A Report of the Amsterdam Forum On the Care of the Live Kidney Donor: Data and Medical Guidelines

Kidney transplant physicians and surgeons met in Amsterdam, The Netherlands, from April 1–4, 2004 for the International Forum on the Care of the Live Kidney Donor. Forum participants included over 100 experts and leaders in transplantation representing more than 40 countries from around the world, including participants from the following continents: Africa, Asia, Australia, Europe, North America, and South America.

(*Transplantation* 2005;79: S53–S66)

The objective of the Forum was to develop an international standard of care with a position statement of The Transplantation Society regarding the responsibility of the community for the live kidney donor. The position statement was adopted by the Council of The Transplantation Society (*1*).

The Mission of the Amsterdam Forum

Abdallah Daar presented the mission statement of the Amsterdam Forum emphasizing the concern of the participants for the welfare of the live donor. Specific objectives of the Forum included the development of an international standard of care for the live donor; the development of a position statement regarding the responsibility of the transplant community for the live kidney donor; and the forging of an alliance with the World Health Organization (WHO) to implement these standards. The intent of the Forum leaders was for conference participants to become subsequent emissaries of these standards within their geographical sphere of influence around the world.

Alliance with the World Health Organization

Carl Groth and Luc Noël provided a background report regarding the involvement of The Transplantation Society with WHO, and the role of the Amsterdam Forum as a continuum of the Madrid WHO conference on organ donation and transplantation in October 2003.

Preamble

This report of the Amsterdam Forum is derived from an international experience of participants and also from evidence-based recommendations; it is not a document of mandatory regulation. Medical judgment as a reflection of published data and physician experience influences the decision to accept (or not) an individual as a live kidney donor.

What Is Known Regarding the Sentinel Events of Live Kidney Donors

Forum participants were charged with outlining what is known—and not known—about the sentinel events regarding living donors in the current era (death, dialysis, and need for a kidney transplant), and developing recommendations for the collection of data to improve the care of potential and actual living donors.

Ahad Ghods and Nasser Simforoosh presented the Iranian experience with live donor outcomes (*2*). As of 2003, a total of 15,948 renal transplants have been performed in Iran (12,504 living unrelated, 3,049 living related, and 395 deceased donor transplants). With over 15,000 live kidney donors in Iran, the perioperative mortality rate of live kidney donation was 3 in 15,000 (0.02%).

Ingela Fehrman-Ekholm and Jonas Wadström presented data of the Swedish Registry. With more than 20 years of follow-up, 85% of over 400 kidney donors were alive, whereas the expected survival rate was 66% (*3*, *4*). Survival was 29% better in the donor group than in the comparative cohort.

Arthur Matas submitted data from a survey of 171 United States kidney transplant centers to determine current living donor morbidity and mortality for open nephrectomy, hand-assisted laparoscopic nephrectomy (LN), and non-hand-assisted LN (*5*). Between January 1, 1999 and July 1, 2001, these centers carried out 10,828 living donor nephrectomies: 52.3% open, 20.7% hand-assisted LN, and 27% non-hand-assisted LN. Two donors (0.02%) died from surgical complications and one is in a persistent vegetative state (all after LN). Reoperation was necessary in 22 (0.4%) open, 23 (1.0%) hand-assisted LN, and 21 (0.9%) non-hand-assisted LN cases ($P=0.001$). Complications not requiring reoperation were reported for 19 (0.3%) open, 22 (1.0%) hand-assisted LN, and 24 (0.8%) non-hand-assisted LN cases ($P=0.02$). Readmission rate was higher for LN (1.6%) versus open (0.6%) donors ($P<0.001$), almost entirely as a result of an increase in gastrointestinal complications in LN donors.

Long-Term Complications of Donors

Ingela Fehrman-Ekholm and Jonas Wadström reported upon the glomerular filtration rate (GFR) and the prevalence of hypertension as compared with age- and gender-expected values. In their series of over 400 donors, no accelerated loss of kidney function was observed in live donors who had normal renal function at the time of nephrectomy (*4*). However, there was deterioration in the renal function of donors with increasing age, similar to what is seen among normal healthy subjects. The average glomerular filtration rate in donors aged 75 years and over was 48 ml/min/1.73 m2. A GFR $<$ 30 ml/min was found in five donors. However, three donors developed renal disease, and one was on dialysis treatment. In two of these cases, hereditary factors were possibly involved.

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There was no increase in age-specific prevalence of hypertension for female kidney donors. However, one-third of the donors (aged 46–91 years) who had donated more than 20 years ago had hypertension; but the age-adjusted prevalence of hypertension among donors was not higher than in the general population. Significant proteinuria (≥1.0 g/L) was found in 3% and slight proteinuria (<1.0 g/L) in 9% of the donors. Proteinuria was associated with hypertension and a lower GFR.

Pregnancy after Live Kidney Donation

Annika Tibell and Anders Hartmann concluded that donor nephrectomy is not detrimental to the prenatal course or outcome of future pregnancies. There are no data to suggest that hyperfiltration associated with the combination of unilateral nephrectomy and pregnancy leads to significant hypertension, proteinuria, change in glomerular filtration rate, or abnormalities of the urinary sediment (*6*, *7*). It was recommended, however, to delay pregnancy until at least 2 months after nephrectomy to assess renal compensation prior to conception with evaluation including blood pressure, GFR, and assessment for microalbuminuria. The emphasis was to verify that postpartum renal function is normal.

Donors Needing Transplants

A total of 56 previous living donors were identified in the database of the United Network for Organ Sharing (UNOS) as having been subsequently listed for deceased donor kidney transplantation, with more than 50,000 live kidney transplants performed since 1987. Of the previous kidney donors, 43 received transplants and 36 had functioning grafts at the time of the published report (*8*). One patient died after transplantation; two candidates died while waiting on the list. At the time of the donation, the donors ranged in age from 17 to 61, with an average age of 31. The time from donation to listing ranged from 2 to 32 years, with a mean and median of 15 years. At listing, 40% had a diagnosis of hypertensive nephrosclerosis. An additional 17% were listed with focal glomerulosclerosis, and 13% with chronic glomerulonephritis.

Bob Metzger brought to attention a current UNOS policy for live kidney donors that assigns an allocation priority for a deceased donor kidney if the previous live kidney donor subsequently become a candidate for a kidney transplant later in life. However, there was no consensus to develop such a policy internationally. Stephen Munn reported that the New Zealand community has no facility in its cadaver organ allocation system for any such priority provision that was not of medical benefit to the list as a whole. Further, 20% of the live donors in New Zealand are from other countries, some of which have no end-stage renal program. Thus, such an allocation priority for previous donors is not feasible to implement internationally.

Fifty Years of Live Kidney Donation

Fifty years have elapsed since the first successful kidney transplant from a live donor and a substantial body of published evidence indicates that there is little long-term medical risk to a healthy donor after unilateral nephrectomy. Gil Thiel brought to attention, however, the potential of underreporting donor complications because of the hesitation of the transplant physicians to reveal them either to the hospital center, future donors, or insurance carriers.

Eduardo Santiago-Delpín stressed the responsibility of transplant centers to assure donor protection, safety, and welfare. Forum participants agreed that prior to donation, the live kidney donor must receive a complete medical and psychosocial evaluation, receive appropriate informed consent, and be capable of understanding the information presented in that process to make a voluntary decision. All donors should have standard tests performed to assure donor safety (*1*). These include blood and urine screening tests, chest X ray, electrocardiogram, cardiac stress test, radiographic assessment of the kidneys and vessels. A complete listing of tests is appended by Andrew Bradley. Human leukocyte antigen (HLA) typing can be useful to determine an HLA identical sibling; otherwise it is not seemingly vital to a successful outcome (*9*). Forum participants discussed the evaluation of various medical issues in the potential donor, such as donor hypertension, body mass index, dyslipidemia, renal function, malignancy, and a history or current presence of infectious diseases such as tuberculosis or hepatitis.

