Renal Transplantation

History

- In 1906, Mathieu Jaboulay performed xenotransplantation in humans. He transplanted the kidney of pigs and goats into the arms of patients with renal failure. Reportedley these xenografts functioned for as long as one hour.

- Dr. Joseph Murray performed the first successful human kidney transplant in 1954 in Boston. The transplant was performed between identical twin brothers, with the healthy twin serving as a healthy donor the recipient lived for eight years before having a recurrent kidney disease.

Murray was awarded the Nobel Prize in Medicine in 1990.

Renal Transplantation

- Kidney transplantation is the most effective and best replacement therapy for end-stage renal disease.

- The incidence of end-stage renal disease (ESRD) in the United States is approximately 380 per million population per year.

- the main causes of ESRD:

1. Diabetes mellitus
2. Glomerulonephritis
3. Hypertension
4. cystic kidney diseases
5. interstitial/pyelonephritis.
6. urologic diseases.

Renal Transplantation

Children < age 18 with renal failure often have congenital urologic conditions such as obstruction, valves, dysplasia, cystic disease, reflux, prune-belly syndrome, inborn errors of metabolism (stones), or neurogenic bladders.

- When dialysis and transplantation are compared, better patient survival, quality of life, and healthcare cost savings are reported for kidney transplant recipients.

Benefits of Transplantation

- Life expectancy
- Cardio-vascular benefits
- Quality of life
- Socioeconomic benefits

Cost to society:

- Annual cost of hemodialysis: $60,000-$80,000
- First year after transplantation: >$100,000
- There after: $10,000 per year.

Mean cumulative costs of dialysis and transplantation are equal for first 3-4 years, then lower for transplantation.

Candidate evaluation (Recipient)

Absolute contraindications are:

- Active malignancy.
- Active or chronic untreated infection.
- Severe cardiovascular disease.
- Neuropsychiatric illness.
- life expectancy of <3 years probably should be maintained on dialysis.

Candidate evaluation (Recipient)

- ESRD Recurrence.
- Psychosocial or Financial Problems.
- Active Infection.
- Malignancy.
- Unsuitable Anatomy for Technical Success with full urinary tract evaluation.
- Life Expectancy Calculation.
- Cardiovascular and gastrointestinal evaluation.
- Immunologic Risk Factors.
- Living Renal Donors.
- Modifiable factors.

Candidate evaluation (Recipient)

- **ESRD Recurrence:**
- That may result in kidney transplant loss due to recurrence of disease. Examples:
- primary oxalosis, cystinosis, atypical hemolytic-uremic syndrome (aHUS), focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, membranous nephropathy, IgA nephropathy, systemic lupus erythematosis, anti-glomerular basement membrane disease, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, renal amyloidosis, and Fabry disease.
- Examples of diseases that do not recur in a kidney transplant are the polycystic renal diseases, renal dysplasia, and chronic pyelonephritis.

Candidate evaluation (Recipient)

- **Psychosocial or Financial Problems:**
- Noncompliance with a complex post-transplant regimen is a preventable cause of kidney graft loss, and psychosocial and financial assessments are performed to identify and correct problems that could result in noncompliance.

Candidate evaluation (Recipient)

- **Active Infection:**
- Urinary tract infection must be resolved or controlled prior to transplantation.
- Screening for pulmonary infectious diseases is with chest x-ray and tuberculosis test.
- Dental infections must be resolved before immunosuppression.
- Cytomegalovirus (CMV) antibody levels are determined because posttransplant CMV infection can result in significant morbidity and mortality.
- If hepatitis B or C viral antibody levels indicate active hepatitis, these patients are excluded from transplantation until cleared by hepatology consultation because of the risk of hepatitis exacerbation with immunosuppression.
- Recipients who are human immunodeficiency virus (HIV)-positive may qualify for transplantation if CD4-lymphocyte counts are satisfactory.

