion that strengthens rather than weakens the therapeutic relationship between the general nephrologist and the patient.

Transplantation, when appropriate, should be the primary choice for patients with CKD progressing to kidney failure, with dialytic therapies used as a bridge to transplantation. Unfortunately, only ~14% of all transplantations performed are either pre-emptive or within the first year of dialysis initiation. The most significant barrier to pre-emptive kidney transplantation remains a timely referral to the transplantation program.

Early contact with the program benefits both the patient and the transplantation center. Transplantation programs equip the potential transplantation candidate with tools and strategies to seek possible living donors while being medically optimized for the transplantation. The ideal timing of pre-emptive transplantation is still unknown but is certainly before the development of uremic symptoms.

Ishani et al showed no significant benefit in performing transplantation on patients at a higher GFR, upholding the clinical practice of delaying pre-emptive transplantations as long as the patients do not have uremic symptoms. Patient-centered factors, such as school and work schedules, may also affect the timing of the transplantation.

Additional Readings

- ▶ Cass A, Cunningham J, Snelling P, Ayanian JZ. Late referral to a nephrologist reduces access to renal transplantation. *Am J Kidney Dis.* 2003;42(5):1043-1049.
- ▶ Ishani A, Ibrahim HN, Gilbertson D, Collins AJ. The impact of residual renal function on graft and patient survival rates in recipients of preemptive renal transplants. *Am J Kidney Dis.* 2003;42(6):1275-1282.
- ▶ Jay CL, Dean PG, Helmick RA, Stegall MD. Reassessing preemptive kidney transplantation in the United States: are we making progress? *Transplantation.* 2016;100(5):1120-1127.
- ▶ OPTN Minority Affairs Committee, U.S. Department of Health and Human Services. Educational Guidance on Patient Referral to Kidney Transplantation. September 2015. Available at <https://optn.transplant.hrsa.gov/resources/guidance/educational-guidance-on-patient-referral-to-kidney-transplantation/>. ★ **ESSENTIAL READING**

Contraindications

Kidney transplantation is appropriate for the majority of candidates who present for a pretransplantation wait list

Box 2. Commonly Accepted Contraindications to Kidney Transplantation

- Active coronary disease or cardiopulmonary disease unsafe for anesthesia and noncardiac surgery (eg, decompensated heart failure, pulmonary hypertension)
- Active illicit substance use that may affect activities of daily living
- Active local infections (eg, podiatric or dental infections)
- Active systemic infections (eg, tuberculosis)
- Advanced-stage nonkidney disease (eg, COPD due to both surgical concerns and reduced life expectancy)
- Atherosclerotic vascular disease that precludes successful allograft anastomosis
- Class III obesity (BMI ≥ 40 kg/m²)
- Expected posttransplantation life expectancy of <5 y
- Frailty with limited medical performance status
- Lack of adequate insurance coverage or plan to cover costs of posttransplantation care
- Lack of robust social support system
- Decompensated cirrhosis, eg, presence of portal hypertension, hepatic encephalopathy (unless simultaneous liver-kidney transplant is planned)
- Nonadherence to prescribed therapies, including medications and dialysis
- Poorly controlled psychiatric illness
- Untreated malignancy or treated but within the period of increased risk for recurrence
- Risks exceed the potential benefits

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease.

evaluation. Nonetheless, there are circumstances under which transplantation is contraindicated (Box 2).

The standard kidney transplantation surgery involves anastomosis of the donor renal artery to the recipient's external iliac artery or, less commonly, to the internal iliac artery. Extensive atherosclerotic disease within the iliac vessels is a surgical technical barrier to a successful operation and is therefore a contraindication to kidney transplantation. As expected, the extent of atherosclerotic disease burden has only increased with the increasing average age of transplantation candidates. In addition to the concern that there will not be a suitable target site on the recipient artery to make the main renal artery anastomosis, there is also the concern that vascular clamps used during the transplantation surgery will lead to subsequent atheroembolic disease involving the ipsilateral lower extremity or the allograft. Vascular adequacy may be assessed using computed tomography (CT) angiography, noncontrast CT of the abdomen and pelvis (Fig 2), or aortoiliac vessel "run-off" during cardiac catheterization.

Kidney transplantation is also contraindicated in recipient candidates with active infections and malignancies due to the concern that immunosuppression (and in particular, high-dose induction immunosuppression) will exacerbate a preexisting infection or malignancy. Furthermore, were this to occur, it would likely result in the need to reduce

the recipient's immunosuppression to allow for immune reconstitution. As might be expected, reduction in immunosuppression early after kidney transplantation is associated with a high risk for acute rejection and potential for early allograft failure.

Active coronary heart disease is a relative contraindication and if severe becomes an absolute contraindication to proceed with kidney transplantation. All recipient candidates undergo a cardiac risk assessment tailored to their risk for cardiac disease. For younger more active candidates, an electrocardiogram may be all that is necessary. However, for candidates who are either older or with a history of long-standing diabetes, an extended dialysis vintage time, or preexisting coronary disease, cardiac stress testing and catheterization should be considered.

Differences in opinion should be anticipated (Box 3). We discuss major potential contraindications that general nephrologists need to consider when referring patients to transplantation centers.

Cause of Kidney Failure

Glomerular diseases—including but not limited to primary focal segmental glomerulosclerosis, membranous nephropathy, immunoglobulin A nephropathy, and lupus nephritis—carry a risk for recurrence after transplantation. Acknowledging that it is not always possible to establish the