As in the general population, based upon age and other medical risk factors (e.g., hypertension, proteinuria, hyperlipidemia, impaired glucose tolerance test), kidney donors should undergo regular long-term follow-up of body weight, blood pressure, blood sugar, serum creatinine, and urinalysis. Abnormalities should be treated promptly by either the local medical physician or the transplant nephrologist. Long-term collaborative prospective studies and comprehensive national registries should be established to determine whether the incidence of medical risk factors and renal dysfunction is different from the general population.

Donor Hypertension

Hypertension has been considered to be a contraindication in potential renal transplant donors. However, the precise risk to donors who have borderline elevation in blood pressure (BP) and those with a family history of hypertension has not been conclusively determined. Greg Obrador noted that the threshold values for hypertension are different depending on the technique used to measure BP. Ambulatory blood pressure monitoring (ABPM) was reported by Fatma Nurhan Ozdemir to be more accurate than in-office blood pressure measurement (OBPM) in recording true potential donor BP (*10*, *11*).

Gil Thiel reported 18 donors who were hypertensive at the time of nephrectomy. At 7 years following nephrectomy, 10 of the 18 donors were on antihypertensive treatment (five donors with one medication, three donors with two medications, and two donors with three medications). One-third of these 18 donors (hypertensive at donation) were normotensive at 7 years following nephrectomy without any treatment. Thus, hypertension at the time of nephrectomy may have been due to stress conditions before donation. In contrast, among 73 normotensive donors at the time of nephrectomy, only 15 were on antihypertensive treatment (12 donors on one medication, two donors on two medications, and one donor on three medications) at 7 years after nephrectomy. The outcome (renal function) of the 18 donors determined to be hypertensive at nephrectomy was no different than the 75 normotensive donors. At 7 years, the mean estimated creati-

nine clearance for the hypertensive donor group was 71±19 (median 67) ml/min/1.73 m^2, not statistically different for the initially normotensive group 75±17 (median 73) ml/min/1.73 m^2.

Mark Stegall reported upon the recent Mayo Clinic experience. The GFR (as determined by iothalamate clearance corrected for body weight) of 25 hypertensive donors was not statistically different than 150 normotensive donors prior to nephrectomy or at 1 year postdonation (*12*). Blood pressure was easily controlled in hypertensive donors with an angiotensin receptor blocker and diuretics; none had microalbuminuria.

The following consensus guidelines regarding hypertensive donors were adopted following discussion by Greg Obrador, M.K. Mani and Ian Dittmer:

- Patients with a BP >140/90 by ABPM are generally not acceptable as donors.
- BP should preferably be measured by ABPM, particularly among older donors (>50 years) and/or those with high office BP readings.
- Some patients with easily controlled hypertension who meet other defined criteria (e.g., >50 years of age, GFR >80 ml/min, and urinary albumin excretion <30 mg/day) may represent a low-risk group for development of kidney disease after donation and may be acceptable as kidney donors.
- Donors with hypertension should be regularly followed by a physician.

Obesity

Gabriel Danovitch and Jose Morales led the discussion on live obese kidney donors. Obesity was defined by a body mass index (BMI) of > 30 kg/m^2. All potential donors should have BMI determined at initial evaluation. Evaluation should also include other comorbidities associated with obesity such as microalbuminuria, impaired GTT, hypertension, hyperlipidemia, cardiovascular disease, sleep apnea, and liver disease.

Obesity should be considered an increased risk for renal disease; however, there is no data on the outcome of such individuals. Jose Morales commented upon patients who underwent unilateral nephrectomy for reasons other than donation, noting an increased risk for proteinuria and renal insufficiency on long-term follow-up if the BMI was ≥30 (*13*). However, Mark Stegall reported that renal function of more than 100 obese donors (≥30 BMI) after donation was no different from that of nonobese donors. Further, the corrected GFR of obese donors was greater than that of nonobese donors, and the morphology of biopsied obese donor kidneys (particularly glomerular volume) is no different from nonobese donors. The selection criteria for all donors at the Mayo Clinic were the same by a corrected GFR >80 ml/min/BSA; normal urinary protein and albumin secretion, and fasting blood glucose <126 mg/dl (for fasting glucose 100–125, a 2-hour GTT is recommended). Finally, in the Mayo experience, hand-assisted donor nephrectomy is safe in obese donors.

The following consensus guidelines were adopted regarding obesity:

- Patients with a BMI >35 kg/m^2 should be discouraged from donating, especially when other comorbid conditions are present.
- Obese patients should be encouraged to lose weight prior to kidney donation and should be advised not to donate if they have other associated comorbid conditions.
- Obese patients should be informed of both acute and long-term risks, especially when other comorbid conditions are present.
- Healthy lifestyle education should be available to all living donors.

Dyslipidemia

Arturo Dib-Kuri noted that various types of dyslipidemia have been associated with decreased kidney function in the general population and with faster rates of progression in patients who have chronic kidney disease. Dyslipidemia should be included along with other risk factors in donor risk assessment, but dyslipidemia alone does not exclude kidney donation.

Acceptable Donor Renal Function

Robert Gaston and Mario Abbud-Filho led the discussion on the level of renal function that defines an acceptable living kidney donor. Individuals contemplating donor nephrectomy should demonstrate "normal" renal function as determined by assessment of GFR. The definition of "normal" GFR changes with age, as renal function deteriorates over time (*14–16*). Carl Cardella noted a decrease in GFR of approximately 1 ml/min/1.73 m^2 per year after age 40. There is a documented acute decrease in GFR of approximately 30% after unilateral nephrectomy; however, the impact of unilateral nephrectomy on this rate of decline in GFR is unknown.

All potential kidney donors should have GFR estimated. Creatinine based methods may be used to estimate the GFR; however, creatinine clearance (as calculated from 24-hour urine collections) may under- or overestimate GFR in patients with normal or near normal renal function (*17*). Calculated GFR values (Modification of Diet in Renal Disease [MDRD], Cockcroft-Gault) are not standardized in this population and may overestimate GFR. These methods may be replaced or supplemented by isotopic estimation of GFR (e.g., iothalamate, 99-technetium clearances) in cases of borderline GFR determination.

Jaime Herrera-Acosta noted that some might have difficulty in obtaining ^{125}Iothalamate clearance, for which his center substitutes creatinine clearances obtained during mild water diuresis and short-term urine collections to make sure that urine flows were exact. An excellent correlation of creatinine clearance with simultaneous ^{125}Iothalamate clearance was achieved in 46 kidney donors ($r=0.84$, $P<0.0001$).

Acceptable GFR in a donor is that which can be predicted to provide adequate GFR for both donor and recipient after donor nephrectomy/transplantation. Robert Gaston and Mario Abbud-Filho cited reports of the literature that reveal donors with GFR ≤80 ml/min before nephrectomy cannot be reliably expected to provide or maintain optimal function after nephrectomy, although as many as 20% of U.S. transplant centers would accept a creatinine clearance as low as 60 ml/min (*18*, *19*).

Dan Brennan noted that donors who are thin, small, and female with a creatinine clearance of <80 ml/min and normalized for body surface area (BSA) could alternatively be normalized for height and a more accurate GFR can be determined. An average-sized 60-year-old person (70 kg body weight) with a serum creatinine of 1.0 mg/dl can be presumed to have a GFR of 80 ml/min (*20*).