Candidate evaluation (Recipient)

- **Malignancy:**
- Patients with treated cancer must have a low probability of recurrence.
- disease-free waiting period is variable with different malignancies.
- Therefore, with some exceptions, a minimum waiting period of 2 years for cancers with a favorable prognosis is desirable. A waiting period of 5 years is desirable for lymphomas, most carcinomas of the breast, colon, or for large (>5 cm) symptomatic renal carcinomas.
- Screening for malignancy is performed only if there is and indication.

Candidate evaluation (Recipient)

- **<u>Unsuitable Anatomy for Technical Success:</u>**
- including full genitourinary evaluation.
- Significant urethral stricture disease and benign prostatic obstruction (BPO) must be treated, or a management plan must be put in place prior to transplantation.
- Any lower urinary tract abnormality or dysfunction must be corrected before transplantation.

Basic urinary tract evaluation.

Step	Checklist
History	UTIs, voiding dysfunction, stones, surgeries, cancer, penile prosthesis, artificial urinary sphincter, sexual function, aristolochic acid, cyclophosphamide, schistosomiasis
Exam	Abdomen, genitalia, prostate if > 50
Imaging	Ultrasound of kidneys, ureters, post-void bladder
Lab	UA, UC, PSA in men >50 years old
Rarely	Voiding cystourethrogram, urodynamics

Candidate evaluation (Recipient)

- **Life Expectancy Calculation.**
- Life expectancy calculations based on Charlson comorbidities can guide the selection of suitable candidates for transplantation.
- Ten-year life expectancies for Charlson Comorbidity scores of 1, 3, 5, and 7 are 96%, 22%, 21%, and 2%, respectively.

Charlson Comorbidity Score/Index.

Points	Comorbidity
1 for	Each decade of age beginning at 50 years
1 for each	Uncomplicated diabetes mellitus, mild liver disease, congestive heart failure, myocardial infarction, chronic obstructive pulmonary disease, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, dementia, connective tissue disease, peptic ulcer disease
2 for each	Diabetes mellitus with end-organ damage; any leukemia, lymphoma, or localized solid tumor; moderate to severe chronic kidney disease, hemiplegia
3 for each	Moderate to severe liver disease
6 for each	6 points for metastatic solid tumor, AIDS

Candidate evaluation (Recipient)

- **<u>Cardiovascular and gastrointestinal evaluation:</u>**
- Cardiovascular disease represents the leading cause of death after kidney transplantation.
- Provocative stress tests are necessary. If any uncertainty exists, the gold standard remains coronary angiography.
- Patients with ESRD often have a history of (GI) problems (PUD). If present, these should be evaluated and resolved prior to transplant.

Candidate evaluation (Recipient)

- **Immunologic Risk Factors:**
- An immunosuppression protocol can often be assigned at the multidisciplinary transplant selection conference based on immunologic risk factors identified during the multidisciplinary recipient evaluation.

Candidate evaluation (Recipient)

- **<u>Living Renal Donors:</u>**
- If a transplant candidate is acceptable for transplantation and has a potential living kidney donor, the potential donor is assessed after he or she calls the transplant program to volunteer.

Candidate evaluation (Recipient)

MODIFIABLE RISK FACTORS

Obesity: Numerous reports have identified obesity (BMI >30 kg/m2) and morbid obesity (BMI >35 kg/m2) as an independent risk factor for increased cardiovascular mortality, decreased graft survival, delayed graft function (DGF), wound complications, post-transplant diabetes, proteinuria, and prolonged hospitalization.

Smoking:

- Tobacco smoking is particularly deleterious for transplant recipients, and patients need to stop prior to transplantation.
- Smoking both accelerates the progression of atherosclerotic cardiovascular disease and is nephrotoxic to the kidney resulting in proteinuria.

Candidate evaluation (Recipient)

Indications for pretransplant nephrectomies.

