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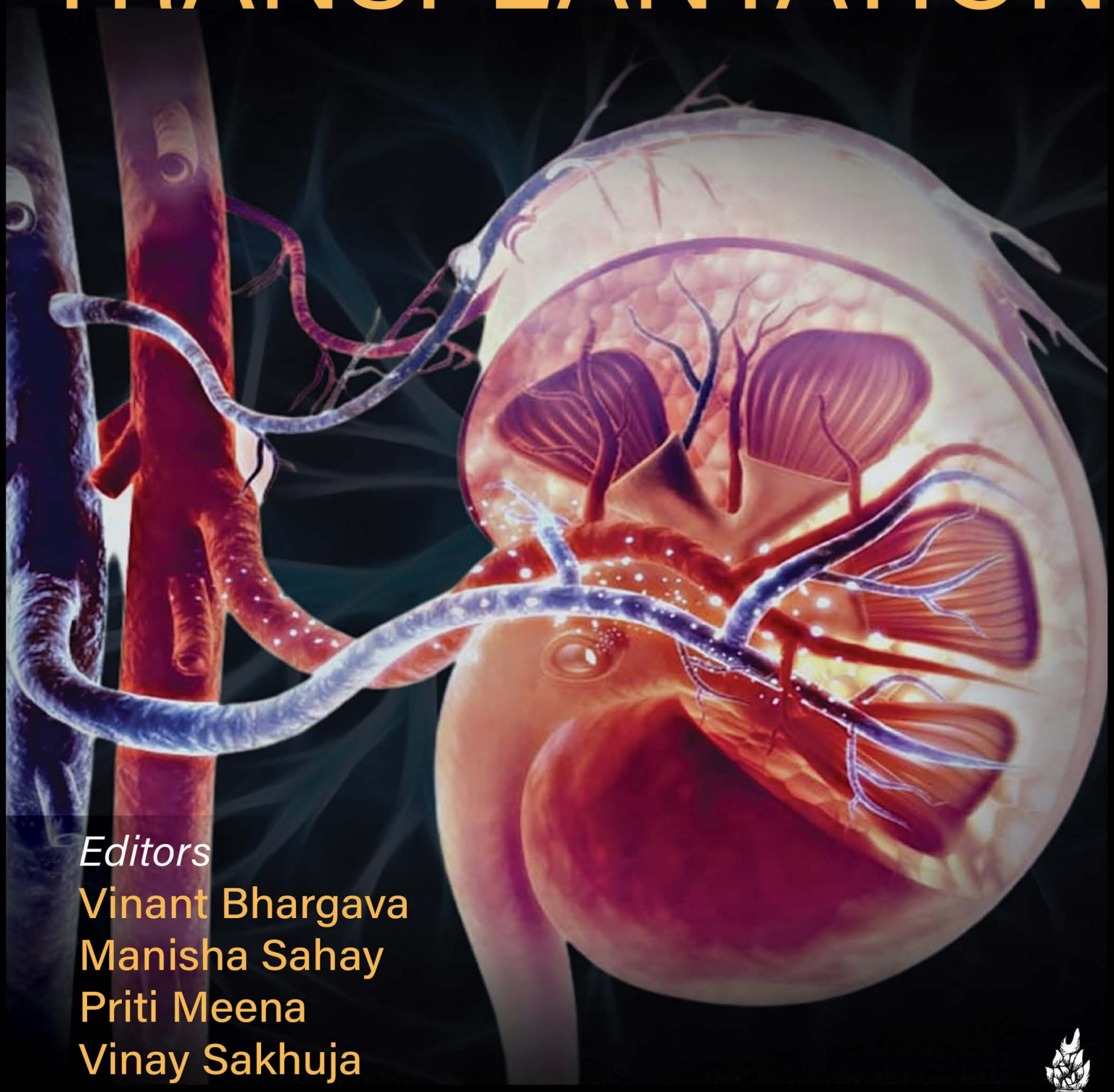
TEXTBOOK OF KIDNEY TRANSPLANTATION



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JAYPEE

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CHAPTER 2

Evaluation of Living Kidney Donors

Ajit S Narula, Mastakim A Mazumder

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CASE VIGNETTE 1

A 45-year-old male kidney donor on urinalysis was found to have three to five red blood cells per high-power field (RBC/HPF) on more than two occasions. There was no albuminuria and the estimated glomerular filtration rate (eGFR) was normal. Urological assessment and a kidney biopsy were done. Would he make a suitable kidney donor?