Bernardo Rodríguez-Iturbe commented that if donors are challenged with a creatinine load, they might not normally increase the tubular secretion of creatinine (revealing an impaired tubular functional reserve) (*21*).

The following consensus guideline was adopted regarding acceptable renal function: a GFR <80 ml/minute or 2 standard deviations below normal (based on age, gender, and BSA corrected to 1.73/m^2) generally preclude donation. Kidneys from live donors with GFR ≤80 ml/min are associated with relative risk of graft loss of 2.28 compared to those with greater prenephrectomy GFR (*22*). However, successful transplantation was noted from some, usually elderly, living donors with GFR as low as 65–70 ml/min, indicating a need for individualization and careful follow-up of donors with GFR of <80 ml/min/1.73/m^2.

Urine Analysis for Protein and Blood

The discussion was initiated by M.K. Mani and Yves Vanrenterghem. Proteinuria is a marker of glomerular pathology and renal disease. Proteinuria should be assessed as a standard part of the donor work up. Dipstick urinalysis for proteinuria and hematuria has been used to screen renal disease, but Gil Thiel suggested that dipstick measurements of proteinuria are not adequate in the assessment of a potential donor. Laboratories vary as to normal values of quantitated urine protein, but a consensus was reached to conclude that a 24-hour urine protein of >300 mg is a contraindication to donation.

The significance of microalbuminuria has been studied mostly in patients with diabetes mellitus. However, even in nondiabetics, it may be the first sign of a glomerular pathology. Gil Thiel suggested that kidney donors merit a screening and follow-up with microalbuminuria measurement (*23*). Albumin and protein concentration in urine should be referenced to either a time-collected specimen or to urinary creatinine concentration. A level of 5 mg (u-albumin/mmol u-creatinine) in a morning urine specimen represents approximately 50 mg albumin/24 h urine. M.K. Mani suggested, however, that the assessment of microalbuminuria is more expensive to perform and has not been well established in all parts of the world. A concern regarding laboratory consistency and accuracy was expressed.

Thus, Forum participants concluded that microalbuminuria determination may be a more reliable marker of renal disease, but its value as an international standard of evaluation for kidney donors has not been determined.

The discussion of hematuria was initiated by Kazuhide Saito and commented upon by Osman Alfurayh. Isolated microscopic hematuria (defined as >3–5 urinary sediment red blood cells (RBCs)/ HPF) may not be a contraindication to donation. RBCs with glomerular origin have a dysmorphic appearance observed by phase-contrast microscopy and automated RBC analysis. Patients with persistent microscopic hematuria should not be considered for kidney donation unless urine cytology and a complete urologic work up are performed. If urological malignancy and stone disease are excluded, a kidney biopsy may be indicated to rule out glomerular pathology such as IgA nephropathy.

Dan Brennan cited a recent report from Japan describing the presence of latent mesangial IgA deposits in approximately 16% of biopsies obtained at the time of transplantation from both living and deceased donors otherwise considered healthy (*24*). In some of the affected individuals, these findings were associated with a mild degree of microhematuria, mesangial proliferation, and glomerular macrophage infiltration, especially with combined IgA and C3 deposition.

Diabetes

The risk of the donor developing diabetic nephropathy following kidney donation was discussed by Connie Davis and Ed Cole. Diabetes is associated with an increased risk of postsurgical complications and future development of renal failure compared to the general population. Data by Silveiro et al. (*25*) were referenced to suggest that a nephrectomy in a patient with Type 2 diabetes might increase the progression of disease. Further, the prevalence of microalbuminuria is increased after nephrectomy.

Individuals who are at risk for developing Type 2 diabetes include those with a familial history, a BMI of >30 kg/m^2, woman with gestational diabetes, and excessive alcohol use. The following guideline was developed: individuals with a history of diabetes or fasting blood glucose ≥126 mg/dl (7.0 mmol/L) on at least two occasions (or 2-hour glucose with OGTT ≥200 mg/dl (11.1 mmol/L)) should not donate.

Stone Disease

Fernando Gabilondo and Mahendra Bhandari led the discussion of stone disease. Patients with lithiasis should be screened for metabolic stone forming abnormalities. Kidneys have been transplanted knowingly containing a renal stone (*26*, *27*).

An asymptomatic potential donor with history of a single stone may be suitable for kidney donation if:

- No hypercalcuria, hyperuricemia, or metabolic acidosis.
- No cystinuria or hyperoxaluria.
- No urinary tract infection.
- Multiple stones or nephrocalcinosis are not evident on computed tomography (CT) scan.

Younger patients have a longer exposure to risk of recurrence. The risk of recurrence after any single stone is difficult to predict in any individual. The younger the donor age (age 25–35), the longer the exposure to the possibility of a recurrence (*28*).

Asymptomatic potential donor with current single stone may be suitable if:

- The donor meets the criteria shown previously for single stone formers, and current stone is <1.5 cm in size or potentially removable during transplant.

Ex vivo ureteroscopy is a technically feasible means of rendering a stone-bearing kidney stone free, without compromising ureteral integrity or renal allograft function (*29*). It is not known whether stone formers who donate a kidney

have worse outcomes with respect to renal function compared to stone formers with two kidneys. However, a recurrent stone may not affect the function of a remaining kidney if it is carefully monitored (*30*).

Stone formers who should not donate are those with: 1) nephrocalcinosis on X ray or bilateral stone disease; and 2) stone types that have high recurrence rates and are difficult to prevent, such as:

- Cystine stones that have a high rate of recurrence and a need for urologic procedures in the donor.
- Struvite stones or infection stones that are difficult to eradicate and thus not feasible to transplant them into an immunosuppressed patient.
- Stones associated with inherited or other systemic disorders, such as primary or enteric hyperoxaluria, distal renal tubular acidosis, and sarcoid, because of the probability of a high rate of recurrence and the risk of renal insufficiency.
- Stones in the setting of inflammatory bowel disease with an increased risk of stones particularly after bowel resection, also increased risk of renal insufficiency.
- Recurrence while on appropriate treatment (i.e., failed therapy).

History of Donor Malignancy

Jeremy Chapman and Domingo Casadei led the discussion of donor malignancy. Living kidney donors should be screened by standard medical guidelines to exclude malignancy, noting that:

- The risk of clinical and subclinical malignancy increases markedly with age, especially over 50 years.
- The risk of different cancers differs between countries.
- Donors with low-grade nonmelanoma skin cancer may be accepted; otherwise the living kidney donor should be free of current or untreated malignancy.

A prior history of the following malignancies usually excludes live kidney donation:

- Melanoma, testicular cancer, renal cell carcinoma, choriocarcinoma, hematological malignancy, bronchial cancer, breast cancer and monoclonal gammopathy (*31–34*).

A prior history of malignancy may only be acceptable for donation if:

- Prior treatment of the malignancy does not decrease renal reserve or place the donor at increased risk for end-stage renal disease (ESRD).
- Prior treatment of malignancy does not increase the operative risk of nephrectomy.

A prior history of malignancy usually excludes live kidney donation but may be acceptable if:

- The specific cancer is curable and the potential transmission of the cancer can reasonably be excluded. Examples include: colon cancer (Dukes A, >5 years ago), nonmelanoma skin cancer, or carcinoma in situ of the cervix.

Consent to receive a renal transplant must include a discussion with the donor and the recipient that transmission of malignant disease cannot be completely excluded.

Screening for Infectious Disease

Essam Elsawy led the discussion of donor screening to prevent transmissible infectious disease through live kidney transplantation.

HIV

The detection of a positive human immunodeficiency virus (HIV-1 and HIV-2) by an ELISA assay for both antigen and antibody in a potential kidney donor should be confirmed by a neutralization test and a western blot analysis. The positive result rules out an individual from being a live kidney donor.