Hypertension uncontrolled with medication
Recurrent pyelonephritis
Renal calculi not removable by minimally invasive procedures
Significant proteinuria (consider angioembolization)
Persistent antiglomerular basement membrane antibodies
Solid tumors
Polycystic kidneys with recurrent pyelonephritis, recurrent bleeding, chronic pain, early satiety, or extension into true pelvis

Renal Donors

- Living Renal Donors
  - related donors
  - un-related donors
- Deceased Renal Donors

- Living kidney donation provides a better patient and graft survival when compared with deceased-donor transplantation, especially when the live donor transplant is performed before the onset of dialysis.

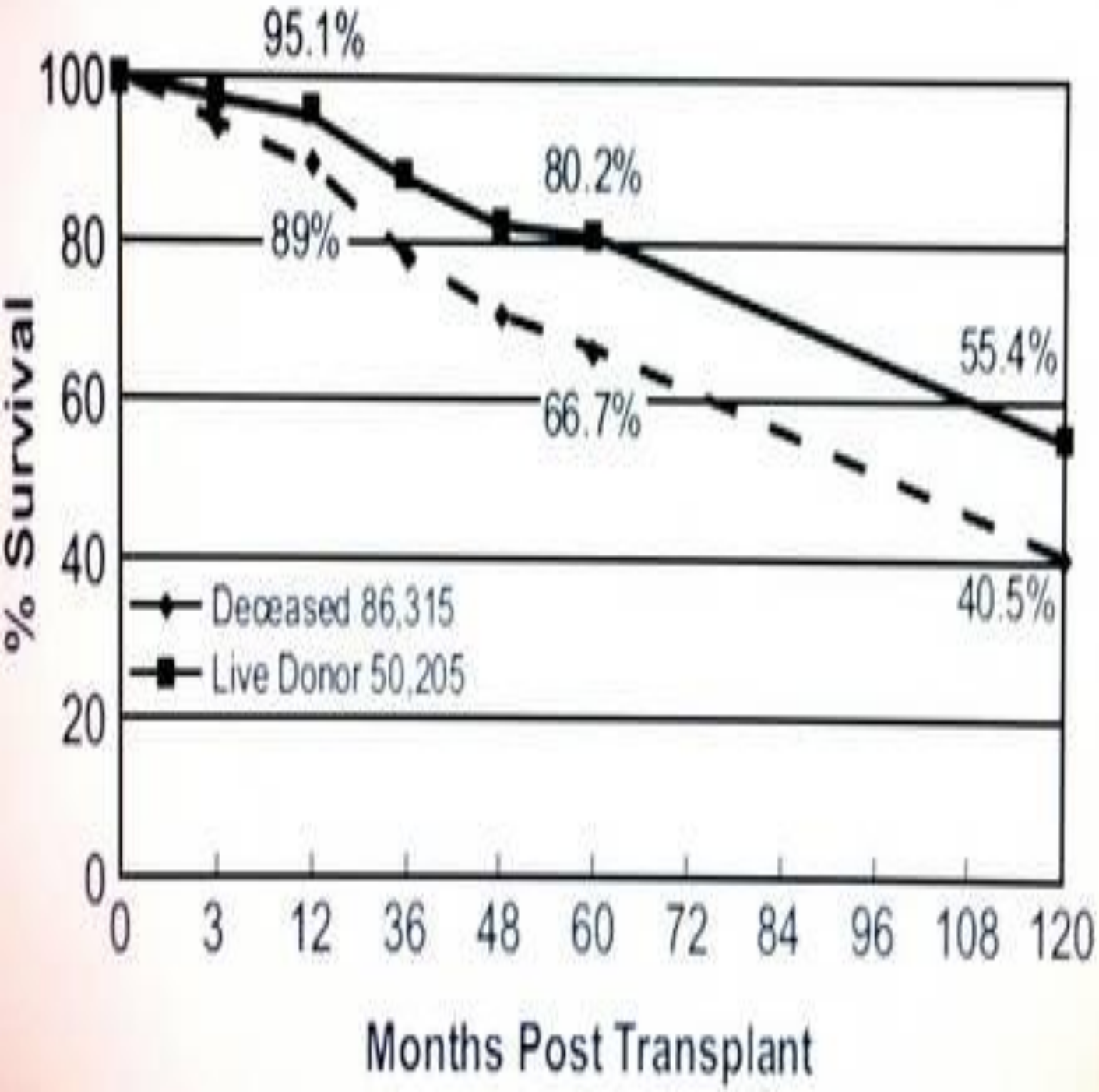
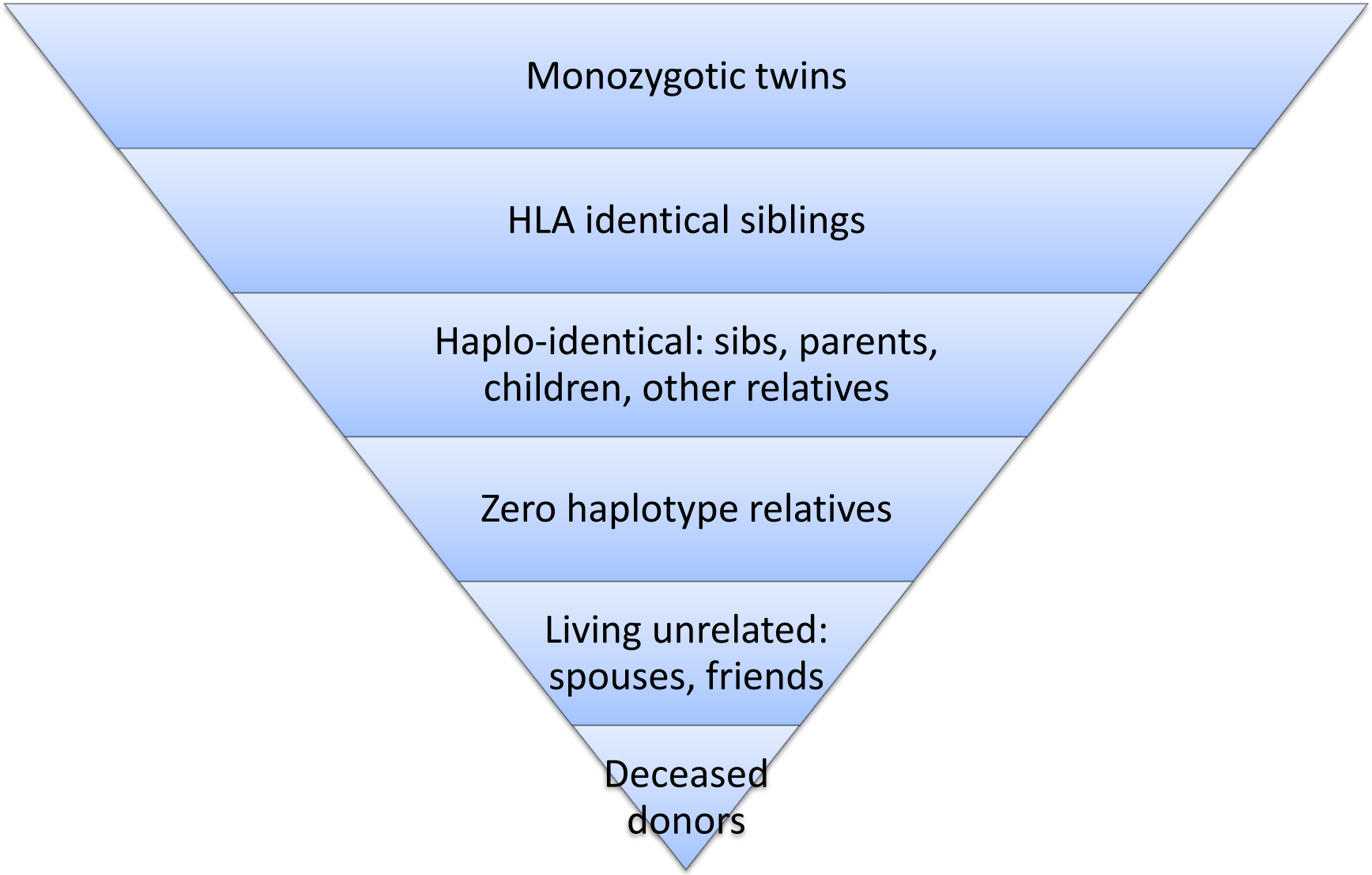


Figure 35–1. Kidney transplant graft survival over 10 years. From the OPTN/UNOS annual report 2005.


