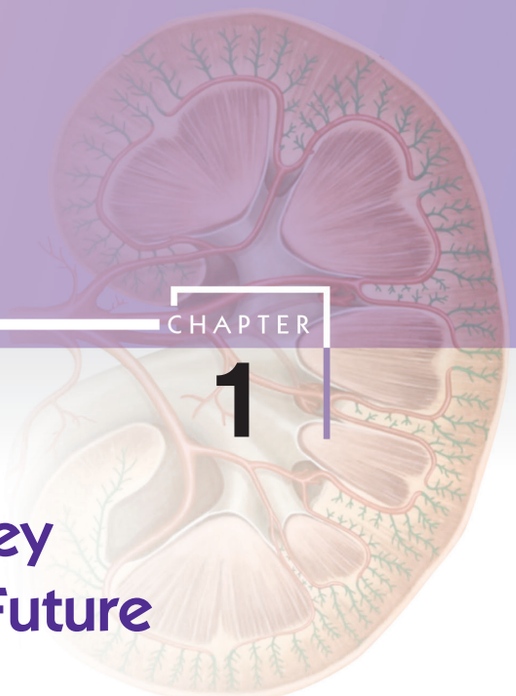

CHAPTER

1

History of Kidney Transplant and its Future

P Venugopal (late), GG Laxman Prabhu (late), Chaitanya Sabnis

OVERVIEW

Man's quest to overcome infirmity due to loss of body parts and end-stage organ disease led to efforts at reconstruction of bodily parts and replacement of organs. The ancient Indian surgical master Sushruta had shown that autologous cutaneous flaps could be used to reconstruct mutilated noses as early as 600 BC.[1]

"Free" skin graft was an extension of this where the transplanted tissue was actually detached from its source which was either the recipient himself (autograft) or a donor from the same species (homograft). Karl Landsteiner's discovery of blood groups in 1901,[2] paved the path for safe transfusion and this was perhaps the first instance of successful transference of cells between individuals of the same species. This also laid the foundation for renal transplantation in the following decades. While Murray's successful effort at renal transplantation between identical twins opened avenues for research in histocompatibility, Carrel's "triangulation" technique of vascular anastomosis considered to be a refinement of existing methods made renal transplantation a doable and a realistic treatment. Advances in anesthesia, technical refinements in dialysis and discovery of immunosuppressant drugs made renal transplantation a reality.

HOMOGRAFT FAILURE

Understanding the fate of homografts was perhaps the crucial point in the success story of transplantation. It was Georg Schöne who showed that homografts always failed and subsequent grafts from the same donor failed more rapidly.[3] Murphy observed that suppressing the lymphocytes by irradiation, splenectomy or benzol extended graft survival.[4]

By the end of 1920s, the tenets of immunology governing transplantation and the pivotal role of the lymphocyte was firmly established by the scientists at Rockefeller Institute.[5]

INITIAL WORKERS IN ORGAN GRAFTING

Although popularly held, Alexis Carrel was not the first to introduce full thickness vascular suturing. Mathieu Jaboulay and Julius Dörfler had shown that it could be done almost a decade before Carrel.[6] Carrel adopted this over partial thickness suturing which he had advocated initially, in organ transplantation which won him the Noble Prize in 1912. Carrrel was also not the first to perform renal transplantation in humans. Jaboulay in 1906 and Unger in 1909 unsuccessfully transplanted animal kidneys in humans but these xenografts never functioned.[7]

Nonetheless, Carrel's relentless work at Rockefeller Institute in animals executed with exceptional skills showed that autografts were consistently successful. This laid the foundation for all future refinements in the surgical technique of transplantation work. Post World War I, working alongside Carrel, Lindbergh developed a pump to preserve organs by perfusion.