HTLV 1

If human T-lymphotropic virus (HTLV) 1 is transmitted from a live kidney donor, the recipient may be at risk for the development of T cell leukemia and neurological disorders such as a subacute myelopathy or spastic paraparesis (*35*). The ELISA test identifies HTLV 1 and 2, but does not distinguish either. Polymerase chain reaction (PCR) is needed to differentiate. The risk for HTLV 2 infection is unknown; it is detected in intravenous drug users.

HTLV is endemic in the West Indies and Japan. Norio Yoshimura presented his personal experience of a recipient developing T cell leukemia from a donor who was HTLV positive; this complication has also been reported from blood transfusion (*36*). Therefore, HTLV has been included in the routine screening (Table 1) assembled by Dr. Bradley. However, Dan Brennan suggested that the disease is rare in other parts of the world, and testing for its detection in live kidney donors is not routinely done.

CMV and EBV

Essam Elsawy screens for cytomegalovirus (CMV) IgM to evaluate recent infection, because CMV-reactive IgG is detected in more than 90% positive of his donors. If the CMV IgM is positive, a PCR for CMV is performed. If the PCR is positive, Essam Elsawy excludes live kidney donation until PCR becomes negative. If the CMV IgM positive and PCR are negative, they proceed with transplantation.

Bill Harmon suggested that a living donor (e.g., a parent) who is either CMV or Ebstein-Barr virus (EBV) positive is still acceptable for a recipient who is CMV or EBV negative.

Most of the adults are EBV and CMV positive; most of the children are EBV negative and many are CMV negative. Gil Thiel and Peter Morris expressed a concern that the incidence of posttransplantation lymphoproliferative disorder (PTLD) is rising in pediatric recipients. Approximately 5% of infants who receive living donor transplants develop PTLD, in part because of the intensity of immunosuppression, but also in the circumstance of an EBV positive donor transplant to a negative recipient. The possibility of EBV vaccination of the recipient was discussed by Ian Dittmer. Alternatively, another parent or a relative within the family might be evaluated to determine if they are either EBV (or CMV) negative. Despite these efforts, the importance and success of a live donor

TABLE 1. Routine screening for the potential living kidney donor

- Urinalysis
  - Dipstick for protein, blood and glucose
  - Microscopy, culture and sensitivity
  - Measurement of protein excretion rate
- Assessment of renal function
  - Estimation/measurement of GFR
- Blood tests
  - Hematological profile
    - Complete blood count
    - Hemoglobinopathy (where indicated)
    - Coagulation screen (PT and APTT)
    - G6PD deficiency (where indicated)
  - Biochemical profile
    - Creatinine, urea, and electrolytes
    - Liver tests
    - Urate
    - Fasting plasma glucose
    - Bone profile
    - Glucose tolerance test (if fasting plasma glucose >6–7 mmol/l)
    - Blood lipids
    - Thyroid function tests (if indicated)
    - Pregnancy test (if indicated)
    - PSA (if indicated)
  - Virology and infection screen
    - Hepatitis B and C
    - Toxoplasma
    - Syphilis
    - HIV and HTLV 1/2
    - Malaria (where indicated)
    - Cytomegalovirus
    - Trypanozome cruzi (where indicated)
    - Epstein-Barr virus
    - Schistosomiasis (where indicated)
    - HHV8 and HSV (where indicated)
    - Strongyloides (where indicated)
    - Typhoid (where indicated)
    - Brucellosis (where indicated)
- Cardiorespiratory system
  - Chest X-ray
  - Electrocardiogram
  - Stress test
  - Echocardiography (where indicated)
- Assessment of renal anatomy
  - Appropriate imaging investigations should allow confirmation of the presence of two kidneys of normal size and enable abnormalities of the collecting system and calcification or stone disease in the renal tract to be detected. They must also delineate the anatomy of the renal vasculature.

PSA, prostate-specific antigen; HIV, human immunodeficiency virus; HTLV, human T-lymphotropic virus; HHV, human herpes virus; HSV, herpes simplex virus.

parental transplant was sufficient to not prohibit the use of a CMV or EBV positive donor for a recipient who is CMV or EBV negative.

Hepatitis C Virus

If the donor has normal liver function tests and the serology test for hepatitis C virus (HCV) is negative (nonreactive antibody determination by ELISA), there is no contraindication for donation. However, if the serology test is positive for HCV, Essam Elsawy recommended that the recipient HCV status be evaluated. If the potential recipient is negative for HCV, the potential positive HCV donor should be excluded. If the potential recipient is also positive for HCV, the potential donor should be assessed by PCR for HCV. If the potential donor is PCR positive, the potential donor should be excluded because of the risk of HCV transmission to the recipient and because the potential donor may have chronic hepatitis (and is not well). If the potential donor is negative by PCR, the potential donor may not necessarily be excluded because the likelihood of transmission of HCV through the kidney is remote.

Nevertheless, Jose Morales expressed concern regarding HCV superinfection if a different HCV genotype of a positive donor is transmitted to a recipient. The Spanish group has transplanted kidneys from deceased donors with HCV reactivity to HCV positive recipients, but they have not performed live kidney transplantation from HCV positive donors (*37*). Further, Chakko Jacob and Nabil Mohsin questioned the justification of removing a kidney from a patient who in the future may develop an HCV-associated renal disease. However, Stephen Munn suggested that if certain HCV genotypes (genotype 4) are treated and eradicated in the donor, the potential donor could be reconsidered (if no evidence of chronic hepatitis or cirrhosis on biopsy).

Hepatitis B Virus

The detection of hepatitis B surface antigen (HBsAg) in a potential donor generally excludes the individual from live kidney donation (*38*). However, Stephen Munn reported that in New Zealand, some of the live kidney donors have been hepatitis B virus (HBV) core antibody positive. An IgM core positive result indicates a recent exposure to the HBV; in contrast, a surface antibody positive result indicates that months may have elapsed since the hepatitis infection. Even if HBsAg is negative, screening for HBV core total antibody (IgM and IgG) should be done to exclude low-level HBsAg and escape mutants of HBV not detectable by the current screening assays for HBsAg.

The ELISA core antibody test can distinguish between IgM and IgG reactivity. If the core antibody result is positive for IgM, a delay in the consideration of the potential donor was recommended to determine whether HBV infection might be progressing. A PCR quantitation of HBV DNA should be performed as appropriate care of the donor. Otherwise, by the New Zealand practice, if the potential donor is PCR negative for HBV, kidneys may be transplanted safely from either an HBV surface antibody positive donor or a donor who is HBV core antibody (IgG) positive into recipients who either have successfully recovered from hepatitis B infection or been immunized against hepatitis B.

Human Herpes Virus 8

Human Herpes Virus 8 (HHV8) has been shown to induce Kaposi sarcoma and can be transmitted by organ transplantation (*39*). Gil Thiel mentioned an ongoing research project of screening donors and recipients for HHV8 in Switzerland, but there is no world wide routine screening of live donors for HHV8.

TABLE 2. Amsterdam Forum Guidelines

Donor evaluation
- Prior to donation, the live kidney donor must receive a complete medical and psychosocial evaluation, receive appropriate informed consent, and be capable of understanding the information presented in that process to make a voluntary decision. All donors should have standard tests performed to assure donor safety.

Hypertension
- Patients with a BP >140/90 by ABPM are generally not acceptable as donors.
- BP should preferably be measured by ABPM, particularly among older donors (>50 years) and/or those with high office BP readings.
- Some patients with easily controlled hypertension, who meet other defined criteria, e.g. >50 years of age, GFR >80 ml/min, and urinary albumin excretion <30 mg/day may represent a low-risk group for development of kidney disease after donation and may be acceptable as kidney donors.
- Donors with hypertension should be regularly followed by a physician.