Microscopic hematuria is typically defined as presence of more than two to five RBC/HPF of urinary sediment on two to three separate occasions unrelated to exercise, trauma, sexual activity, or menstruation. To assess the suitability of such kidney donors, it is recommended to do a urine culture to assess for infection. Cystoscopy and imaging should be done to look for nephrolithiasis or urinary tract malignancy. A 24-hour urine stone panel to assess for high-risk stone formers, and a kidney biopsy to look for glomerular diseases. Donors with microscopic hematuria which resolves after treatment of urinary infection or those with thin basement membrane disease on a kidney biopsy may be accepted as kidney donors.

CASE VIGNETTE 2

A 27-year-old woman wishes to donate a kidney to her brother. In an earlier pregnancy, she has history of preeclampsia. Her blood pressure now is 120/70 mm Hg, eGFR 100 mL/1.73 m^2 body surface area (BSA), and albuminuria is undetected. In the future, she plans to have a second child. Can she be accepted as a kidney donor?

In women donors in the reproductive age groups, prior hypertensive disorders of pregnancy or the desire for future pregnancies should be enquired. Women with a prior hypertensive disorder of pregnancy may be acceptable for donation if their otherwise long-term postdonation risks are acceptable. Early small studies did not identify any increased risk of pregnancy complications in women after donation. However, in subsequent larger series, an increased risk of gestational hypertension and preeclampsia has been reported after kidney donation. To reduce the risk of complications in postdonation pregnancies, several dietary and lifestyle interventions including interventions to reduce or prevent obesity have the potential to reduce the risk of preeclampsia.

INTRODUCTION

Recent publications have described the long-term medical risks of kidney donors. In order to properly select donors who are at minimal risk of developing future kidney disease or other medical complications, numeric thresholds of various risk parameters have been suggested. The risks due to a specific abnormal parameter should be assessed in the context of other potential risk factors and not in isolation. In this chapter, we review the evaluation of the living kidney donors and various risk factors[1] for a living kidney donation **(Table 1)**. The contraindications to living kidney donation[2,3] are given in **Box 1**, and the usual kidney-specific, history, examination, and laboratory investigations are given in **Table 2**.

TABLE 1: Risk factors for living kidney donation.

Diabetes mellitus	HbA1c ≥6.5%, fasting plasma glucose ≥126 mg/dL, random plasma glucose of ≥200 mg/dL, plasma glucose concentration ≥200 mg/dL 2 hours after a 75-g anhydrous glucose load in an oral glucose tolerance test
Prediabetes	Fasting plasma glucose of 110–125 mg/dL and 1-hour post 75-g anhydrous glucose load, a plasma glucose of 140–199 mg/dL
Hypertension	BP ≥140/90 mm Hg on at least two occasions or mean ABPM or home measurements of SBP of 135 mm Hg or greater or DBP of 85 mm Hg or greater or history of hypertensive medications
Persistent hematuria	>2–5 red blood cells per high-power field of urinary sediment on 2–3 separate occasions
Pyuria	Presence of 10 or more white cells/mm^3 in an unspun urine specimen or three or more white cells per high-power field of unspun urine
BMI	A measure of weight scaled for height, as: • Underweight (<18.5 kg/m^2) • Normal weight (18.5–24.9 kg/m^2) • Overweight (25–29 kg/m^2) • Obese (30–34.9 kg/m^2); morbidly obese (>35 kg/m^2)

(ABPM: ambulatory blood pressure monitoring; BMI: body mass index; BP: blood pressure; DBP: diastolic blood pressure; HbA1c: hemoglobin A1c; SBP: systolic blood pressure)

BOX 1: Contraindications for living kidney donation.

- Age <18 years
- Uncontrolled hypertension or hypertension with end-organ damage
- BMI ≥35 kg/m^2 (Relative)
- Active malignancy,* active infection
- High-risk kidney stone formers
- Untreated psychiatric conditions
- Albuminuria >100 mg/g creatinine, glomerular pathology†
- GFR less than accepted threshold
- Bilateral renal artery atherosclerosis or fibromuscular dysplasia involving the orifices of both renal arteries
- Donor coercion, unable to give consent

*Cancers with low risk of transmission may be considered.
†Thin basement membrane nephropathy is acceptable.
(BMI: body mass index; GFR: glomerular filtration rate)

TABLE 2: Evaluation of living kidney donors.