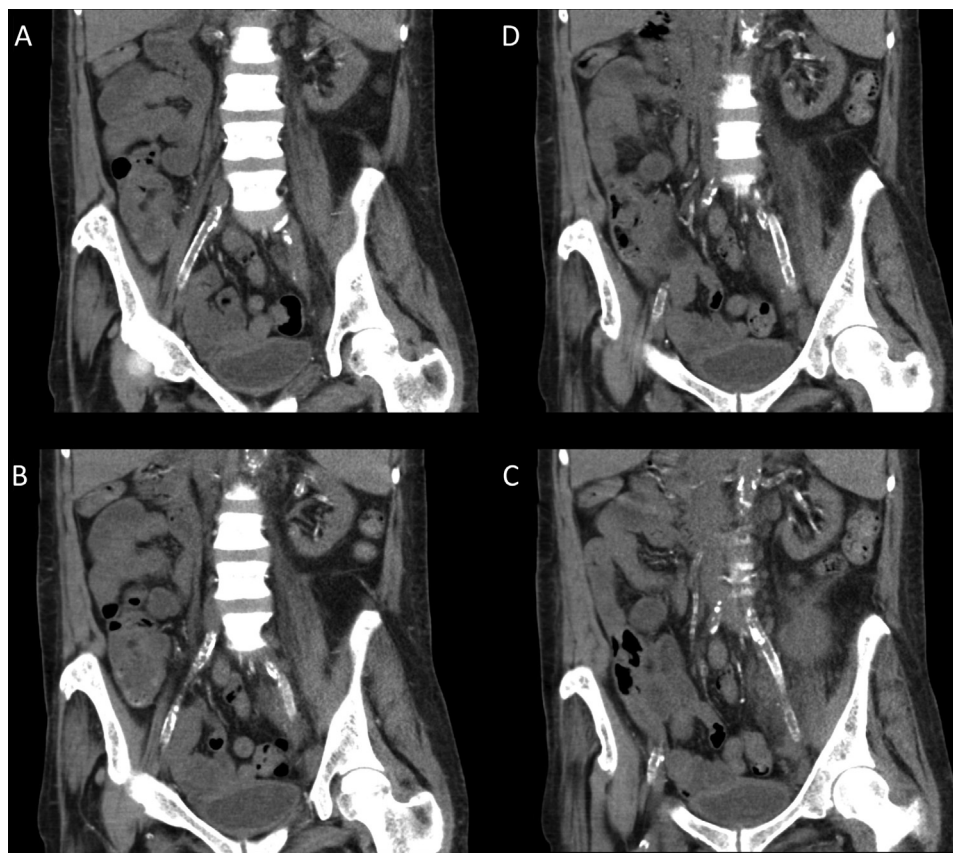


Figure 2. Vascular contraindication to transplantation. Series of images from computed tomography of the abdomen show extensive vascular calcification in the (A, B) right and (C, D) left pelvic vascular beds, a surgical contraindication for allograft implantation.

Box 3. Common Areas of Variation in Evaluation of Candidates Among Transplantation Programs

- Upper age limit, and if so, what age
- Cardiovascular testing requirement and preferred modality
- BMI target
- Need and modality of pelvic vessel imaging
- Contrast use for coronary and aortoiliac imaging in candidates with residual kidney function
- Control of secondary hyperparathyroidism and/or iPTH goal
- Nonfrailty and how to best assess for frailty
- Tobacco/marijuana use and duration of substance-free period if required
- Duration of disease-free survival from a previously diagnosed malignancy
- Dental evaluation and clearance
- Candidates unwilling to accept blood products

Abbreviations: BMI, body mass index; iPTH, intact parathyroid hormone.

cause of the kidney disease is helpful when informing potential recipients of this risk. Although a diagnosis made by a kidney biopsy remains the standard practice, we envision genetic testing (eg, whole-exome sequencing) playing an ever-increasing role in the diagnosis of kidney disease of unclear cause, especially in younger candidates. Recurrent and de novo allograft glomerulonephritis accounts for about 18% to 22% of death-censored graft failure. Most glomerulonephritides progress to a pattern of either focal or global glomerulosclerosis, often masking the true initial pattern of injury. It is in these situations that whole-exome sequencing has helped identify underlying mutations (eg, COL4A mutations in late-onset Alport nephropathy with a focal segmental glomerulosclerosis–like pattern on biopsy) that have influenced the posttransplantation care. Pretransplantation levels of antibodies to M-type phospholipase A₂ receptor (anti-PLA₂R) have been shown to predict posttransplantation outcomes in patients with membranous nephropathy. The knowledge of the cause of native kidney failure significantly influences posttransplantation surveillance of recurrent glomerulonephritis.

Returning to Ms Smith in the patient vignette, candidates with CKD should be referred for transplantation before reaching kidney failure. In this way, the evaluation can potentially be completed before GFR decreases to 20 mL/min and the candidate can be registered on the waiting list at the earliest possible time. Age is not a strict contraindication for kidney transplantation. Although a period of recurrence-free survival from cancer is often mandated, history of cancer is not a contraindication either. Ms Smith's transplant remains functional and she does not yet require dialysis. Thus, the correct answer is (d).

Age, Frailty, and Functional Status

Case, continued: *While full of life, the years following Ms Smith's kidney transplantation were not without medical complications. One year ago, she had an acute myocardial*

infarction that was emergently treated with percutaneous balloon angioplasty. Following this cardiac event, her previously normal cardiac ejection fraction (EF) is now reduced to 40% and she has had a recent admission for congestive heart failure. Too deconditioned, she was discharged to a skilled nursing facility but has since returned home.

Question 2: Which of the following is likely to preclude Ms Smith from kidney transplantation?

- Current EF of 40%
- History of myocardial infarction within the past 2 years
- Current body mass index (BMI) of 36 kg/m²
- Deconditioning requiring an extended stay at a skilled nursing facility

For the answer to the question, see the following text.

“Biological age” is a better predictor of peritransplantation complications and posttransplantation outcomes than the “chronological age” of the recipient candidate. Furthermore, posttransplantation survival of recipients older than 70 years has improved during the past 2 decades. As far as it has been measured, age is not supported as a contraindication by the literature. However, by the seventh or eighth decade, many potential KTRs have comorbid conditions that make a successful surgical and medical outcome less likely. Furthermore, many older candidates have features consistent with frailty, a state of reduced functional reserve and inability to tolerate significant medical stressors. The physiologic stress caused by kidney transplantation should not be underestimated.

Approximately 20% of all transplant recipients are older than 65 years. Some groups have supported the transplantation of patients older than 70 years while accepting the increased early postoperative risks. Gill et al investigated the expected survival duration in patients older than 70 years. Compared with patients who remained on the waiting list, transplant recipients were found to have a 3.7-year increase in their expected survival. In another study of octogenarian KTRs, median 5-year patient survival was 55%.