EARLY EFFORTS AT RENAL TRANSPLANTATION

The first human to human kidney transplantation was done by the Soviet surgeon Yu Yu Voronoy in 1933. It was an unsuccessful effort as the kidney had been transplanted across major blood group mismatch and procured six hours after the death of the donor.[8]

In most initial transplantation 'experiments', failures were due to rejection and researchers were looking for antibody response as they thought that this was the only mechanism of rejection.[9] Sadly, Leo Loeb's work in 1930s on cell mediated immunity remained unrecognized owing to contemporary professional jealousy.[10]

Even though success of renal transplantation seemed remote, non availability of dialysis prompted surgeons to justify their continued efforts at kidney transplantation in the first quarter of the twentieth century. In 1951, Küss in Paris used kidneys retrieved from guillotined criminals for transplantation. The kidneys were placed in the retroperitoneum and revascularized using iliac vessels while the ureter was anastomosed to the bladder. The method devised by Küss is still the standard approach.[11] Around the same time, in Boston, David Hume tried his hand with placing the graft in the thigh with ureter exteriorized.[12] Both the Paris and Boston exercises confirmed the futility of renal homografting but the workers from these two centers had reached the threshold of modern era of transplantation.

THE FIRST SUCCESSFUL RENAL TRANSPLANTATION

Rupert Billingham in his reminiscences published in 1991 gives an account of how he and his mentor Peter Medawar had chanced upon the finding of acceptance of skin grafts exchanged between chimeric bovine fraternal twins which proved to be the key to understanding tolerance.[13] Barely 14 months after this report, Boston witnessed the most adored landmark in the history of renal transplantation on 23rd December 1954. Joseph Murray used patient's identical twin as donor to bypass the obstacle of rejection.[14] Viewed rationally, it was only a technical success as it was a well known fact that skin grafts between identical twins were not rejected.[15]

Rejection continued to haunt Murray's team as chimerism was difficult to induce in humans and an identical twin as donor was an extremely rare chance! Murray and

colleagues used total body irradiation (TBI) and donor bone marrow to condition the immune status of recipients in a total of 12 patients. All 11 of these 12 died but the one who survived had received the organ from his fraternal twin. This recipient had not received bone marrow from the donor.[14] It had been postulated then that, the donor and donee had become chimeric during gestation by the exchange of tolerogenic blood. Around the same time, Rene Küss in Paris showed that TBI alone was sufficient in recipients who received organs from non-twin donors[16] and chimerism was not necessary for successful outcomes.

QUEST FOR DRUG-INDUCED IMMUNOSUPPRESSION

Although, Hamburger and Küss used adrenal corticosteroids and 6-mercaptopurine (6-MP) along with TBI, it was in 1960, Schwartz and Dameshek reported that cutaneous homografts had an extended survival when the recipient was pretreated with 6-MP. This was an entirely drug based immunosuppression.[17] Encouraged by this work, Roy Calne in London used the same drug in dog kidney homografts and observed a significant enhancement in the graft survival.[18] When Calne tried 6-MP in humans he was in for disappointment. All his three human recipients died without any function in the grafts.[19] Thereafter, Calne obtained a research fellowship with Joseph Murray and while doing this, Murray advised him to persist with TBI. Instead, Calne obtained azathioprine, a derivative of 6-MP from its originators Hitchings and Elion and used it in his dog kidney homografts with considerable success. Both Hitchings and Elion were subsequently awarded Nobel Prize for developing this immunosuppressive agent. This work stimulated Murray's team to use this drug in human renal transplantation. In spite of availability of this immunosuppressant, renal homografts rarely survived beyond 1 year. In 1963, Tom Starlz from Denver presented results with "cocktail immunosuppression" at the National Research Council Conference held in Washington. When Azathioprine was combined with prednisone, the renal graft survival was more than 70% at one year. This protocol soon became the standard and remained so for next two decades.[5]

EVOLUTION OF RENAL TRANSPLANTATION AS RENAL REPLACEMENT THERAPY

The period between 1964 and 1980 saw the evolution of renal transplantation as a feasible therapy for patients with end-stage renal disease.

Willem Kolff pioneered hemodialysis in Holland during World War II. Chronic kidney disease could now be treated by hemodialysis alone after the successful introduction of long-term vascular access by Belding Scribner in 1960.[20] In 1966, Cimino and Brescia introduced subcutaneous arteriovenous fistula creation to arterialize the superficial veins which could be used for hemodialysis. Soon hemodialysis was established as one of the methods of renal replacement therapy.