Obesity
- Patients with a BMI >35 kg/m^2 should be discouraged from donating, especially when other comorbid conditions are present.
- Obese patients should be encouraged to lose weight prior to kidney donation and should be advised not to donate if they have other associated co-morbid conditions.
- Obese patients should be informed of both acute and long-term risks, especially when other comorbid conditions are present.
- Healthy lifestyle education should be available to all living donors.

Dyslipidemia
- Dyslipidemia should be included along with other risk factors in donor risk assessment, but dyslipidemia alone does not exclude kidney donation.

Acceptable donor renal function
- All potential kidney donors should have GFR estimated.
- Creatinine based methods may be used to estimate the GFR; however, creatinine clearance (as calculated from 24-hour urine collections) may under or overestimate GFR in patients with normal or near normal renal function.
- Calculated GFR values (MDRD and Cockcroft-Gault) are not standardized in this population and may overestimate GFR.
- A GFR <80 ml/min or 2SD below normal (based on age, gender, and BSA corrected to 1.73/m^2) generally precludes donation.

Urine analysis for protein
- A 24-hour urine protein of >300 mg is a contraindication to donation.
- Microalbuminuria determination may be a more reliable marker of renal disease, but its value as an international standard of evaluation for kidney donors has not been determined.

Urine analysis for blood
- Patients with persistent microscopic hematuria should not be considered for kidney donation unless urine cytology and a complete urologic work up are performed. If urological malignancy and stone disease are excluded, a kidney biopsy may be indicated to rule out glomerular pathology, such as IgA nephropathy.

Diabetes
- Individuals with a history of diabetes or fasting blood glucose ≥126 mg/dl (7.0 nmol/l) on at least two occasions (or 2-hr glucose with OGTT ≥200 mg/dl (11.1 mmol/l) should not donate.

Stone Disease
- An asymptomatic potential donor with history of a single stone may be suitable for kidney donation if:
  - No hypercalcuria, hyperuricemia, or metabolic acidosis.
  - No cystinuria, or hyperoxaluria.
  - No urinary tract infection.
  - If multiple stones or nephrocalcinosis are not evident on CT.
- An asymptomatic potential donor with a current single stone may be suitable if:
  - The donor meets the criteria shown previously for single stone formers and current stone <1.5 cm in size, or potentially removable during the transplant.
- Stone formers who should not donate are those with:
  - Nephrocalcinosis on x ray or bilateral stone disease.
  - Stone types with high recurrence rates, and are difficult to prevent (see text).

Malignancy
- A prior history of the following malignancies usually excludes live kidney donation:
  - Melanoma, testicular cancer, renal cell carcinoma, choriocarcinoma, hematological malignancy, bronchial cancer, breast cancer and monoclonal gammopathy.
- A prior history of malignancy may only be acceptable for donation if:
  - Prior treatment of the malignancy does not decrease renal reserve or place the donor at increased risk for ESRD.
  - Prior treatment of malignancy does not increase the operative risk of nephrectomy.
- A prior history of malignancy usually excludes live kidney donation but may be acceptable if:
  - The specific cancer is curable and potential transmission of cancer can reasonably be excluded.

Urinary tract infections
- The donor urine should be sterile prior to donation; asymptomatic bacteria should be treated per donation.
- Pyuria and hematuria at the proposed time of donation is a contraindication to donation.
- Unexplained hematuria or pyuria necessitates evaluation for adenovirus, tuberculosis, and cancer. Urinary tuberculosis or cancer are contraindications to donation.

Live unrelated donors
- The current available data suggest no restriction of live kidney donation based upon the absence of an HLA match. An unrelated donor transplant is equally successful to the outcome achieved by a genetically related family member such as a parent, child, or sibling, who is not HLA identical to the recipient.

Determination of cardiovascular risk
- The clinical predictors of an increased peri operative cardiovascular risk (for non-cardiac surgery) by the American College of Cardiology/American Hospital Association standards fall into 3 categories: major, intermediate, minor.
  - All major predictors: unstable coronary syndromes, decompensated heart failure, significant arrhythmias and severe valvular disease are contraindications to live kidney donation. Most of the intermediate predictors: mild angina, previous myocardial infarction, compensated or prior heart failure, diabetes mellitus are also contraindications to donation; Minor predictors: older age, abnormal ECG, rhythm other than sinus, low cardiac functional capacity, history of stroke or uncontrolled hypertension warrant individual consideration.

Assessment of pulmonary issues
- A careful history and physical examination are the most important parts of assessing risk.
- Routine preoperative pulmonary function testing (PFT) is not warranted for potential live kidney donors unless there is an associated risk factor such as chronic lung disease.
- Increased risk of post operative pulmonary complication is assoc with an FEV1 <70% or FVC <70% of predicted, or a ratio of FEV1/FVC <65%.

Smoking cessation and alcohol abstinence
- Smoking cessation at least 4 weeks prior to donation is advised based on recommendations for patients undergoing elective surgical procedures.
- Cessation of alcohol abuse defined by DSM-3: 60 gm of alcohol/day sustained over ≥6 months should be avoided for a minimum of 4 weeks to decrease the known risk of postoperative morbidity.

BP, blood pressure; ABPM, ambulatory blood pressure monitoring; GFR, glomerular filtration rate; BMI, body mass index; BSA, body surface area; CT, computed tomography; ESRD, end-stage renal disease; HLA, human leukocyte antigen.

Tuberculosis

Essam Elsawy presented the following information regarding tuberculosis. Active *Mycobacterium tuberculosis* infection is a contraindication for donation because tuberculosis has been transmitted from live kidney donors to their recipients (*40*). Further, a past history of pulmonary tuberculosis is relative contraindication to donation. However, there were instances reported by Forum participants where individuals with history of treated pulmonary tuberculosis have donated a kidney.

Enrique Ona presented that many of the Philippine live kidney donor population may have fibrosis of the lung apex, which radiologists read as evidence of a past tuberculous infection by this "primary complex." The radiologist's evaluation is important to determine active infection by a comparative current chest x-ray with a previous one (if available). They are accepted as donors if it is proven that they don't have an active pulmonary infection and after it is shown that they don't have genitourinary tract tuberculosis. If active pulmonary infection is suspected, the donors are treated (as are most of the recipients) with prophylactic isoniazid (INH) for about 4 months. Thus, a potential donor with a past history of pulmonary tuberculosis who has received adequate treatment may still be an acceptable donor if there is no renal infection. Enrique Ona suggested that donors treated for pulmonary tuberculosis require a more specific and extensive examination of the urinary tract and the kidneys prior to donation.

Pyuria or an anatomical defect on renal ultrasound or intravenous pyelogram (IVP) may be indicative of donor urinary tract infection with tuberculosis. Urinary tuberculosis is contraindication for donation. Essam Elsawy suggested that donors previously treated for urinary tuberculosis might have dormant tuberculosis within the kidney, and thus remain unsuitable for donation. Further, tuberculous pyelonephritis usually results in a decreased GFR of the diseased kidney, making it unsuitable for donation.

M.K. Mani presented the following information. Urinary culture for tuberculosis is not done routinely as it is a poor screening tool; however, the potential donor is usually assessed for pyuria and anatomical radiographic abnormalities of the urinary tract and kidneys, despite a normal chest X ray. Mahendra Bhandari concurred to report in his experience that genitourinary tuberculosis might exist without chest X ray evidence. Finally, in some regions of the world (from Fernando Gabilondo and Nasser Simforoosh), a purified protein derivative (PPD) skin test of tuberculosis is still used to screen potential kidney donors, even though some of the donors may have been vaccinated with Bacille Calmette-Guerin (BCG), a genetically-altered tubercular bacteria rendered avirulent. However, in Egypt, Essam Elsawy noted that BCG vaccination is mandatory for all the population from birth. A positive PPD on that basis may not be helpful to screen a potential live kidney donor. In New Zealand, neither Stephen Munn nor Ian Dittmer screens their donors with a PPD.