Frailty is best described as a constant state of inflammation with greater vulnerability to stressors on account of diminished physiologic reserve and dysregulation of multiple physiologic systems. Independent of age, frailty was found to be associated with 94% increased risk for delayed graft function, 60% increased risk for early rehospitalizations, and more than double the risk for death in those undergoing kidney transplantation. It thus becomes imperative that a comprehensive functional assessment including functional status, physical performance, and independence in activities of daily living be assessed in potential KTRs undergoing evaluation. Although some transplantation professionals believe they can identify frail patients in appropriate for kidney transplantation using the “eyeball test,” evidence suggests otherwise. Considerable research has been invested toward studying and removing the subjective component of the frailty assessment. Perhaps

Box 4. Fried Frailty Phenotype Index**Criteria**

- Weakness, as measured by grip strength within lowest quintile (by sex and BMI)
- Slowness, as measured by 15-ft walking time within lowest quintile (by sex and height)
- Low level of physical activity, as measured by Kcal/wk in the lowest quintile (<383 Kcal/wk for men or <270 Kcal/wk for women)
- Exhaustion/poor endurance, by self-reported exhaustion
- Weight loss/sarcopenia, as determined by >10 lb of unintentional weight loss in the past year

Scoring

- Positive for frailty phenotype: ≥3 criteria present
- Intermediate (prefrail): 1 or 2 criteria present
- Not frail: no criteria present

Note: By convention, 1 MET is considered equivalent to the consumption of 3.5 mL O₂ · kg⁻¹ · min⁻¹. Therefore, METs × 3.5 × body weight (kg) × minutes ÷ 200 = Kcal. A 70-kg male will therefore need to walk at a brisk pace (3.5 mph ≈ 4.3 METs) for 73 minutes per week to achieve 383 Kcal per week of activity. Similarly, a 70-kg female will need to walk at a brisk pace for 51 minutes per week to achieve 270 Kcal per week of activity.

Abbreviations: BMI, body mass index; MET, metabolic equivalent.

the most well known is the Fried Frailty Phenotype index, which is based on 5 physical frailty criteria (Box 4). The 5 frailty criteria include unintentional weight loss, exhaustion, low physical activity, slowness, and weakness. The index can quickly be completed by transplantation physicians and nurse coordinators in the transplantation office setting, and unlike more sophisticated measures of physical performance, requires minimal staff training to correctly perform.

Additional Readings

- ▶ Cosio FG, Cattran DC. Recent advances in our understanding of recurrent primary glomerulonephritis after kidney transplantation. *Kidney Int.* 2017;91(2):304-314.
- ▶ Francis JM, Beck LH Jr, Salant DJ. Membranous nephropathy: a journey from bench to bedside. *Am J Kidney Dis.* 2016;68(1):138-147.
- ▶ Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* 2001;56(3):M146-M156.
- ▶ Garonzik-Wang JM, Govindan P, Grinnan JW, et al. Frailty and delayed graft function in kidney transplant recipients. *Arch Surg.* 2012;147(2):190-193.
- ▶ Gill JS, Tonelli M, Johnson N, Kiberd B, Landsberg D, Pereira BJ. The impact of waiting time and comorbid conditions on the survival benefit of kidney transplantation. *Kidney Int.* 2005;68(5):2345-2351.
- ▶ Lønning K, Midtvedt K, Leivestad T, et al. Are octogenarians with end-stage renal disease candidates for renal transplantation? *Transplantation.* 2016;100(12):2705-2709.
- ▶ McAdams-DeMarco MA, Law A, King E, et al. Frailty and mortality in kidney transplant recipients. *Am J Transplant.* 2015;15(1):149-154. ★ **ESSENTIAL READING**
- ▶ Voora S, Adey DB. Management of kidney transplant recipients by general nephrologists: core curriculum 2019. *Am J Kidney Dis.* 2019;73(6):866-879. ★ **ESSENTIAL READING**

Cardiac Evaluation

A potential KTR's candidacy depends heavily on their cardiac disease history. It is well established that the probability of coexisting cardiovascular disease increases as GFR declines. This relationship extends into the post-transplantation experience. In support of this fact, cardiovascular disease is now known to be the leading cause of death with a functioning allograft.

Patients with arteriosclerotic heart disease that places them at high risk for a perioperative cardiac event during intermediate-risk procedures are likely to be disqualified. Likewise, patients with moderate or severe congestive heart failure (either with reduced or preserved EF) who are less likely to tolerate the anticipated fluid shifts post-operatively may similarly be disqualified.

Screening for arteriosclerotic heart disease is expensive and not without its risks, particularly if being repeated on a surveillance basis for patients waiting to undergo transplantation. For potential KTRs being monitored with serial nuclear myocardial perfusion imaging, the cumulative exposure to medical radiation requires some thoughtfulness, particularly in this population, which is commonly exposed to multiple radiographic studies. For this reason, the need and modality of coronary artery disease screening should be tailored to the candidate. Exercise stress testing has the benefit of providing additional insight into physical performance status. Some candidates will either not be able to run on the treadmill or be unable to achieve the required heart rate for the study to be informative. In these cases, pharmacologic nuclear myocardial perfusion imaging and dobutamine echocardiogram studies should be considered. Multivessel coronary artery disease can result in balanced ischemia and lead to a false-negative myocardial perfusion imaging result. Many transplantation candidates will require a cardiac catheterization based on the stress test findings, especially in patients with a high pretest probability of coronary artery disease. Preservation of residual kidney function should be weighed against the benefit of contrast exposure in these patients.

Each transplantation center is at liberty to decide whether a reduced EF is a contraindication to transplantation, as well as determine what EF threshold to use. When evaluating a potential candidate's EF, it is important to consider the probability of an improvement in EF following transplantation or whether the patient meets criteria for a combined heart-kidney transplant. Unfortunately, there are potential KTRs with an EF too low for a kidney transplant alone, but too high to qualify for a combined heart-kidney transplant.

Measures of pulmonary hypertension (PH) correlate with adverse events and outcomes following surgery in general and kidney transplantation in particular. Though direct pulmonary artery pressure measurement should be pursued to confirm the diagnosis of PH, it can be noninvasively estimated with echocardiography by

determining the right ventricular systolic pressure, which is calculated through measurement of the peak tricuspid regurgitant jet velocity. Acknowledging that the majority of candidates with PH likely have pulmonary-venous hypertension secondary to fluid overload and that measures of PH may normalize with restoration of kidney function, transplantation centers are often reluctant to proceed given the surgical risks and concern that allograft function will be compromised by the high venous pressures. Often, the general nephrologist will need to optimize the diuretic therapy of these candidates or initiate dialytic therapies for ultrafiltration.

Obesity

The approach to patients with obesity (BMI > 30 kg/m²) varies from center to center. Undoubtedly, obesity is an independent risk factor not only for cardiovascular mortality but also for perisurgical and anesthetic complications. Delayed graft function, wound infections, wound dehiscence, and peri-allograft fluid collections are more commonly seen in patients with obesity. There is a greater probability that the incision will need to be opened, drained, and irrigated and require negative pressure wound therapy. Additionally, immunosuppressant medication-associated metabolic complications and new-onset diabetes after transplantation are more commonly seen in patients with obesity and metabolic syndrome. Despite the higher incidence of these complications, kidney transplantation reduces the overall mortality of patients with obesity by ~50%, though interestingly, this benefit seems to diminish as BMI approaches 40 kg/m².