In 1968, the Harvard ad hoc committee on brain death published its recommendations, according to which irreversible cessation of brain function could be accepted as death. It took several decades for nations to legislate brain death as the end point at which organ retrieval could be initiated.

By 1963, considerable refinements in organ preservation were made.[21] Collins in 1969 introduced pre transplantation infusion of the kidney with cold solution into the renal

artery, which became the standard. Folkert Belzer used University of Wisconsin solution as a perfusate to extend the preservation time of harvested kidney.[22] Soon *in vivo* and *ex vivo* techniques for cooling of the organs using cold perfusates were standardized which are practiced world over today. Organ preservation for longer durations made organ sharing among transplantation centers which eventually led the US congress to pass National Transplant Act in 1984.

Tissue matching became a reality when Jean Dausset discovered the first human leukocyte antigen in 1958.[23] Antibodies against this antigen were soon identified in transfused patients and in multiparous women[24] (van Rood et al. 1958) Paul Terasaki developed a microcytotoxicity assay which tested donor cells against recipient's serum.[25] Since then, typing improved with the discovery of additional histocompatibility antigens including those on class II locus (D and DR).[26]

During this period, Starlz used antilymphocyte serum (ALS) clinically and demonstrated its efficacy in renal allografts. Monoclonal derivatives of ALS directed at T lymphocytes and their subsets or their interleukin 2 receptors were soon developed and these became the mainstay of induction therapy in the pecking order of immunosuppressants.[27]

Then came the "wonder drug"-cyclosporine, a fungal derivative with immunosuppressive properties.[28] It is Calne again to use it as a single drug regimen in 1979. He found it more potent than azathioprine but toxic at higher doses causing infections, tumors and renal failure[18] (Calne 1979). Soon Starzl showed that adding prednisone resulted in marked improvements in graft survival.[29] Cyclosporine stood its ground till 1989 when Starzl et al. showed that Tacrolimus could contain organ rejection resistant to cyclosporine and steroids.[29]

IN THE LAND OF SUSHRUTA—INDIAN SCENARIO

The first ever human kidney transplantation in India was attempted at the KEM Hospital in Mumbai in May 1965 by PK Sen and DS Pardanani. The kidney from a deceased donor was transplanted in a recipient who had a hypernephroma but no renal failure. The same team had made a second attempt in April 1966, again the kidney had come from a deceased donor but it was for a case of chronic renal failure this time. The details of these two transplants are available in the *Indian Journal of Surgery* published in February 1967. Both these patients had perished in the early postoperative period. The death of the first patient on 11th postoperative day due to myocardial infarction, snatched the glory of accomplishing the first ever renal transplantation in India from the erstwhile Bombay team although the patient had a functioning graft.

The second patient died on postoperative day 3 due to bilateral pneumonic consolidation. This team made its third attempt in a recipient with chronic renal failure using a cadaver kidney. To its disappointment, this patient succumbed to sepsis on post-operative day 12.[30] This was followed by an attempt at deceased donor transplant by Dr Udupa and his team with its meager facilities in Banaras Hindu University, Varanasi in 1968.[31]

The credit for doing the first successful live donor renal transplant in India goes to CMC Hospital in Vellore. This epoch making feat was achieved on 2nd February 1971, by a team which comprised Dr M Mohan Rao (Urologist); KV Johny (Nephrologist)

and Martin Isaac (Anesthesia). According to recorded accounts of this landmark effort, the administration then in Vellore was skeptical about it and the director Dr JKG Webb would give the team only one chance and warned it of closing the program in event of failure. Since two theatres were required, the team had been forced to work in the night after the day's work had been completed. As there was only one chance, the team had readied two pairs of donor and recipients to enhance the chances of success! An account of first five successful kidney transplantation appeared in Indian Practitioner in July 1972. Team Vellore conclusively showed that renal transplantation was feasible in India and has a future. (The Golden Years 1965–2015, Department of Urology).[32]

It has been an arduous journey since then to the Promised Land for patients with end stage renal disease. Soon the quest for drugs to improve graft survival followed. Commerce crept into the world of kidney transplantation when potential donors were remunerated with middle men ruling the roost. When laws (THOTA) were promulgated for the first time in 1994 accepting brain death as end of life, organ retrieval from deceased donors was possible.