Syphilis

Donors should be screened for syphilis (*Treponema pallidum*) with the rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) slide test. The RPR and the older VDRL test detect reactive antibodies. There are several conditions that may cause a false positive test: HIV, Lyme disease, mycoplasma pneumonia, malaria, and systemic lupus erythematosus. Therefore, these screening tests, if found to be positive, must be confirmed by a more specific test for syphilis such as a fluorescent treponemal antibody (FTA) absorption test. Donors with a positive confirmatory FTA should be treated according to stage and donation should be delayed until successful treatment is accomplished. There may be a risk of syphilis transmission if the donor is untreated (*41*). The recipient could receive treatment following transplantation, if there is an urgent need to perform transplant. Secondary syphilis is associated with reversible renal disease.

Chagas Disease

Chagas disease is endemic in parts of Central and South America and Mexico, where an estimated 16–18 million people are infected with *Trypanosoma cruzi* (*42*). Trypanosomiasis has been transmitted to kidney transplant recipients from an infected donor (*43*). Donors from endemic areas should be screened by serologic tests (there are at least three of them). A complement fixation test (Machado-Guerreiro reaction) becomes positive in the acute stage at one month postinfection and remains positive thereafter. The Machado-Guerreiro has a low sensitivity and specificity that yields high incidence of false positives and negatives. The precipitin test (hemagglutination reaction) is 95% positive in the early stages. The immunofluorescence and ELISA tests are highly sensitive and specific, although false-positive reactions occur with malaria, leprosy, and leishmaniasis. If two of the screening tests are positive, the detection of the trypanosome should be ruled out in the blood by a xenodiagnostic test that entails the following: uninfected laboratory-raised insects are fed on a patient, and then examined 30 days later for metacyclic trypanosomes in their hindgut or feces. If positive, the potential donor must be treated and cannot donate until parasitemia turns negative. Otherwise, Mario Abbud-Filho, José Medina-Pestana, and Domingo Casadei suggested that there is no contraindication to live kidney donation from a serology positive donor. In a referenced report by Sousa, nine recipients of kidneys were obtained from Chagas seropositive donors among 239 kidney transplantations between 1992 and 1997 (*43*). All were treated with benznidazole (5 mg/kg/d) for 14 days. None of them experienced acute Chagas disease or seroconversion even after 10 years follow-up. The Forum participants concluded that donors with positive serology for Chagas disease should not be excluded.

Schistosomiasis

Essam Elsawy suggested that uncomplicated bilharziasis of living kidney donors does not adversely affect either the function or the morphology of the remaining kidney, provided that the donor had functionally and morphologically intact kidneys and bilharzia was treated before donation. There has been no significant difference between bilharzial and nonbilharzial renal transplants in graft function and incidence of graft rejection after 10 years of follow up (*44*). Nabil Mohsin posed a question regarding the routine treatment of schistosomiasis in an asymptomatic donor who resides in an endemic area. Essam Elsawy replied that treatment is not given unless the donor has an active infection. If there is active schistosomiasis in an otherwise healthy donor, the do-

nor is treated at least one month before transplantation by combined antischistosomal drugs (praziquantel and oxamniquine). Cure without impairing renal function has been observed without a negative impact on the transplant outcome.

Strongyloides

Larvae of *Strongyloides stercoralis* penetrate the skin or mucosa from fecally contaminated soil, are carried by the blood stream to the lungs, break into the alveoli, ascend, are swallowed, and then reach the small intestine. The female worms produce larvae parthenogenically (without fertilization), and the larvae are passed in the host's feces. The presence of nematode larvae in a fecal sample is characteristic of strongyloidiasis; however, an ELISA assay is available for serological detection of strongyloides. Potential donors should be screened for strongyloides in endemic areas because strongyloides has been transmitted via a kidney transplant (*45*).

Brucellosis

Brucellosis is derived from the bacteria of the genus *Brucella*, primarily passed among animals and acquired by humans from contact with animals or animal products that are contaminated with these bacteria. Brucellosis has been transmitted to recipients of bone marrow transplants (*46*). Nasser Simforoosh suggested that a patient successfully treated for brucellosis infection may still be a suitable live kidney donor.

Malaria

Malaria has been transmitted from an organ donor to multiple transplant recipients, resulting in the death of a heart transplant recipient (*47*). Potential live kidney donors who either reside or have traveled to endemic areas should be screened for *Plasmodium falciparum*. Automated hematology analyzers have been used to detect malarial parasites in peripheral blood samples.

Urinary Tract Infections

The donor urine should be sterile prior to donation. Pyuria and hematuria at the proposed time of donation is a contraindication to donation. Asymptomatic bacteruria should be treated predonation. Unexplained hematuria or pyuria necessitates evaluation for adenovirus, tuberculosis, and cancer. Urinary tuberculosis and cancer are contraindications to donation.

Essam Elsawy presented the following information. A history of recurrent cystitis is not a contraindication to donation from a healthy young female; however, unexplained recurrent pyelonephritis is a contraindication to donation. Persistent infection (same pathogen recurs after treatment) warrants anatomic evaluation of urinary tract by upper tract study (IVP, CT scan) and cystoscopy. In men, persistent infection may be associated with chronic bacterial prostatitis. There is no association of renal infection with chronic bacterial prostatitis.

Recurrent urinary tract infection from childhood may indicate reflux and potential donors should undergo a voiding cystourethrogram (VCUG) and an upper tract study. Donation is contraindicated until anatomical cause is ruled out.

Blood Donor Regulation and Organ Donor Screening

Stephen Munn and Carl Cardella noted blood donor services in North America, Australia, and New Zealand have precluded individuals from donating blood if they resided in the United Kingdom during the bovine spongiform encephalopathy (BSE) risk period (during the 1980s and early 1990s) and ate meat (*48*). Chris Rudge also reported that the U.K. national blood service has issued an instruction to not permit blood donation from anybody who has received a blood transfusion within the last 24 years. Andrew Bradley suggested that, for live kidney donation, the remote risk could be discussed with a prospective recipient and they could accept that risk or not. In contrast, the donor of a blood transfusion is usually to an anonymous recipient. Chris Rudge agreed that regulations for blood and tissues should not apply to organs because the risk/benefit ratio is different, citing the example of screening for HTLV and variant for Creutzfeld-Jacob disease (v-CJD). The conclusion of the Forum participants was that a center transplanting a kidney from a live donor who falls into at-risk categories for v-CJD (residency in the U.K. or a family history of unexplained neurodegenerative disease) has a responsibility to explain the possibility of transmission to the recipient. Nevertheless, the risk is likely to be extremely low and not prohibit live donor kidney transplantation.

Live Unrelated Donors

In Mexico and some European countries, unrelated kidney transplantation is currently illegal. Enrique Ona posed the following question to participants: "Since live donors are more commonly done in the Philippines, what is a minimum HLA-DR antigen match acceptable for transplantation? Blood relation in our part of the world extends to distant relatives and not just from siblings, parents or children. The same is true with the adoption of incentives, gifts, or gratitudinal reciprocity to the donation process which can easily be misconstrued as 'commercialization' or sale."

Chris Rudge presented data from the U.K. evaluating the degree of HLA match in transplants from different donor types and the influence of HLA match on the outcome of all living donor transplants in the U.K. (*49*). Transplants from unrelated living donors were significantly less well matched. There were two HLA-DR mismatches in 41% of living unrelated donor transplants but less than 5% in living related donor transplants. Nevertheless, there were no significant differences in one-year transplant survival between the two living donor transplant groups.