Although each center may specify their target goals and approach each patient with obesity in a personalized manner based on surgical experience, availability of live donors, and comorbid conditions, preoperative optimization of BMI is essential in achieving a favorable outcome.

Often the initial transplantation referral motivates the patient to lose weight and set targets while they go through the rest of their evaluation. A multidisciplinary approach including involvement of the primary physicians, general nephrologists, and transplantation center (especially transplantation dietitians) should be undertaken. It is commonly seen that patients with progressive CKD and higher BMI often find it difficult to lose weight with conventional methods and need bariatric surgery to bring BMI to <40 kg/m².

For candidates with large body frames or high lean muscle mass, both BMI and waist-to-hip circumference ratio may overestimate obesity. CT of the abdomen and dual-energy x-ray absorptiometry can be used to better measure visceral adiposity in cases in which obesity is suspected.

Additional Readings

- ▶ Awan AA, Niu J, Pan JS, et al. Trends in the causes of death among kidney transplant recipients in the United States (1996-2014). *Am J Nephrol*. 2018;48(6):472-481.

- ▶ Hossain M, Woywodt A, Augustine T, Sharma V. Obesity and listing for renal transplantation: weighing the evidence for a growing problem. *Clin Kidney J*. 2017;10(5):703-708. ★ **ESSENTIAL READING**
- ▶ Lentine KL, Costa SP, Weir MR, et al. Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *J Am Coll Cardiol*. 2012;60(5) 434-480. ★ **ESSENTIAL READING**
- ▶ Lentine KL, Villines TC, Axelrod D, Kaviratne S, Weir MR, Costa SP. Evaluation and management of pulmonary hypertension in kidney transplant candidates and recipients: concepts and controversies. *Transplantation*. 2017;101(1):166-181.
- ▶ Palepu S, Prasad GV. Screening for cardiovascular disease before kidney transplantation. *World J Transplant*. 2015;5(4):276-286.

Infection

Human Immunodeficiency Virus

Due to the obvious concern that antirejection medications would enhance the immune dysfunction resulting from human immunodeficiency virus (HIV) infection and promote opportunistic infection, HIV was historically a contraindication to kidney transplantation. However, with an increasingly diversified palette of antiretroviral medications to choose from to treat and navigate around viral resistance, HIV infection was transformed from an incurable fatal disease to a manageable chronic illness. With improved highly active antiretroviral therapy (HAART) as a backdrop, and uncertainty about the safety of proceeding, kidney transplantation was trialed in highly select recipients with HIV infection. The first multicenter pilot study on this topic was published in 2003.

Counterintuitively, early studies showed that recipients with HIV infection are at increased risk for acute rejection, thereby demonstrating that the alloreactive immune response is preserved in the setting of controlled HIV infection. These studies were cautious in that no induction agent was used and cyclosporine was the backbone of the maintenance immunosuppressive regimen. Building on this early experience, Gathogo et al assessed the impact of tacrolimus versus cyclosporine on the development of acute rejection in HIV-positive KTRs. Consistent with HIV-negative recipients, HIV-positive recipients treated with tacrolimus had a lower rate of rejection (21% vs 58% at 1 year). Consequently, many if not most transplantation centers have adopted the use of a tacrolimus-based regimen for their HIV-infected recipients. Encouragingly, despite being on immunosuppression treatment, viral loads remained undetectable when simultaneously treated with HAART. Although allograft survival and rates of both acute rejection and opportunistic infection remain inferior to matched HIV-negative controls, the early studies conclude that kidney transplantation is acceptable and appropriate for highly select recipients with HIV infection.

The general consensus is that an HIV-infected KTR should be on and have demonstrated adherence with HAART, have a stable CD4 count > 200 cells/μL for at least 3 months, and have a viral load that is no higher than 50

RNA copies/mL for at least the past 3 months (though undetectable levels of virus are preferable and a listing requirement for many programs). It is also recommended that no opportunistic infections occurred in the preceding 6 months to transplantation. Presence of an AIDS-defining illness remains a contraindication to transplantation. It is desirable to optimize a candidate's HAART before transplantation to avoid any drug interactions with the immunosuppressive medications in the posttransplantation period.

Signed into law in November 2013, the HIV Organ Policy Equity (HOPE) Act modified the existing organ transplantation rules as they pertain to allocation of organs from HIV-positive individuals. Previously, these organs were illegal to use for transplantation in the United States. Importantly, under the HOPE Act, only similarly HIV-infected recipient candidates are eligible to receive organs from HIV-positive donors. Not all transplantation centers are currently participating in the HOPE Act. Therefore, referral of any HIV-seropositive recipient candidate to a participating center should be considered to take advantage of this opportunity.

Hepatitis C Virus

Treatment of chronic hepatitis C virus (HCV) infection has undergone a tectonic shift during the past decade and continues to be an exciting and evolving area of organ transplantation. Most of this monumental change can be attributed to the development of the direct-acting antiviral drugs. These significant changes have positively affected HCV-infected donors and recipients alike.

In the past, treatment of HCV-infected recipients following kidney transplantation was with recombinant interferon alfa monotherapy and subsequently in combination with ribavirin. The rate of sustained virologic response was rather poor during this era. Furthermore, the use of interferon incurred a higher risk for allograft rejection owing to its ability to activate the immune system. For these reasons, treatment of HCV infection before transplantation was encouraged to avoid placing the allograft at risk from delayed treatment. Progression of underlying HCV-mediated liver disease was also a significant concern contributing to the decision to treat HCV-infected patients with kidney failure earlier in their course of disease.

Arising from fears that HCV-infected recipients would become co-infected with a second strain of HCV, use of HCV-positive donor organs was largely restricted to recipients with HCV genotype 1 in the United States. HCV genotype testing until recently would take more time than is available to be completed on deceased donors before organ procurement and allocation. Present in nearly 75% of HCV infected people, genotype 1 is the most common HCV genotype in the United States. Accordingly, it made statistical sense to assume that organ donors without HCV genotype data available at the time of organ allocation were genotype 1 and distribute the organs accordingly.