India has made great strides in organ transplantation since then. From the mythical time line of transplanting an elephant's head to revive his son *Ganesha* by *Lord Shiva* and the successful rhinoplasty using skin flaps by *Sushruta* approximately in mid first millennium BCE, our ancient land has come a long way!

INDUCING TOLERANCE—THE ULTIMATE GOAL

Lifelong immunosuppression is a need for organ survival after transplantation owing to a near assured risk of rejection. Several drugs were added to the immunosuppressive armamentarium of transplant physicians by 1990s. Modified cyclosporine, mycophenolic acid basiliximab, daclizumab, sirolimus, everolimus and belatacept are some of these (Nelson et al. 2022). For the organ recipients, the drug free immunosuppression by inducing tolerance will be the ultimate gift scientists can give.

MINIMAL ACCESS AND ROBOTICS

When Ratner did the first live donor nephrectomy laparoscopically in 1995, it was hard to imagine a delicate surgery like organ retrieval could be achieved by this route (Ratner 1995)[33] The next triumph was registered by Stuart R. Geffner by performing the first robot-assisted kidney transplant in the world at Saint Barnabas Medical Center, New Jersey in 2008.[34] Drs Pranjal Modi and Rajesh Ahlawat are the pioneers of robotic renal transplantation work in India.[35]

Advent of minimal access techniques and robotics in the surgical arena brought about further improvements in the surgical execution of organ retrieval and transplantation.[36,37]

XENOGRAFTS REVISITED

In 2023, in the US, gene edited pig kidney was transplanted into a brain dead recipient which survived for a few days. This is perhaps the beginning of a new era of hope for hundreds and thousands of patients waiting to receive an organ.[38]

NOBEL LAUREATES GALORE

History of organ transplant is the success story of mankind and man's quest to extend life after irreversible organ damage. No wonder then, a total of 19 Nobel prizes have been awarded to the workers in this field.[5]

FUTURE

The quest for a genetically engineered organ built in the lab which can be placed in the recipient's body and calls for no immunsuppressives continues. This is where future of organ transplantation lies. But that day seems distant!

Acknowledgements: The authors acknowledge the research inputs received from Dr Sujata Patwardhan and Dr Pankaj N Maheshwari, Mumbai, India during preparation of this chapter.

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CHAPTER

2

Medical Optimization of Chronic Kidney Disease Patients before Prospective Kidney Transplantation

Abhijit Konnur

INTRODUCTION

The steadily rising prevalence of chronic kidney disease (CKD) represents a significant health challenge globally. Among the various renal replacement therapies for end-stage renal disease (ESRD), kidney transplantation is considered as the gold standard due to its potential to provide better long-term outcomes and improved quality of life when compared to dialysis. Kidney transplant recipients have significant all cause and cardiovascular mortality benefits as compared to dialysis patients and also better quality of life.[1] However, successful kidney transplantation requires meticulous medical optimization of CKD patients to enhance their medical outcomes transplantation and to minimize perioperative risks. This chapter aims to explore the medical optimization strategies for CKD patients in preparation for kidney transplantation.

RATIONALE FOR MEDICAL OPTIMIZATION

Improved graft survival: A well-optimized patient offers a healthier environment for the transplanted kidney, leading to improved long-term graft function and reduced risk of rejection and failure.

Reduced surgical complications: Optimizing medical factors like blood pressure and diabetes control minimizes perioperative risks and promotes faster recovery.

Enhanced posttransplant outcomes: By addressing underlying medical conditions, patients experience improved overall health, QOL and a better quality of life after transplantation.

When: All patients with progressive chronic kidney disease (CKD) G4-G5 (glomerular filtration rate [GFR] <30 ml/min/1.73 m^2) should be educated about, and considered for kidney transplantation irrespective of socioeconomic status, gender identity or race/ethnicity.