History	• Hypertension, diabetes, kidney stones • Proteinuria, hematuria • Recurrent urinary tract infections • Cancers • Family history of kidney diseases
Examination	• Blood pressure-two readings and if high normal or if >140/90 mm Hg, then AMBP monitoring • BMI • Psychosocial evaluation by a psychiatrist
Laboratory investigations	• eGFR, confirmed by mGFR or 24-hour creatinine clearance • Spot albumin/creatinine ratio, confirmed with AER • Urinalysis and culture • Fasting glucose, HbA1c and/or oral GTT if high risk • Serological/molecular tests for hepatitis B and C, HIV, CMV • EB virus, COVID-19 • 24-hour urine calcium, oxalate, uric acid, citrate, creatinine, sodium in those with present/history of kidney stones • Pregnancy test (if indicated) • Complete blood count and coagulation profile, electrolytes, and liver function tests • Cancer screening as for general population • Echocardiography, stress test if indicated
Radiology investigations	• Confirm Kidney size, asymmetry, masses/cysts/stones, hydronephrosis • Isotope kidney scans • Anatomy of renal arteries and veins • Patency of iliofemoral vessels
Compatibility tests	• ABO blood grouping • HLA testing and crossmatch for anti-HLA antibodies

(AER: albumin excretion rate; BMI: body mass index; CMV: cytomegalovirus; EB: Epstein–Barr; eGFR: estimated glomerular filtration rate; GTT: glucose tolerance test; HbA1c: hemoglobin A1c; HIV: human immunodeficiency virus; HLA: human leukocyte antigen; mGFR: measured glomerular filtration rate)

INFORMED CONSENT

A psychiatric evaluation is recommended to confirm that the donor has the mental capacity to provide informed consent for evaluation and organ donation. The components of informed consent include information on the process of evaluation, the short- and long-term risks of organ donation, and the freedom to withdraw consent at any stage of the evaluation.[4]

AGE

The lower age limit of 18 years for living kidney donation is the age accepted for giving a legally valid consent. No upper age limit has been defined. Many centers are accepting donors over the age of 60 years and even 70 years on a case-by-case basis. Rather than the chronological age, donor glomerular filtration rate (GFR) and other coexisting medical conditions are important determinants for accepting kidney donors. Young potential donors with borderline risk factors are at relatively higher risk for developing medical complications or end-stage kidney disease (ESKD) in the long term, when compared to older donors with the same abnormality. For example, unlike in young donors, older donors with impaired glucose tolerance may not have enough years in their life to progress to diabetes or ESKD. Studies looking at perioperative outcomes such as operative time, blood loss, and hospital length of stay have reported similar outcomes in selected elderly donors when compared to younger donors.[5-8]

GLOMERULAR FILTRATION RATE

Glomerular filtration rate can be calculated by using estimating equations (eGFR), creatinine clearances (CrCl), or measured by exogenous filtration markers such as iohexol/chromium 51-labeled ethylenediaminetetraacetic isotopes (^{51}CrEDTA).[9] Measured GFR (mGFR) most closely reflects the true GFR. 24-hour urine creatinine clearance as a measure of GFR tends to overestimate it by 10–20%.[2] eGFR using creatinine, cystatin, or both is not an accurate measure of GFR but is often used as the first step in estimating GFR because of the ease of use, followed by confirmatory test using CrCl or mGFR. To reduce interpatient variability and facilitate donor selection, GFRs are expressed standardized to BSA of 1.73 m^2.[9] The differential kidney function is determined by technetium-99m dimercaptosuccinic acid (^{99m}TcDMSA) scanning.[10] The evaluation of GFR in living kidney donors is given in **Table 3**.[9] In cases where there is an asymmetry in GFR, parenchymal abnormalities, vascular abnormalities, or urological abnormalities, which do not preclude donation, the more severely affected kidney should be used for transplantation.[10]

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TABLE 3: Guideline recommendations for glomerular filtration rate (GFR) assessment in living kidney donor candidates.