The number of HCV-infected donor kidneys identified and recovered exceeds the number of recipients waiting who are similarly HCV infected. Therefore, there was an initially high rate of discard for HCV-infected kidneys. With the arrival of the direct-acting antiviral drugs, particularly with drugs that have the ability to treat each of the known genotypes and more so the ability to effectively treat in a pan-genotypical manner, treatment of chronic HCV infection following kidney transplantation is now frequently delayed until the posttransplantation interval in patients spared from significant liver disease. In doing so, this group of patients can potentially undergo transplantation with similarly infected HCV kidneys sooner than would be the case were they not HCV infected. That is to say, infection with chronic HCV has become in some situations an advantage (ie, shortened waiting time) for receiving a kidney transplant from a deceased donor. In addition to using high-quality kidneys that previously were discarded, transplants from HCV-positive donors reduce the overall cost burden without increasing the rate of organ rejection. With the high efficacy of the direct-acting antiviral drugs, kidney transplantation from HCV-positive donors to HCV-negative recipients is now being explored in research protocols.

Until the economics of HCV donor organ supply-demand shifts, treatment of recipient candidates before kidney transplantation should only be undertaken when there is clear and present danger to the liver. For this reason, it is advisable that the general nephrologist discusses the waiting time consideration with the hepatologist before initiation of therapy.

All potential transplant recipients are screened for chronic hepatitis as a component of the transplantation center's minimum listing criteria testing. Candidates discovered to have cirrhosis are typically declined for kidney transplantation alone and referred to transplant hepatology to be evaluated for simultaneous liver-kidney transplantation. In rare cases, such as when no findings to indicate the patient has portal hypertension (absence of varices and ascites, normal platelet count, and ideally, confirmation that the hepatic venous pressure gradient is normal), candidates with advanced liver fibrosis will be appropriate for kidney-alone transplantation. Invariably, a transplantation center will meet a KTR candidate who has liver disease that is too advanced to safely proceed with kidney transplantation, but liver disease too well compensated to drive the Model for End-Stage Liver Disease (MELD) score high enough to be allocated a liver transplant. Patients in this circumstance pose a dilemma for which there is no suitable management option.

Returning to our patient, Ms Smith's recent extended stay at a skilled nursing facility points toward her being frail. She is predicted to have slower recovery following kidney transplantation complicated by higher morbidity (eg, delayed graft function) and mortality than a nonfrail recipient. The patient's EF, while reduced, is acceptable to proceed. Although the American Heart Association

recommends waiting 6 weeks after a myocardial infarction before proceeding with elective surgery, most transplantation centers will wait closer to 6 months (2 years is excessive in the absence of new events). Most, perhaps all, programs will approve candidates with BMI of 36 kg/m². Thus, the correct answer is (d).

Additional Readings

- ▶ Alameddine M, Jue JS, Zheng I, Ciancio G. Challenges of kidney transplantation in HIV positive recipients. *Transl Androl Urol*. 2019;8(2):148-154.
- ▶ Bowring MG, Kucirka LM, Massie AB, et al. Changes in utilization and discard of HCV antibody-positive deceased donor kidneys in the era of direct-acting antiviral therapy. *Transplantation*. 2018;102(12):2088-2095.
- ▶ Chute DF, Chung RT, Sise ME. Direct-acting antiviral therapy for hepatitis C virus infection in the kidney transplant recipient. *Kidney Int*. 2018;93(3):560-567. ★ **ESSENTIAL READING**
- ▶ Cohen-Bucay A, Francis JM, Gordon CE. Timing of hepatitis C virus infection treatment in kidney transplant candidates. *Hemodial Int*. 2018;22(suppl 1):S61-S70.
- ▶ Gathogo E, Harber M, Bhagani S, et al. Impact of tacrolimus compared with cyclosporin on the incidence of acute allograft rejection in human immunodeficiency virus-positive kidney transplant recipients. *Transplantation*. 2016;100(4):871-878.
- ▶ Salvadori M, Tsalouchos A. Hepatitis C and renal transplantation in era of new antiviral agents. *World J Transplant*. 2018;8(4):84-96.
- ▶ Stock PG, Roland ME, Carlson L, et al. Kidney and liver transplantation in human immunodeficiency virus-infected patients: a pilot safety and efficacy study. *Transplantation*. 2003;76(2):370-375. ★ **ESSENTIAL READING**

Malignancy

Case, continued: Seven years ago, Ms Smith presented with diarrhea and abdominal pain. A previously imaged native kidney Bosniak 2F cyst overdue for follow-up was incidentally noted on CT to have a solid mass component. Magnetic resonance imaging of the mass was consistent with RCC measuring 4 cm. The kidney was removed and pathology confirmed the diagnosis of RCC. In accordance with recommended guidelines, urology has done interval surveillance screening for disease recurrence.

Question 3: Which of the following statements is true for patients with a history of malignancy seeking kidney transplantation?

- a) A period of recurrence-free survival is required for all cancers before a patient can undergo transplantation and safely receive immunosuppression.
- b) Patients who have been treated for cancer cannot be registered on the United Network for Organ Sharing (UNOS) kidney transplant waiting list until they have completed the period of recurrence-free survival.
- c) Similar to potential transplant recipients without cancer, patients registered on the waiting list as UNOS status 7 ("temporarily inactive") also accumulate waiting time.
- d) Because it is rarely "cured," a patient with multiple myeloma (MM) in remission is not a candidate for kidney transplantation.

For the answer to the question, see the following text.

Although organ transplantation would not be possible without it, immunosuppression raises the risk for future malignancies and infections. As noted, kidney transplantation is contraindicated in the setting of malignancies that are not cured or are not in remission. However, this contraindication will be time limited for most patients being treated for cancer. Following a period of disease- and recurrence-free survival, recipient candidates with a malignancy history can safely proceed with kidney transplantation (Box 5). Therefore, to not unnecessarily place recipient candidates at a disadvantage while completing their required malignancy recurrence-free survival interval, most transplantation centers will complete the candidate's evaluation and list the candidate as temporarily inactive (UNOS status 7). This allows candidates who have not yet reached kidney failure to begin accumulating waiting time toward deceased donor transplantation. Beginning in late 2014 when the UNOS new Kidney Allocation System went into effect, all recipient candidates already receiving dialysis at the time of transplant listing are back credited their preregistration time to the date of dialysis initiation. Given this entitlement and the unfortunate reality that not all patients with cancer will be successfully and durably cured of their disease, transplantation centers will commonly inform candidates with a recent history of cancer who are already receiving dialysis that the evaluation will be suspended until the recurrence-free interval has elapsed. While patients may perceive delaying their candidacy evaluation as "denying them of hope," it is appropriate from a programmatic perspective when the resources required to actively manage patients who are status 7 is taken into consideration.