Monozygotic twins
HLA identical siblings
Haplo-identical: sibs, parents, children, other relatives
Zero haplotype relatives
Living unrelated: spouses, friends
Deceased donors

Living Donors

- Living renal donation is not without risk.
- The 90-day mortality rate is 3.1/10,000 laparoscopic donor nephrectomies, and the corresponding rate for laparoscopic nondonor nephrectomy is 260 in 10,000.
- The lifetime risk of a kidney donor developing ESRD is 90 in 10,000 cases, and the lifetime ESRD risks for healthy nondonors, and unscreened nondonors have been reported to be 14 in 10,000 cases and 326 in 10,000 cases, respectively.
- The published evidence indicates that there is little long-term medical risk to a healthy donor after unilateral nephrectomy.
- Following nephrectomy compensatory hypertrophy and incraese in the GFR occurs in the remaining kidney.

Living Donors

- Clinical practice guidelines have been developed for the screening of living kidney donors to minimize harm to the donors.
- there is general agreement that nephrologists should assess the medical suitability, surgeons should assess surgical risk.

Living Donors

Criteria for living donor selection :

- Basically :absence of infection, absence of renal disease, absence of transmissible malignancy.
- Blood relative
- Highly motivated
- ABO compatible
- HLA identical or haploidentical with –ve cross match
- Excellent medical condition with normal unilateral renal function .

Living Donors

- **Generally accepted criteria for exclusion of a living renal donor are as follows:**
- under-age minor
- apolipoprotein L1 variant in African ancestry donor candidate
- renal function below normal for age
- proteinuria >300 mg/day; microalbuminuria >30 mg/day
- body mass index >35 kg/m2
- blood pressure >140/90 with or without treatment
- diabetes mellitus
- nephrolithiasis if multiple stones, bilateral stone disease or high recurrence probability because of metabolic condition or anatomic abnormality
- malignancy with risk of transmission to the recipient; malignancy with a future need for nephrotoxic therapy
- infection with risk of transmission resulting in recipient morbidity or death
- coercion; mental illness; and lack of social support and coping mechanisms.

Living Donors

- Imaging in the renal donor candidate to define renal vasculature, renal structure and volume, collecting system anatomy, and presence or absence of urolithiasis.
- Three-dimensional spiral CT with and without intravenous contrast satisfies all these requirements.
- One of the principles of living renal donation is to leave the better kidney with the donor.
- Laparoscopic donor nephrectomy is the most common surgical approach.
- The left kidney is favored by recipient surgeons because of its longer, less delicate vein.

Deceased Renal Donors

- The goals of deceased donor kidney retrieval are: no transmission of infection, no transmission of cancer, and retrieval of transplantable organs.
- Kidney retrieval is most often part of a multiorgan retrieval process.

- **RECIPIENT SELECTION:**
- A national point system for selection of a deceased donor kidney transplant recipient.
- The donor and recipient must be ABO-compatible and have a negative donor–recipient lymphocytotoxic crossmatch.

Deceased Renal Donors

Most deceased donor organs come from brain dead donors.