Guideline	*GFR*	*GFR-based criteria*
British Transplantation Society (2018)[10]	mGFR in everyone after initial screening using eGFR	Provides age- and sex-specific GFR criteria
KDIGO (2017)[1]	eGFR, followed by confirmation with mGFR, CrCl	Donor candidates with GFR ≥90 mL/min/1.73 m^2 should be considered acceptable, and those with GFR ≤60 mL/min/1.73 m^2 should be excluded. Decision to approve donor candidates with GFR 60–89 mL/min/1.73 m^2 should be individualized on the basis of demographic and health profile in relation to the transplant program's acceptable risk threshold
OPTN (2021)[48]	mGFR or 24-hour CrCl	No specific recommendations provided
Canadian KPD Protocol (2015)[49]	GFR on two separate occasions, followed by 24-hour CrCl on two separate occasions or mGFR	Provides age-specific criteria
ERBP (2013)[11]	eGFR; mGFR when more exact knowledge of GFR is needed or where there is doubt regarding the accuracy of eGFR	Recommends age-dependent GFR cut-offs such that the GFR of the remaining kidney will be 37.5 mL/min/1.73 m^2 at the time the donor reaches the age of 80 years
CARI (2010)[50]	eGFR, at least on two separate occasions or CrCl; mGFR if there is doubt regarding the accuracy or eGFR or CrCl	Recommends against accepting kidneys from donors with GFR <80 mL/min/1.73 m^2
Amsterdam forum (2005)[51]	eGFR or CrCl; mGFR may be used in patients with borderline GFR determination	• GFR <80 mL/min/1.73 m^2 or body surface area-adjusted GFR, 2 SD below normal on the basis of age and sex generally preclude donation • Additionally noted successful transplantation from some, usually elderly living donors with GFR as low as 65–70 mL/min/1.73 m^2 indicating a need for individualization in donors with GFR <80 mL/min/1.73 m^2

(CrCl: creatinine clearance; eGFR: estimated glomerular filtration rate; mGFR: measured glomerular filtration rate; SD: standard deviation)
Source: With permission from Garg N, Poggio ED, Mandelbrot D. Evaluation of kidney function in living kidney donor candidates. Kidney360. 2021;2:1523-30.

URINARY ABNORMALITIES: ALBUMINURIA/ MICROSCOPIC HEMATURIA/PYURIA

Albuminuria is a sign of an underlying kidney disease. The initial screening is performed using a spot urine albumin-to-creatinine ratio and confirmed by either using albumin excretion rate (AER) expressed as mg/day or albumin creatinine ratio (ACR) expressed as mg/g in a timed urine specimen. The acceptable threshold of AER for kidney donation is <30 mg/day or ACR of 30 mg/g of creatinine. AER >100 mg/day or ACR >100 mg/g is a contraindication to donation. Orthostatic albuminuria and transient exercise-induced albuminuria are benign conditions and do not preclude a donation.[1,3] For albuminuria in the range of 30–100 mg/day, the decision to accept a donor is based on age, GFR, and other risk factors.[1,11]

Persistent hematuria indicates a kidney or a urological disease. A urine culture, urine cytology, and renal imaging are done routinely. Cystoscopy is indicated in patients aged 35 years or older to exclude urinary tract malignancy.[12] Donors with uroepithelial malignancy are unfit for donation. In the absence of an identified cause, for the urinary abnormality, a kidney biopsy is advised. Donors with thin basement membrane nephropathy may be accepted as kidney donors.[13]

Donors with pyuria due to urinary tract infection, which has been treated, are acceptable while those with sterile pyuria need further investigations.[14]

DIABETES MELLITUS/PREDIABETES

Donors with diabetes mellitus are commonly excluded from living donation. In prediabetes, there is a risk of progression to diabetes and there are conflicting recommendations for accepting prediabetics as kidney donors. This is due to low-quality evidence examining new-onset proteinuria, hypertension, rate of decline of GFR, and end-stage renal disease (ESRD) between donors with and without prediabetes.[1] The risk of developing diabetes and subsequent renal impairment in a young potential kidney donor with prediabetes may not be acceptable, but elderly prediabetic donors who may not develop diabetes during their lifetime may be accepted as kidney donors.[10]

OBESITY

Obesity is considered a relative contraindication to living kidney donation because of the increased risk of surgical complications and the adverse impact of obesity on renal function in the longer term. Multiple guidelines recommend body mass index (BMI) >35 kg/m^2 as an absolute

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or relative contraindication to donation. In donors with BMI >30 kg/m^2, a careful evaluation of other comorbidities is recommended.[1,15,16]