Patients with MM require additional consideration when evaluating a candidate's appropriateness for kidney transplantation. MM can lead to kidney injury through multiple mechanisms (eg, cast nephropathy, light chain amyloidosis, and monoclonal immunoglobulin deposition disease) and progression to kidney failure is not an uncommon occurrence. In the past, MM was considered a contraindication to kidney transplantation due to concerns that immunosuppression would lead to disease recurrence. However, while MM remains a disease that cannot be cured, with contemporary therapies (eg, bortezomib and carfilzomib), durable remission can be achieved. Consequently, treated patients with MM can now expect a median survival in excess of 5 years. With these therapeutic improvements, transplantation centers have cautiously proceeded with performing transplantation on patients with MM in remission. However, an improvement in the quantitative assessment of both serum and urine paraproteins (eg, normal serum free light chains), as well as normalization of the bone marrow, should be confirmed before proceeding. Furthermore, potential transplant recipients with MM can be genetically screened for chromosomal abnormalities that carry a high risk for early relapse within the first 24 months following treatment.

Box 5. Suggested Disease-Free Wait Times for Various Treated Malignancies**No recurrence-free interval required**

- Asymptomatic T1 renal cell carcinoma
- Carcinoma in situ, cervix
- Microscopic prostate cancer
- Monoclonal gammopathy of undetermined significance
- Nonmetastatic nonmelanoma skin cancer
- Superficial bladder cancer

Minimum 2 years of recurrence-free interval recommended

- Breast cancer, in situ
- Invasive bladder cancer
- Kaposi sarcoma
- Leukemias
- Lymphomas
- Macroscopic prostate cancer
- Melanoma in situ
- Multiple myeloma
- Renal cell carcinoma with suspicious features
- Stage A/B colorectal cancer
- Testicular cancer
- Thyroid or other endocrine tumors
- Uterine cancer
- Wilm tumor

Minimum 5 years of recurrence-free interval recommended

- Colorectal cancer, stage C
- Malignant melanoma
- Stage II breast cancer
- Symptomatic renal cell carcinoma (lesion > 5 cm)

Transplantation not recommended

- Advanced breast cancer (stage III)
- Colorectal cancer, stage D
- Liver cancer, not meeting the Milan criteria
- Uncontrolled or untreated malignancies

Note: These disease-free waiting times are based on relatively low-quality evidence and may need to be individualized based on the patient's circumstances. "Disease free" indicates that the cancer was either completely resected or treated to cure.

Ms Smith's history of RCC does not necessarily disqualify her from repeat transplantation. Patients who have been treated for cancer can be registered on the waiting list. However, many will be listed as status 7 (temporarily unavailable). Patients are not disadvantaged while they are status 7. They continued to accumulate waiting time toward transplantation. Some minor cancers do not require any period of recurrence-free survival before listing is acceptable (eg, nonmetastatic non-melanoma skin cancer). Thus, the correct answer is (c).

Additional Readings

- Penn I. The effect of immunosuppression on pre-existing cancers. *Transplantation*. 1993;55(4):742-747.
- Sprangers B, Nair V, Launay-Vacher V, Riella LV, Jhaveri KD. Risk factors associated with post-kidney transplant malignancies: an

article from the Cancer-Kidney International Network. *Clin Kidney J*. 2018;11(3):315-329. ★ **ESSENTIAL READING**

- Van den Bosch I, Sprangers B, Gertz M. Multiple myeloma and kidney transplantation: the beginning of a new era. *Clin Kidney J*. 2019;12(2):213-215.

Diabetes

Diabetes is the leading cause of both CKD and kidney transplantation listing in the United States. Furthermore, nearly every metric used to assess kidney transplantation (eg, patient survival and allograft survival) will show poorer outcomes for the diabetic KTR. Much of this increased risk comes as a result of a higher cardiovascular and peripheral vascular disease burden in diabetic patients. Many people with diabetes will have extensive atherosclerotic disease beyond that which would allow for anastomosis of an allograft. Accordingly, transplantation centers need to thoroughly screen their diabetic candidates for evidence of advanced disease that will preclude them from undergoing transplantation.

Beyond the obvious elevated risk for perisurgical complications and wound infections in diabetic patients, the risk for posttransplantation diabetes mellitus is higher with a higher pretransplantation hemoglobin A_{1c} level. Although there are no established hemoglobin A_{1c} level cutoffs, medical prudence lies in optimizing diabetic control pretransplantation to not only lower the perisurgical infection risk but also to decrease the burden of posttransplantation diabetic complications. Given long wait times, the general nephrologist plays an important role in managing this chronic disease.

Immunizations

Multiple separate issues require consideration when discussing immunizations in the potential KTR. Live as well as live-attenuated vaccines cannot be safely administered to patients receiving immunosuppression owing to the fear that they will be at risk for severe viremia and potentially catastrophic illness. For this reason, only fully inactivated (dead) and recombinant vaccines can be safely dosed following transplantation. Ideally, all patients being evaluated for kidney transplantation should be up to date with the age-appropriate immunizations. Because transplantation centers have limited contact with the recipient candidates before transplantation, this responsibility should be shared between the general nephrologist and primary care physician.

All live vaccine series (eg, shingles; measles, mumps, and rubella; and oral typhoid) should be completed at least 4 to 6 weeks before kidney transplantation. Splenectomized candidates, or those who are at a higher risk for posttransplantation splenectomy, must be appropriately immunized against encapsulated organisms, including *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae*. In addition, immunization against *Neisseria meningitidis* should strongly be considered for potential KTRs, particularly those with a history of atypical hemolytic

uremic syndrome or other disease that may require the use of a complement inhibitor (eg, eculizumab) post-transplantation. A recent report suggests that treatment with eculizumab leads to impaired opsonophagocytic killing of meningococci, resulting in a greater than 1,000-fold increased risk for meningococcal disease. For this reason, antimicrobial prophylaxis should be considered for potential KTRs requiring eculizumab not previously vaccinated against *N meningitidis*.

Although vaccination with dead and recombinant vaccines is permissible posttransplantation, immunosuppressed recipients have a lower probability of successfully mounting a protective immunologic response. For this reason, it is recommended that routine vaccinations (eg, seasonal influenza virus vaccine) be deferred until after the patient has exited periods of intense immunosuppression, such as the first 3 to 6 months following induction.