Francis Delmonico presented current U.S. data that examined whether HLA matching influences the outcome of living donor kidney transplants. Among living unrelated donor transplant recipients, there was no independent effect of DR matching on graft survival, as indicated by 5-year survival rates of 86% (reference group), 85% ($P=0.85$) and 84% ($P=0.64$) for zero, one, and two HLA-DR mismatched grafts, respectively.

Thus, the current available data suggest no restriction of live kidney donation based upon the absence of an HLA match. An unrelated donor transplant is equally successful to the outcome achieved by a genetically related family member such as a parent, child, or sibling who is not HLA identical to the recipient.

Live Donor Exchanges

ABO blood type incompatibility or T cell crossmatch reactivity has generally precluded successful kidney transplantation. A crossmatch performed between the prospective donor and recipient may detect antibodies that would result in an accelerated rejection of the allograft. Natural antibodies to the A or B blood types can also cause immediate allograft loss. These biologic realities have circumvented the intent of a willing kidney donor to provide for needy recipient, until now (*50*). Recently however, protocols have been developed to overcome these barriers by using plasma exchange to remove either the isoagglutinin or HLA antibodies (see below) (*51*). Nevertheless, these "conditioning" regimens are still associated with an unpredictable rate of biological graft loss that could be averted by other innovative methods of live donor transplantation. One such approach is live donor exchange (i.e., exchanging donors incompatible with their intended recipients so that, instead, each donates to a compatible recipient). With donor exchange, the hazard of either blood type or crossmatch incompatibility can be avoided, while both recipients still derive the benefit of a living donor kidney transplant.

Section 301 of the U.S. National Organ Transplant Act of 1984 (NOTA), 42 U.S.C. 274e states: "It shall be unlawful for any person to knowingly acquire, receive, or otherwise transfer any human organ for valuable consideration for use in human transplantation". Valuable consideration under NOTA § 301 has traditionally been considered to be monetary transfer or a transfer of valuable property between donor, recipient, and/or organ broker in a sale transaction.

However, in some regions of the world, the live donor exchange is considered to be valuable consideration; thus, it is not permitted. For example, Jeremy Chapman brought to attention a law in Australia that prohibits such exchanges that have occurred in the United States or Korea (*52*, *53*). These exchanges are considered illegal in Australia because the donor is deemed to receive valuable consideration in return for the donation; therefore, it is not considered to be an altruistic donation. Carl Cardella presented a different interpretation to suggest that receiving a transplanted kidney is not the same as getting a monetary value; and that although it is obviously of value, it is not the same as buying and selling organs.

The Gender Imbalance

Data were presented by Gil Thiel, Mahendra Bhandari, S. Adibul Hasan Rizvi, and Bob Metzger to reveal the following international experience: approximately 65% of live kidney donors have been women and approximately 65% of recipients have been men.

Abdullah Alkhader Al Sayarri observed that among some living kidney transplants, there might be an unethical component of coercion and family/social pressures to bear. Participants agreed that these gender data display an excessive disparity, perhaps reflecting a psychological submission of women or discrimination of woman in many countries, including Western nations. However, there are more males than females with end stage renal disease, which may partly explain why there are more wives than husbands who donate in the case of transplants between spouses (*54*, *55*).

S. Adibul Hasan Rizvi noted a Nobel laureate perspective to say, "the burden of hardship often falls disproportionately on women." In some parts of the world, female gender bias is historically deep rooted. When the live related renal transplantation program was begun at the Sindh Institute of Urology and Transplantation, the factor of coercion was anticipated. In the prevailing culture, it was highly probable that females would have no choice but to donate a kidney. Dr. Rizvi reported that this donor coercion was encountered in the initial period, but it was subsequently overcome by efforts of a dedicated transplant team. Presently, despite existing cultural barriers, the female to male donor ratio at the Sindh Institute of Urology and Transplantation is 0.9:1.

Mahendra Bhandari endorsed the objective of establishing a genuineness of voluntary donation. In India, however, the family elder's domination is a reality of that culture; it is rare to find a prospective donor bold enough to decline. The issue is extremely sensitive and relevant in the case of female spouses as prospective donors.

Sadek Beloucif observed that accepting to donate depends on a number of contradictory considerations: the wish to help a member of one's family, with the family's opinion in the background, and the anticipation of possible loss of body integrity. The role of the doctor, who is the mandatory intermediary in the situation of donor consent, cannot be overlooked.

Data and Perspective Regarding Minors as Donors

A review of the U.S. experience was presented by Bill Harmon. Minor donor kidneys were transplanted more frequently to adults than to pediatric recipients. Only 12% of the recipients from minor donors were identical twins (*56*). In some instances, minors gave their kidney to grandparents.

The use of a minor donor provided no better outcome than that expected from an adult donor. With the excellent outcome of unrelated transplantation from an adult living donor currently achieved, Forum participants agreed with the consensus proposal by Eduardo Santiago-Delpín that minors less than 18 years of age should not be used as living kidney donors.

Risk Estimation for Donor Candidates with Medical Abnormalities

R. Steiner suggested that the ethical position of transplant centers could be best validated if kidney donor candidates were presented a defensible and quantitative estimate of medical risk. This risk assessment applies not only to "normal" donors but also to donors with isolated medical abnormalities (IMAs) such as hematuria, low grade proteinuria, hypertension, stone disease, and borderline normal GFR (*57*). Centers may accept some IMA donors considering the small risk of ESRD developing as result of the IMA (*18*). However, donors may reasonably ask whether their IMA entails an ESRD risk of 1 in 10, 1 in 100, or 1 in 1,000.

Steiner proposed that the risk of ESRD for many IMAs can be estimated semiquantitatively by knowing the prevalence of the IMA in the general population, and the incidence of the kind of ESRD with which that IMA might be associated. For example, suppose an IMA is present in millions of people in a population, but only one person a year in that population develops ESRD from that IMA. The risk is therefore much less

than for an IMA, present in 100 people in a population, that generates 50 new cases of ESRD caused by that IMA each year.

In the year 2000, almost 20,000 new cases of hypertensive ESRD were reported in the United States (*58*). Hypertension is common in the U.S. population, afflicting perhaps 25% of the population (*59*). The U.S. population in 2000 was about 280 million; therefore, there were about 70 million hypertensive patients, who produced almost 20,000 cases of hypertensive ESRD that year. When these data are expressed to "normalize" the yearly incidence of hypertensive ESRD for the prevalence of hypertension in the same population, the fraction has the units "new cases of hypertensive ESRD per hypertensive year." This fraction is the raw yearly risk for hypertensive ESRD for that hypertensive population. The raw yearly risk for hypertension in the United States is therefore 20,000/70,000,000 or 1 case in 3500 patient years. The 20-year risk for ESRD is 20 times the yearly risk, or 20 in 3500 (1 in 175). Based upon these data, the lifetime risk of ESRD that is associated with their isolated mild to moderate hypertension is less than 1 in 100.

The estimate of any IMA risk (hematuria, etc.) can be determined by the formula developed by R. Steiner:

Yearly risk for risk factor A = (Yearly incidence of ESRD A) / (Prevalence of risk factor A)

The risk over the next *n* years is $n \times$ the yearly risk. The yearly risk for ESRD for "medical condition A" that is assumed to be the only cause of "ESRD A" (e.g., hypertension and hypertensive ESRD) is the yearly incidence of "ESRD A" in the general population divided by the prevalence of "condition A."