A. STANDARD CRITERIA DONORS:

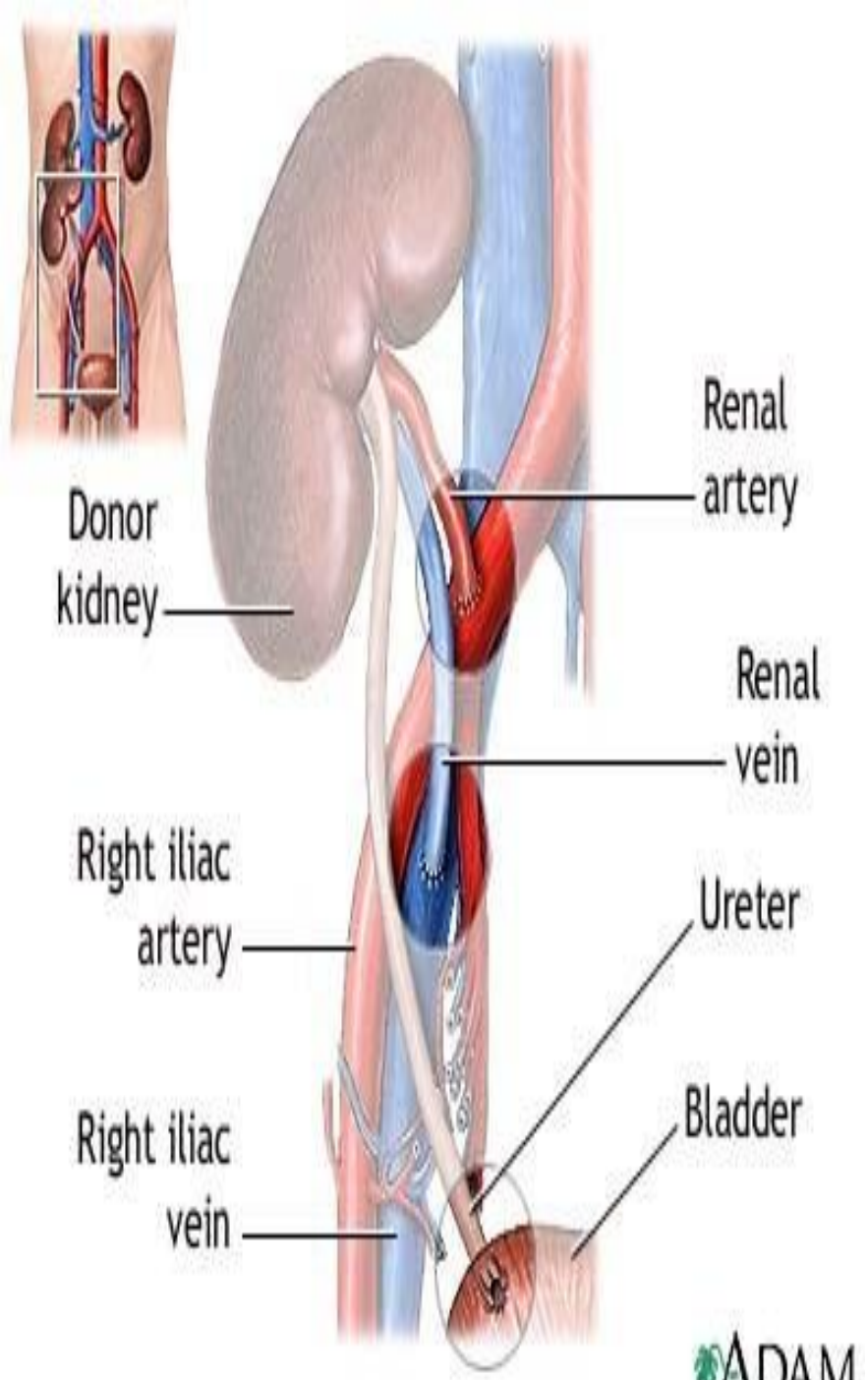
- Most individuals that meet the criteria for brain death from age 5–60 years with normal kidney function and no history of systemic or infectious disease.