Hyperparathyroidism

The approach to secondary hyperparathyroidism (sHPT) in prospective candidates remains an issue of debate in the transplantation community. For some candidates, a significantly elevated intact parathyroid hormone (iPTH) level represents nonadherence with phosphate-binder use and the recommended low-phosphate diet. Others simply fail to achieve goal levels of sHPT control despite following recommendations. Patients and providers in this latter group frequently find themselves in conflict with the transplantation center's required acceptable iPTH upper limit for listing and transplantation. Although no target levels are agreed on, incorporating an iPTH criterion into the center's minimal listing criteria is perhaps justified. Poorly controlled sHPT is associated with higher rates of all-cause mortality (hazard ratio [HR], 1.46), allograft loss (HR, 1.85), bone disease, and a 7.5-fold increased risk for fractures over 5 years following kidney transplantation.

Poorly managed sHPT before transplantation increases the probability that the recipient will develop significant tertiary hyperparathyroidism (tHPT) following transplantation. Characterized by hypercalcemia and hypophosphatemia, tHPT is treated either medically with cinacalcet or surgically with a subtotal parathyroidectomy in cases that do not regress. Recent work indicates that surgical correction is slightly superior to cinacalcet at normalizing serum calcium and iPTH levels. Furthermore, from a health care economics perspective, it was calculated that the surgical approach to tHPT management becomes more cost-effective if the duration of cinacalcet therapy were to extend beyond 14 months.

A recent publication studying data collected for the US Renal Data System (USRDS) showed that subtotal parathyroidectomy was associated with significant risk for morbidity and mortality (2% died within 30 days following the procedure). While this analysis was not restricted to patients listed or undergoing evaluation for

transplant listing (whom we envision might fare better), these data should be viewed as cautionary. The pre-transplantation sHPT treatment modality of choice will need to be decided on an individual patient basis, weighing the unique risks and benefits.

Psychosocial/Substance Abuse

The goal of the psychosocial evaluation is to recognize candidates with risks and barriers requiring multidisciplinary interventions, both before and after transplantation. Careful prelisting evaluation of premorbid psychiatric state, past adaptation to stressors and coping skills, history of treatment adherence and medication self-management, substance abuse history, anxiety, depression, health-related quality of life, quality of affect, and levels of daily activities and social support, including community and faith-based support systems, is a necessity. Preexisting psychological disorders have been identified as contributors to poor posttransplantation outcomes, in part due to nonadherence to therapy as well as modification of immunologic and stress responses. Psychiatric evaluation of candidates often requires a referral to subspecialists well versed with the changes in mental health that come with solid-organ transplants. This is of even more importance when evaluating teenagers and young adults to assess the impact of the transplant on their body image.

Neurocognitive health should be assessed both pre- and posttransplantation because common immunosuppressant medications are known to contribute to neurocognitive decline over time. This evaluation may even help guide initial maintenance therapy away from calcineurin inhibitor use.

Substance addiction and abuse is a relative contraindication to kidney transplantation. Often the initial referral to the transplantation center provides the motivation for some patients to seek treatment for their addiction. Transplantation centers work with patients to establish "goals" that the patient needs to meet to be considered for a kidney transplant. Candidacy is not denied, rather put on hold until the patient can demonstrate a sustained change in high-risk behavior.

Retransplantation

For both living and deceased donors, 10-year overall kidney allograft survival has increased compared with a decade earlier. Though this improvement has occurred, progress toward further improving long-term allograft survival appears to have stagnated and remains a significant challenge. Recipients who underwent transplantation in youth and early adulthood should anticipate the likelihood that their allograft will eventually fail and require repeat transplantation or necessitate the need to return to maintenance dialysis. As a consequence, per USRDS data, the percentage of patients returning to the waiting list following failure of a prior allograft is now significant because ~17% of registered candidates have a history of prior kidney transplantation.

Prior transplant recipients returning to the waiting list do not receive priority over first-time registrants. Some recipients are under the false impression that the time they had waited for their first transplant, or a portion of it, will be credited toward their subsequent transplant. While this is incorrect, it is not uncommon for transplant candidates returning to the wait list to have a higher allocation score as a consequence of being sensitized by their prior transplants.

The benefit of failed allograft nephrectomy remains an unresolved issue. Transplantectomy may increase a recipient's calculated panel-reactive antibody level, thereby making it more challenging to identify a match with a future donor. Therefore, the failed allograft should only be removed for the benefit of reducing symptoms attributable to the failed transplant (periallograft pain, hematuria, chronic inflammation, etc). It need not be routinely removed in preparation of repeat transplantation.

Weaning off immunosuppression is similarly an unresolved issue. It comes as no surprise that immunosuppressed patients receiving dialysis are at higher risk for developing infection. This, as well as the increased cumulative long-term risk for malignancy development, favors complete discontinuation of immunosuppression when the allograft has failed. Maintenance of residual GFR and urine production and prevention of allosensitization form the basis for contrasting concerns.

Additional Readings

- ▶ Adeyi OA, Girnita AL, Howe J, et al. Serum analysis after transplant nephrectomy reveals restricted antibody specificity patterns against structurally defined HLA class I mismatches. *Transpl Immunol.* 2005;14(1):53-62.
- ▶ Augustine JJ, Woodside KJ, Padiyar A, Sanchez EQ, Hricik DE, Schulak JA. Independent of nephrectomy, weaning immunosuppression leads to late sensitization after kidney transplant failure. *Transplantation.* 2012;94(7):738-743.
- ▶ Callender GG, Malinowski J, Javid M, et al. Parathyroidectomy prior to kidney transplant decreases graft failure. *Surgery.* 2017;161(1):44-50. ★ **ESSENTIAL READING**
- ▶ Coemans M, Susal C, Dohler B, et al. Analyses of the short- and long-term graft survival after kidney transplantation in Europe between 1986 and 2015. *Kidney Int.* 2018;94(5):964-973.
- ▶ Cruzado JM, Moreno P, Torregrosa JV, et al. A randomized study comparing parathyroidectomy with cinacalcet for treating hypercalcemia in kidney allograft recipients with hyperparathyroidism. *J Am Soc Nephrol.* 2016;27(8):2487-2494. ★ **ESSENTIAL READING**
- ▶ Ishani A, Liu J, Wetmore JB, et al. Clinical outcomes after parathyroidectomy in a nationwide cohort of patients on hemodialysis. *Clin J Am Soc Nephrol.* 2015;10(1):90-97.
- ▶ Konar M, Granoff DM. Eculizumab treatment and impaired opsonophagocytic killing of meningococci by whole blood from immunized adults. *Blood.* 2017;130(7):891-899.
- ▶ Messa P, Regalia A, Alfieri CM, et al. Current indications to parathyroidectomy in CKD patients before and after renal transplantation. *J Nephrol.* 2013;26(6):1025-1032.
- ▶ Sheu A, Depczynski B, O'Sullivan AJ, Luxton G, Mangos G. The effect of different glycaemic states on renal transplant outcomes. *J Diabetes Res.* 2016;2016:8735782.