When this epidemiologic method is used to calculate the baseline lifetime risk for any form of ESRD in the general U.S. population, assuming a population of 275,000,000, a yearly incidence of ESRD of 85,000, and a 70-year life span, the calculated lifetime ESRD risk is strikingly close to the figure determined by more sophisticated methods (2% for whites and 7% for blacks) (*60*). However, the formula above estimates the baseline two-kidney risk for ESRD that is associated with a given IMA, irrespective of donation. Predicting the effect of uninephrectomy on the progression of postdonation ESRD is a separate problem that applies only to the small fraction of donors with IMAs who actually will develop renal disease. Predicting the effect of nephrectomy is also a problem for "normal" donors, as some "normal" donors will develop diabetic nephropathy or other forms of ESRD after donation later in life (*58*). Even though their risks for ESRD are often lower, "normal" donors also need to know their risks, for the same reasons that apply to donors with IMAs.

Determining Equipoise in the Risk-Benefit Analysis

Thomas Gutmann suggested the following: "In developing international standards of care for the live kidney donor and standards of medical suitability, the risk-benefit ratio of any proposed living donor transplant should be determined not only by medical facts, but ultimately by personal value judgments. These judgments should generally be made by the one most affected by the outcome—i.e., the prospective donor him/herself. After appropriate information has been given to the patients, the question of whether it is 'worth it' and the risks [are] 'acceptable' to the particular donor can only be based on the character and values of that person and their actual relationship with the intended recipient."

Pre-, Peri-, and Postoperative Issues

Determination of Cardiovascular Risk

Stephen Munn presented the following information. The clinical predictors of an increased perioperative cardiovascular risk (for noncardiac surgery) by the American College of Cardiology /American Hospital Association standards fall into three categories: major, intermediate, and minor (*61*). All major predictors (unstable coronary syndromes, decompensated heart failure, significant arrhythmias and severe valvular disease) are contraindications to live kidney donation. Most of the intermediate predictors (mild angina, previous myocardial infarction, compensated or prior heart failure, diabetes mellitus) are also contraindications to donation, although a history of a myocardial infarction many years prior to the possible donation may not be an absolute contraindication. Minor predictors (older age, abnormal electrocardiogram, rhythm other than sinus, low cardiac functional capacity, history of stroke, or uncontrolled hypertension) warrant individual consideration.

Most potential donors will need only an electrocardiogram prior to surgery. Few potential donors may need a stress test such as a dobutamine stress echocardiogram (perhaps some >60 years of age), because most individuals with a significant cardiac risk factor should have been excluded from donation.

Smoking Cessation

Mehmet Haberal and Frederic Oppenheimer presented the following information. Pneumonia is the most serious complication following noncardiac surgery. It ranks as the third most common postoperative infection, behind urinary tract and wound infections (*62*). Smokers have a higher risk of pulmonary and wound infections after surgery than nonsmokers (*63*). No current evidence exists to suggest that smoking increases morbidity or mortality of live kidney donors; however, observational evidence suggests a benefit to cessation before surgery (*64*). Cigarette smoking is associated with an increase in tracheobronchial secretions and a decrease in mucociliary clearance. In smokers, the respiratory epithelium is altered, and poor ciliary activity combined with the production of more viscous mucus leads smokers to be more reliant on the cough to clear secretions from their lungs.

Abstinence of smoking for only 12 hours can greatly reduce carboxyhemoglobin concentrations, improve oxygen content and availability, and reverse negative inotropic and arrhythmic effects (*65*, *66*). Smokers' polycythemia and increased blood viscosity take a few days to reverse (*67*). If smoking is stopped, sputum production declines over a 6-week period (*65*).

Alcohol Abstinence

Mehmet Haberal and Frederic Oppenheimer presented the following information. An increase in postoperative morbidity is reported for alcohol abusers who drink at least five drinks (>60 g ethanol) a day (*68*). Specific studies are lacking, but the result from observational evidence in other clinical settings is that alcohol misuse should be included in the pre-

operative assessment of live donors and withdrawal is recommended for at least 1 month before the operation (*69*).

Despite the high risk of complications, it was the experience of some Forum participants that recommendations to stop smoking and alcohol before elective surgery are not often heeded. There is a need for clinical guidelines for smokers and alcohol abusers in living donors undergoing surgery that include up-to-date patient information and four weeks of abstinence before surgery.

Forum Statement on Smoking Cessation and Alcohol Abstinence

- Smoking cessation at least 4 weeks prior to donation is advised, based on recommendations for patients undergoing elective surgical procedures.
- Cessation of alcohol abuse defined by DSM-3: 60 g alcohol/day sustained ≥6 months should be avoided for a minimum of 4 weeks to decrease the known risk of postoperative morbidity.
- All potential donors should have a health-promoting dialogue with the anesthesiologist or another health professional, which focuses on alcohol and smoking cessation in the context of other risk factors.

Assessment of Pulmonary Issues

Abdias Hurtado presented the following information regarding the determination of pulmonary risk in donor surgery. A careful history and physical examination are the most important parts of assessing risk (*70*). Routine preoperative pulmonary function testing (PFT) is not likely warranted for potential live kidney donors unless there is an associated risk factor such as chronic lung disease. Preoperative PFTs can be reserved to these patients. There are no cut-off values in PTFs; however, increased risk of postoperative pulmonary complication is associated with FEV1 <70% or FVC <70% of predicted, or a ratio of FEV1/FVC <65% (*71*). Patients with chronic pulmonary disease, who are at risk of the development end-stage pulmonary disease, should not be candidates for living kidney donation. Patients with asthma who are well controlled, and with a peak flow measurement > 80% predicted, can be considered on an individual basis for live kidney donation (*71*).

Venous Thromboembolism

Factor V-Leiden, a variant of the coagulation protein Factor V, is associated with venous thrombosis, especially in oral contraceptive users. Factor V-Leiden is the most common hereditary blood coagulation disorder, present in 3–8% of the healthy white population (*72*). Marwan Masri has detected Factor V-Leiden mutant genes in 2% of living donors. In Britain, 5% of the population carries one or more genes for Factor V Leiden (far more than the number of people who will actually suffer from thrombosis). However, the odds ratio of a venous thrombolic event is 11 times greater in women taking oral contraceptives who have the Factor V Leiden mutation than for those who do not (*73*). Dan Brennan has also identified such a high rate of Factor V-Leiden in the U.S. population, suggesting that oral contraceptives and hormone replacement therapy be withheld for 3 months prior to an elective surgery.

Jonas Wadström suggested that potential living kidney donors should evaluated by a comprehensive coagulation profile to include PT, PTT, antithrombin 3, protein S, and protein C, Activated protein C (APC) resistance, as well as an PT-prothrombin mutation, cardiolipin antibodies, and lupus anticoagulants. APC resistance is due to an inherited disorder of the Factor V molecule (usually Factor V-Leiden) and is again associated with venous thromboembolism.

However, there was no consensus on this particular issue of screening for a coagulopathy. Mark Stegall recommended that a history of venous thromboembolism be ascertained prior to an in-depth coagulation workup. Unless the history reveals a medical concern that would necessitate a comprehensive coagulation profile, these tests were considered expensive and not likely to yield consequential information.

Vascular Imaging

Sunil Shroff suggested that a noninvasive method of imaging such as magnetic resonance imaging or spiral CT scan (rather than a conventional contrast angiogram) could now be recommended, as these approaches are associated with less morbidity for the donor.

Conclusions

This report of the Amsterdam Forum presents a comprehensive review of the international practice of live kidney donation. Forum participants emphasize concertedly that medical judgment regarding the suitability of the potential donor is derived from a reflection of published data and physician experience. This report is intended to provide a compilation of information upon which appropriate medical judgment can be applied in the medical evaluation of every potential live kidney donor.

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