HYPERTENSION

Hypertension contributes to causation of chronic kidney disease (CKD). GFR reduction from kidney donation may accelerate the risk or progression of hypertension over time to a greater extent than expected from normal aging. Ambulatory blood pressure monitoring or home monitoring is recommended to exclude white coat or masked hypertension. If blood pressure is not controlled to <140/90 mm Hg on one or two antihypertensive drugs or there is evidence of end-organ damage (retinopathy, left ventricular hypertrophy, proteinuria, and previous cardiovascular disease) or there is an unacceptable risk of lifetime incidence of ESRD, then donors are excluded from donation.[10,17-20]

KIDNEY STONES

Kidney stones are a common cause of CKD. However, a current small single stone <1.5 cm may be acceptable in a donor. A kidney donation is not accepted in the presence of an uncorrectable metabolic cause for kidney stones (cystinosis or hyperoxaluria), in presence of struvite stones, bilateral kidney stones, multiple stones, nephrocalcinosis, and from those who have a high risk of recurrence of kidney stones (age <40 years, recurrent kidney stones in past and a family history of kidney stones).[21] In accepted donors, it is preferable to remove the kidney containing the stone. If the stone is very small, it may be left in situ or may be removed, ex vivo, by uretero-nephroscopy before implanting the donor's kidney.[22]

HEREDITARY RENAL DISEASES

The possibility of inherited kidney disease or a genetic predisposition should be suspected in every kidney donor with a positive family history of kidney disease. However, a negative family history does not exclude a hereditary renal disease.[13] With the exception of autosomal dominant polycystic kidney disease (ADPKD), most familial renal diseases are rare in a transplant program.

Donors with ADPKD should not donate, but donors with a family history of ADPKD in a first-degree relative may be acceptable for donation if they meet age-specific imaging or genetic testing criteria that reliably exclude ADPKD. Age-dependent ultrasound criteria for diagnosis and disease exclusion have been established for at-risk adults with unknown ADPKD gene type. In the absence of any cyst or with one cyst, ultrasound has a negative predictive value (NPV) of 100% in patients aged older than 40 years, but only 96% for younger kidney donors.[23,24] Using a total of >10 cysts as a test criterion in subjects younger than 30 years of age, an MRI provides a sensitivity and specificity of 100% in excluding ADPKD.[25] Gene testing can also sometimes help to diagnose or exclude ADPKD.[26]

ALPORT SYNDROME

Alport syndrome in majority is inherited as an X-linked trait. Most heterozygote Alport women will have microscopic hematuria and are at low risk to progress to kidney failure, though ESKD has been reported. In males, urinary abnormalities appear in childhood with progression to kidney failure in adulthood. The outcome after kidney donation is uncertain in Alport women, and it is recommended to use alternative kidney donors. In a small series of women Alport donors, new-onset hypertension, proteinuria, and reduced renal function during a follow-up period of 2–14 years were reported. An X-linked heterozygous Alport mother over 45 years of age who has no clinical manifestation of the disease may be considered a kidney donor as a rare event.[27,28]

APOLIPOPROTEIN L1 RISK ALLELES

Individuals of African ancestry carrying both the risk alleles of the apolipoprotein L1 (*APOL1*) gene are associated with focal segmental glomerulosclerosis, HIV-associated nephropathy, CKD, and adverse donor and recipient outcomes after living kidney donation. However, the precise risk for kidney failure in an affected individual after kidney donation is unknown. Given the potential impact of *APOL1* variants on the safety of living kidney donation, the American Society Transplant Expert Group opined that all African–American living donors should be informed about the associations of *APOL1* risk alleles.[29-31]

MALIGNANCY

In donors with history of treated cancers, there is a risk of recurrence of cancers and transmission of latent cancers. The Ad Hoc Disease Transmission Advisory Committee (DTAC) of the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) has categorized six levels of risk for donor cancer transmission to the recipient.[32] Donors with active or treated cancers with less than minimal (0–0.1%) lifetime risks of recurrence or transmission (basal cell carcinoma skin, squamous cell carcinoma skin, resected renal cell carcinoma <1 cm, in situ cervical carcinoma, vocal cord carcinoma, solitary papillary thyroid carcinoma ≤0.5 cm, minimally invasive follicular carcinoma thyroid ≤1.0 cm) may be accepted for donation.[1]

RENAL CYSTS

A common finding in donors of increasing age is kidney cysts. A small simple single (Bosniak I) cyst is acceptable for kidney donation. Donation of a kidney with a Bosniak II renal cyst should proceed only after assessment to exclude a cystic renal cell carcinoma. A kidney with high-grade Bosniak renal cysts (III or higher) or small (T1a) renal cell

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carcinoma which can be resected prior to implantation may be acceptable on a case-by-case basis.[33]

INFECTIONS

Screening for latent infections in the donor minimizes the risk of transmitting infections to the recipient. Kidney donors are usually screened for tuberculosis, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), cytomegalovirus (CMV), Epstein–Barr virus (EBV), and lately for COVID-19 infections.