Living Donor Candidates

Case, continued: Eager to receive another preemptive kidney transplant and avoid starting on dialysis, Ms Smith has already notified many of her friends and family members that her kidney transplant is slowly failing. She is active on social media and posted a message to share her search for a living donor with people in her community. Through social media, she has shared her blood type and the telephone number for interested people to use to contact the transplantation center. Ms Smith's adult daughter is already interested in being evaluated but was told that she does not have the same blood type as her mother. Ms Smith is blood type O and her daughter is type B.

Question 4: Which of the following statements is correct?

- a) Transplantation centers discourage patients from using social media as part of their search for a living donor.
- b) Though Ms Smith cannot directly receive her daughter's kidney secondary to ABO incompatibility, transplantation through Paired Kidney Exchange ("kidney swap") should be considered.
- c) A living donor recipient who receives a kidney from an unmatched donor is expected to have inferior outcomes compared to waiting on the list for a phenotypically matched deceased donor organ.
- d) Confident that her daughter is a healthy and suitable donor candidate, Ms Smith should discontinue her search for a living donor.

For the answer to the question, see the following text.

Living donor kidney transplants are associated with a higher probability of immediate allograft function. Delayed allograft function is an infrequent occurrence in this setting. Accordingly, recipients overall have a less complex and less complicated posttransplantation course during the early interval. The benefits of a transplantation that occurs under more controlled circumstances, coupled with the improved organ quality derived from a living donor donating while in peak physical condition, contribute to longer allograft survival. Perhaps of ever-increasing value as the waiting list population continues to grow, waiting time is not a consideration for living donor transplantation. Furthermore, a living donor recipient who received a transplant from an unmatched donor is expected to have superior outcomes compared to a prolonged wait on the list for a phenotypically matched deceased donor organ. Acknowledging that some candidates may feel hesitant entertaining living donation, living donor kidney transplants should nonetheless be strongly encouraged for all candidates undergoing evaluation. Every donor-recipient relationship is unique and the reason for this hesitancy is often complex and personal.

Each transplantation program is unique, and some practices may be based on a combination of local

resources, surgical and medical expertise, and comfort and mastery gained from experience with prior recipients. Additionally, kidney transplantation is a field that is continuing to evolve. When social media was in its infancy, most transplantation centers were wary about evaluating and accepting donors found online. This caution was born out of concern the donor might expect more than appreciation and gratitude from the recipient in exchange for the kidney. Furthermore, with the passing of the National Organ Transplantation Act in 1984, the sale of an organ became an illegal practice in the United States. A transplantation center that knowingly allowed a transplantation to occur when there was concern that the organ was exchanged for something of monetary value would be in violation of federal law. Acknowledging that social media is now mainstream has changed how we communicate, and transplantation centers have shifted toward encouraging the use of social media.

Some living donor candidates that would have been declined in the past may now be suitable for donation. The opposite is also true. For example, centers have different levels of comfort in using donors with hypertension that requires multiple antihypertensive drugs to achieve goal blood pressure control. Most transplantation centers have a procedure through which potential donor candidates are prescreened either over the telephone or through an internet-based questionnaire. The general nephrologist is discouraged from determining a living donor candidate's eligibility without transplantation center involvement.

Patients encounter friends, family members, and acquaintances who express varying degrees of interest in being evaluated as a living donor. When these conversations occur, the pair frequently discloses their respective blood types in an attempt to determine their organ compatibility. While this discussion is well intentioned, it may leave the potential living donor with the incorrect impression that they are not an acceptable match. This is because many individuals who believe they know their blood type are either wrong or are unaware that blood types need only to be compatible rather than identical for transplantation or both. Paired living donor kidney exchange, a program through which incompatible donor and recipient pairs are jointly entered into a "swap," can lead to a successful transplant for otherwise incompatible pairs. This opportunity can only be seized upon if the living donor candidate engages with the transplantation center. For these reasons, it is advisable that all recipient candidates ask interested potential donors to contact the transplantation center for additional information rather than attempt to determine a donor's suitability on their own.

Though Ms Smith is blood type incompatible with her daughter, her daughter can donate to her through paired kidney exchange. Thus, the correct answer is (b).

Closing Thoughts

The general nephrologist plays a key role in the evaluation of patients for kidney transplantation. Although the decision to list and perform transplantation on a potential recipient ultimately lies with the transplantation center, the general nephrologist is often the provider who encourages suitable candidates to present for evaluation. Moreover, given their close relationship with their patients, general nephrologists help interpret, clarify, and explain the significance of findings discovered during the evaluation process, particularly when the candidate has been deemed unsuitable to proceed.

It is our hope that the information conveyed through this review provides the general nephrologist with better understanding of how potential candidates are evaluated by the transplantation center. While we broadly discuss the evaluation processes and practices followed at most transplantation centers, we acknowledge that each transplantation program differs in its approach and requirements. General nephrologists would do well to familiarize themselves with the specific criteria adopted by the centers to which they refer their patients. Collaboration and communication between general nephrologists and transplantation centers promote both timely referral of candidates and keep the general nephrologist abreast of local practices. The collective goal should be to identify suitable candidates, ensure timely referral, facilitate evaluation, and successfully perform transplantation on patients for whom this may be an appropriate therapy.

Article Information

Authors' Full Names and Academic Degrees: Sarthak Virmani, MBBS, and William S. Asch, MD, PhD.

Authors' Affiliations: Section of Nephrology, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT (WSA).

Address for Correspondence: William S. Asch, MD, PhD, Section of Nephrology, Department of Internal Medicine, Yale University School of Medicine, 330 Cedar St, New Haven, CT 06520-8029. E-mail: william.asch@yale.edu

Support: None.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Peer Review: Received September 23, 2019, in response to an invitation from the journal. Evaluated by 3 external peer reviewers and a member of the Feature Advisory Board, with direct editorial input from the Feature Editor and a Deputy Editor. Accepted in revised form January 18, 2020.