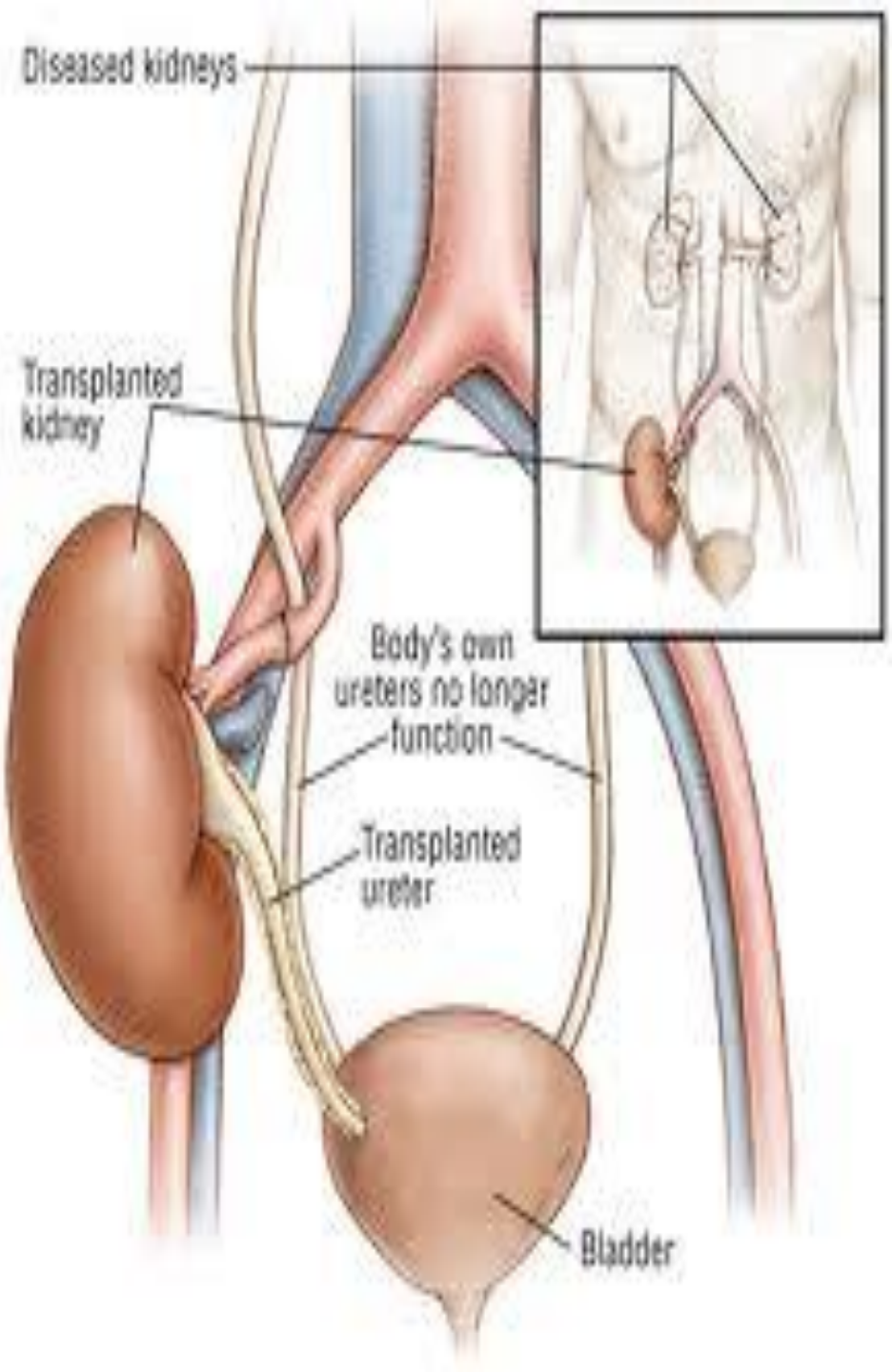
B. EXPANDED CRITERIA DONORS:

- Kidneys from brain-dead donors with a 1.7 times relative risk of graft failure. These include any donor > age 60 or > age 50 with a history of hypertension, CVA death or creatinine >1.5mg/dL.
- Due to imbalance between the supply of brain-dead deceased donors and the growing demand for kidneys.
- a number of donor organs with extended criteria that convey about a 10% worse overall graft survival have been incorporated into the donor pool.