In endemic areas, there are no reliable methods to diagnose latent tuberculous infection. The tuberculin skin test and interferon gamma release assay are of limited use.[34] Screening for latent tuberculosis is limited to a medical history and X-ray/computed tomography (CT) scan of chest.

According to the regional epidemiology and individual-based history, donor candidates should undergo testing for strongyloidiasis, *Trypanosoma cruzi*, West Nile virus, histoplasmosis, and/or coccidioidomycosis. To screen donor candidates for emerging infections, transplant program centers should develop their own protocols.

Screening of HIV, HBV, and HCV should ideally be performed within 28 days of donation.

In all donor candidates, testing for immunoglobulin G (IgG) hepatitis B core antibody (anti-HBcAb) and hepatitis B surface antigen (HBsAg) should be done. HBV deoxyribonucleic acid (DNA) nucleic acid testing (NAT) can be performed in donor candidates from HBV endemic areas with anti-HBcAb+, suspected to have possible mutant HBV infections, with abnormal liver function tests or have a past history of liver disease of unknown etiology. Transplantation of kidneys from HBsAg+ donors with active viral replication is contraindicated[35] and so also transplanting kidneys from HBsAg+ donors into nonvaccinated HBV-naive recipients.[1,10,36] The proposed management for several types of donor and recipient pairs according to the results of HBV serology tests is shown in **Flowchart 1**. The presence of HBV-DNA positivity increases the risk of transmission in immunized recipients.[35] (Read Chapter 12.2.4 for details.)

Hepatitis C virus testing involves testing for anti-HCV antibody and HCV-RNA.[37] With the advent of new direct-acting antiviral drugs, donation from anti-HCV+ donors is no longer considered a contraindication irrespective of the recipient HCV status. (Read Chapter 12.2.3 for details.)

All donor candidates (living or deceased) should be screened for HIV by testing antibodies to HIV [i.e., anti-HIV 1/2 Ab or HIV antigen/antibody (Ag/Ab) combination assay]. (Read Chapter 12.2.5 for details.)

The other common latent/past infections screened in the donor–recipient pair are CMV and EBV infections.[38] (Read Chapters 12.2.1 and 12.2.6 for details.)