Who: Potential kidney transplant candidates should be evaluated at least 6–12 months prior to anticipated dialysis initiation to identify potential donors and plan for

possible preemptive transplantation. Potential candidates are medically stable dialysis requiring patients whose underlying kidney failure is deemed irreversible. Preemptive transplantation (living or deceased donor) in recommended in adults when the estimated glomerular filtration rate (eGFR) is <10 ml/min/1.73 m^2 or earlier and onset of uremic symptoms especially nausea/vomiting or weight loss. Preemptive transplantation (living or deceased donor) in considered children when the eGFR is <15 ml/min/1.73 m^2 or earlier with uremic symptoms.[2,3]

Who is not a candidate?[3,4]

1. Multiple myeloma, light chain deposition disease or heavy chain deposition disease. Exception are post stem cell transplant and in stable remission.
2. AL amyloidosis with systemic involvement
3. Progressive neurodegenerative disease of brain or spinal cord
4. Severe irreversible obstructive or restrictive lung disease
5. Severe uncorrectable and symptomatic cardiac disease
6. Decompensated cirrhosis (consider for combined liver-kidney transplant)

Who require optimization?

1. Current Substance abuse affecting decision making or may trigger posttransplant risk.
2. Unstable psychiatric disorder affecting decision making or posttransplant self care
3. Adherence deficit for medications or safe lifestyle habits
4. Partially treated active infection (excluding hepatitis C virus infection)
5. Active malignancy
   Exceptions: Indolent and low-grade cancers
   Prostate cancer (Gleason score ≤6)
   Incidentally detected renal tumours (≤1 cm in maximum diameter)
6. Active symptomatic cardiac disease (e.g., angina, arrhythmia, heart failure, valvular heart disease) not evaluated by physician
7. Active symptomatic peripheral arterial disease
8. Active symptomatic gastrointestinal disorders: Peptic ulcer disease, diverticulitis, acute pancreatitis, gallstone/gallbladder disease, inflammatory bowel disease.
9. Recent stroke or transient ischemic attack
10. Acute hepatitis
11. Severe hyperparathyroidism.

PATHOPHYSIOLOGY OF CHRONIC KIDNEY DISEASE AND OPTIMIZATION GOALS

Understanding the pathophysiology of CKD is essential for the effective disease risk stratification and optimization of patients after kidney transplantation. Some renal diseases have high risk of recurrence.

1. **Primary focal segmental glomerulosclerosis (FSGS):** It does not warrant exclusion but the risk of recurrence should be highlighted. Recurrence of FSGS lesion in previous transplant and graft failure indicates a high risk of recurrence in subsequent transplantation. Genetic testing (e.g., for podocin and nephrin gene mutations) especially in children and young adults should help promote transplantation as

recurrence in such cases is rare. The current recommendation is to avoid routine use of pretransplant plasmapheresis or rituximab to reduce the risk of recurrent FSGS.[5–7]