Technique - recipient

- The kidney graft is usually placed extraperitoneally in the contralateral iliac fossa through a modified Gibson incision so that the renal pelvis and ureter are the most medial and superficial of the hilar structures.
- The commonest arterial anastomosis is renal artery or, in the case of a deceased donor kidney transplant, an aortic patch, to the side of the external iliac artery.
- The renal vein is usually anastomosed to the side of the external or common iliac vein.
- Urinary tract reconstruction is usually by extravesical ureteroneocystostomy.


Donor kidney
Renal artery
Renal vein
Right iliac artery
Ureter
Right iliac vein
Bladder
A.D.A.M.


Diseased kidneys
Transplanted kidney
Body's own ureters no longer function
Transplanted ureter
Bladder

Outcome

The major reasons leading to improved outcomes are:

- more potent yet selective immunosuppression.
- better surgical techniques.
- more sensitive cross-matching.
- and better prophylaxis and treatment of morbid infections.

- There is also an emerging consensus that transplantation, immediately prior to the need to dialysis, is advantageous in reducing much morbidity and even mortality.

Complications

- Delayed Graft Function.
- Kidney Transplant Rejection.
- Immunosuppression Side Effects.
- Hematuria.
- Hemorrhage.
- Graft Rupture due to acute rejection or renal vein thrombosis.
- Renal Artery Stenosis.
- Renal Artery Thrombosis.
- Fluid Collection with or without Hydronephrosis: pus, lymphocele, urinoma.

Complications

- Wound Infection.
- Urinary Tract Infection.
- Other Infections.
- Renal Calculi.
- Deep-Vein Thrombosis and Pulmonary Embolism.
- Post-transplant Hypertension: Causes for this are intrinsic renal disease, rejection, transplant renal artery stenosis, and calcineurin inhibitor toxicity
- Vascular Disease.
- New-Onset Diabetes Mellitus.
- Urologic Malignancy.

Types of rejection

- Hyperacute (at time of operation).
- Acute 2-3 months later.
- Chronic after years.

Hyperacute rejection

- Mediated by preformed antibodies which recognize HLA antigens in donor organ.
- Usually these are formed as a consequence of pregnancy, blood transfusion, autoimmune disease prior organ transplantation.
- Fibrinoid necrosis leads to immediate graft loss .
- Delayed form may occur several days following transplantation.
- Treatment: Plasmapheresis and pulse steroids may be used.

Acute rejection

- Mediated by activated T-lymphocytes
- Manifests usually in the first 6 months
- Increased serum Cr with or without Oliguria.
- Treatment: pulse steroids, antithymocyte globulin(muromunab), tacrolimus, IVIG.
- More than 90% of episodes can be reversed.

Chronic rejection

- Clinically manifests as slow gradual decline in renal function usually> 6 months after the transplant, and is typically accompanied by moderate to heavy proteinuria.
- Histologically characterized by Glomerulosclerosis, interstitial fibrosis, and obliteration of arteriolar lumina.
- Treatment is unsatisfactory.

Immuno-suppressive Medications

- Induction:
  - Corticosteroids
  - Anti-thymocyte globulin(ATG)
  - IL-2receptor antagonists
- Maintenance:
  - Corticosteroids
  - Calcineurin inhibitors(CNIs)
  - mTORinhibitors
  - Antimetabolites

  - Immunosuppression is usually started during the deceased donor kidney transplant procedure. For elective living renal donor kidney transplantation, immunosuppression is commonly started a week before transplantation.

Renal transplantation

Major cause of long-term allograft failure:

1. Chronic rejection
2. Death with functioning graft

Most common cause of death after kidney transplant:

1. Cardiovascular disease
2. Infection

Chronic Allograft Dysfunction: Why Do Grafts Fail?

- Chronic low-grade immune injury.
- Long-standing hypertension.
- Recurrentdisease (diabetic nephropathyor glomerulo-nephritis).
- Repeated episodes ofacute rejection.
- Donordisease.
- Calcineurin inhibitor nephrotoxicity.