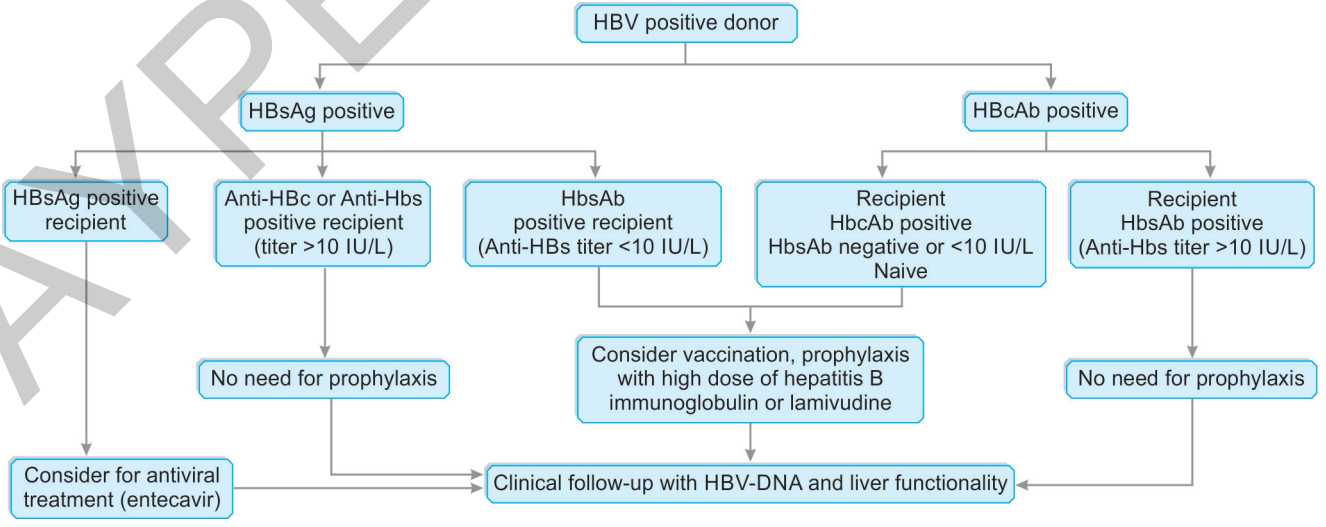
PREGNANCY RISKS

Women should not be excluded from donation solely because they desire to conceive children after donation. They need to be counseled about the risk of gestational hypertension or preeclampsia and on how to reduce the risk of complications in future pregnancies by maintaining a healthy prepregnancy weight.[39]

LIVING MARGINAL DONORS

To meet the shortage of organs the selection criteria for living donors have been widened to include the use of marginal donors (MDs) who would have otherwise been unsuitable to donate. While a clear definition of living marginal donors

Flowchart 1: Proposed management of HBV donor and recipient pairs.



(DNA: deoxyribonucleic acid; HBcAb: hepatitis B core antibody; HBsAb: hepatitis B antibody; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus)

Source: With permission from Massimiliano V, Vincenzo A, Daniela C, Giaquinta A, Ekser B, Sinagra N, et al. Kidney transplantation from donors with hepatitis B. Med Sci Monit. 2016;22:1427-4.

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also known as Expanded Criteria Living Donors (ECLDs)[40] is lacking, donors are generally of older age, have diabetes, hypertension, microalbuminuria, nephrolithiasis, border line eGFRs, and kidney cysts. The functioning grafts from marginal donors appears comparable to that of grafts from standard deceased donors, but inferior to that of standard living donors. The concerns regarding the use of these organs are related more to the potential harm to the donor rather than the quality of the graft.[41,42]

There is limited data on living kidney donors older than 70 years, but it is shown that donor nephrectomy is safe and postdonation survival and recovery is similar to that of younger donors. In accepting marginal donors rather than actual age itself, the presence of other comorbidities determines whether an older living kidney donor should be accepted. Impaired kidney function may be considered more acceptable for older donors than for younger ones because of shorter life expectancy. Rather than a single comorbidity like hypertension or high normal albuminuria, the combination of both increases the postdonation risk of impaired kidney function.[40]

Decisions on how to approach potential marginal donors are complicated by the lack of postdonation long-term follow-up studies hence the choice to accept a marginal donor often becomes subjective.

OUTCOMES IN THE LIVING KIDNEY DONOR

In living kidney donation, there are risks related to the surgery and long-term health risk related to the development of hypertension, proteinuria, and preeclampsia in women donors.

An annual check of blood pressure, albuminuria, serum creatinine with eGFR estimates, and BMI measurements is recommended.[1]

The reduction in renal mass increases the risk of kidney failure in donors when compared to the nondonor population with similar demographic and risk factors. This risk is nonlinear with younger donors at a higher lifetime risk of developing kidney failure. In an analysis, the 15-year kidney failure risk was 30.8 per 10,000 donors whereas it was 3.9 per 10,000 in their matched healthy nondonors.[43] The risk is higher in subgroups with hypertension, diabetes, obesity, moderate albuminuria, lower eGFRs, and history of smoking.[44] Risk prediction tools that combine the effects of demographic and health factors are available at www.transplantmodels.com. To improve the kidney risk stratification, genetic markers are being incorporated.

Surgical complications are reported in 6–29% donors, with <3% experiencing a major complication.[45,46] The risk of death within 90 days of donation is reported at 0.03%.[47] The most common causes of death after living donation are pulmonary emboli, hepatitis, and cardiac events.[10] In an Indian study using the Kocak-modified Clavien–Dindo system to grade and report the severity of complications in 1,430 patients who had undergone live donor nephrectomy, the overall complication rate was 8.6% with 0.06% mortality rate.[43]

To summarize, living kidney donation may increase the risk to donors for some adverse outcomes. Understanding the acceptable thresholds of these risks and taking care of the living donors are important for donor safety and the success of a transplant program.

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