2. **Membranous nephropathy (MN):** Increased levels of autoantibodies to phospholipase A2 receptor (PLA2R) pretransplant increase the risk of recurrence. Pretransplant Rituximab or alkylating agents usage is not recommended to reduce the risk of recurrent MN especially patients with quiescent PLA2R levels.[8–10]
3. **IgA nephropathy (IgAN) and IgA vasculitis:** Do not require exclusion but the risk of recurrence of 10–60% should be explained.[11–13]
4. **Immune complex-mediated membranoproliferative glomerulonephritis (IC-MPGN) and C3 glomerulopathy (C3GN):** Risk of recurrence is very high. Early investigation and treatment of an infective, autoimmune, or paraprotein-mediated cause of IC-MPGN prior to transplantation should be undertaken decrease risk of recurrence. Candidates with C3GN should be screened for genetic or acquired causes for the dysregulation of the complement alternative pathway and predict recurrence. Loss of a prior graft due to recurrent C3GN indicates a very high risk of recurrence and deceased donation kidneys are best option.[6,14–17]
5. **Lupus nephritis:** Lupus activity should be clinically quiescent with requirement of minimal immunosuppression prior to transplantation. Primary or secondary antiphospholipid antibodies syndrome does not exclude candidates from kidney transplantation; however, the risks of posttransplant thrombosis and perioperative anticoagulantion plan must be finalized before surgery. The APS should be clinically quiescent prior to transplantation and anticoagulation (e.g. aspirin, warfarin) should be continued even on waitlist.[18–22]
6. **Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis:** Its suggested that ANCA-vasculitis should be clinically quiescent prior to transplantation.[23–28]
7. **Antiglomerular basement membrane (anti-GBM) disease:** Anti-GBM antibody titres should be undetectable prior to transplantation.
8. **Hemolytic-uremic syndrome (HUS):** renal failure due to HUS infection with a Shiga-toxin producing organism, usually *E. coli* (STECHUS) can undergo kidney transplantation as recurrence is unusual. Candidates with suspected atypical HUS (aHUS) due to genetic or acquired defect in complement regulation or other genetic causes of aHUS have high-risk of recurrence. In such candidates having abnormality in complement regulation gene places them at high risk of recurrence especially with CFR homozygous gene deletion. Kidney transplantation should not proceed unless a complement inhibitor can be administered or combined liver-kidney transplant can be performed.[29–34]
9. **Systemic sclerosis:** In the absence of severe pulmonary, gastrointestinal, or other life-threatening extrarenal disease, patient can undergo kidney transplantation.[35,36]
10. **AA amyloidosis:** Adequate treatment of the underlying cause is undertaken and presence of severe extrarenal organ involvement, especially cardiac amyloidosis detected by cardiac MRI excludes patient as candidate.[37–40]
11. **Hyperoxaluria (oxalosis), primary and secondary:** Candidates with primary hyperoxaluria type 1 should be considered for combined or sequential liver-kidney transplantation. Genetic testing to identify the cause of primary hyperoxaluria

should be undertaken and correctable hyperoxaluria—pyridoxine responsive or secondary may undergo transplantation but with due risk of recurrence. Strategies to lower total body oxalate burden prior to transplantation should be undertaken including intensive dialysis, dietary modification, and pyridoxine treatment as appropriate on a case-by-case basis. Lumasiran and nedosiran are newer drugs which decrease oxalate levels. There is limited knowledge with regards to kidney transplantation. Lumasiran are small interfering RNA therapies which targets glycolate oxidase and decreases hepatic oxalate synthesis, systemic oxalate release continues after single-organ kidney transplantation, requiring close follow-up with rigorous hyperhydration.[41–45]

12. **Cystinosis, Fabry disease, sickle cell disease, Alport's syndrome:** They are rare disease which can be considered for kidney transplantation when severe extrarenal manifestations are absent.

Active Infections

Kidney transplantation should be deferred until active infections (bacterial, fungal, viral [except hepatitis C], parasitic) are treated and preferably cured.

1. **Colonization:** Asymptomatic bacterial, parasitic or fungal colonization does not require delaying renal transplantation but local infection control protocols for detection and management of colonization with drug resistant organisms should be followed.
2. **Urinary tract infections (UTIs):** Symptomatic UTIs need to be treated prior to kidney transplantation with at least 1 urine culture report negative prior to surgery. Prophylactic nephrectomy for recurrent pyelonephritis or cyst infections are not routinely required but undertaken when there is chronic, recurrent, relapsing infection or with MDRO.[46]
3. **Tuberculosis:** Although complete treatment of active TB prior to kidney transplantation is suggested as per World Health Organization, many centres including ours utilise the intensive 4 drug regimen including rifampicin for 2 or 3 months and then transition to 2or 3 drug non-rifampicin based regimen before undertaking a transplantation. Its imperative that the patient show symptoms of improvement in terms of weight gain and appetite, resolution of fever, cough, hemoptysis and lymphadenopathy. Also there should be resolution of radiological findings and sputum smear negative before surgery. In case rifampicin is deemed necessary even after transplantation, tacrolimus dose should be started 2 weeks prior and surgery undertaken only after stable therapeutic levels attained. The dose required may be 2–7 times more than in routine non rifampicin based regimens. Also no active drug toxicities like hepatitis, joint pains, INH encephalopathy, optic neuritis must be present before surgery. Screening for latent TB involves chest X-rays and sonographic assessment and CT scans as extrapulmonary TB is common in CKD population.[47–53]
4. **Screening** for periodontal disease and dental evaluation is recommended.
5. **Viral infections:**
   a. *Human immunodeficiency virus (HIV):* Patients with HIV infection in remission can undergo kidney transplantation in a centre with experience in this area.

Patient should be asymptomatic with no AIDS defining lesions, have CD4 levels >500/mm^3, undetectable RNA copies, non-protease inhibitor containing stable antiviral regimen.[54–56]

b. *Hepatitis C virus (HCV):* Kidney transplantation is the best therapeutic option for patients with CKD 5D even in the presence of HCV infection. All candidates with HCV infection be evaluated for severity of liver fibrosis and presence of portal hypertension. Only patients with HCV and compensated cirrhosis (without portal hypertension) may undergo isolated kidney transplantation and patients with HCV and decompensated cirrhosis should be considered for combined liver-kidney transplantation. Although AASLD recommendation is to defer HCV treatment until after transplantation, many centers start and complete therapy of HCV over 3 months on dialysis during work up and patients with Sustained viral response can undergo kidney transplantation. Factors which influence timing of HCV treatment before or kidney transplantation are based on donor type (living vs. deceased donor), waitlist times, center-specific policies regarding the use of kidneys from HCV-infected deceased donors, HCV genotype and severity of liver fibrosis. Candidates with HCV infection and having a living kidney donor should undergo kidney transplantation at earliest and antiviral treatment can continue before or after transplantation according to HCV genotype. Due to shortage of organs, HCV NAT-positive patient can undergo transplantation with an HCV positive kidney and be treated for HCV infection after transplantation.[57,58]

c. *Hepatitis B virus (HBV)* requires screening for HBV infection with HBsAg, anti-HBs, and anti-HBc. HBV DNA titre is assessed for patients with a positive HBsAg or anti-HBc. HBsAg positive and/or HBV DNA positive candidates should be seen by a hepatologist for appropriate HBV infection antiviral treatment. HBsAg positive and/or HBV DNA positive candidates can undergo isolated kidney transplantation if they do not have decompensated cirrhosis and are stable on antiviral therapy. Anti-HBc antibody positive (HBsAg negative) are considered low risk for reactivation and do not require antiviral prophylaxis but require posttransplant monitoring of HBsAg and HBV DNA for a minimum of 1-year post transplantation.[59,60]

d. *Endemic infections:* Syphilis, strongyloidiasis, Chagas' disease, malaria treatment prior to transplantation, if infection is identified.

Vaccinations

Vaccination using an accelerated schedule, if required, is undertaken prior to kidney transplantation for any inactivated vaccines and can be completed even after transplantation. For live attenuated vaccines, vaccination must be completed prior to kidney transplantation and a 4-week delay in kidney transplantation is enforced if a live vaccine is administered (e.g. MMR, VZV, shingles, yellow fever, oral typhoid, oral polio vaccine). Splenectomized candidates or those at increased risk for posttransplant splenectomy should receive pretransplant pneumococcal, *Hemophilus*, and meningococcal vaccination. Candidates who receive complement inhibitor therapy need to undergo meningococcal vaccination and appropriate antibiotic prophylaxis till 1 month of vaccination is elapsed. Some vaccines are

recommended based on age, direct exposure, residence or travel to endemic areas, or other epidemiological risk factors like rabies, tick-borne meningoencephalitis, Japanese encephalitis (inactivated), *Meningococcus*, *Salmonella* Typhi (inactivated), Yellow fever.[61–64]

Cancer Screening

Recommended for candidates as per local guidelines for the general population:[65–71]

1. Chest X-ray prior to transplantation in all candidates with CT chest for current or former heavy tobacco abusers (≥30 pack-years).
2. Candidates at increased risk for renal cell carcinoma (e.g. ≥3 years dialysis, family history of renal cancer, acquired cystic disease or analgesic nephropathy) assessed with ultrasonography or CT KUB with contrast. Cystoscopy to screen for bladder carcinoma in candidates at increased risk, such as those with high-level exposure to cyclophosphamide or heavy smoking (≥30 pack-years).
3. Ultrasound, α-fetoprotein and PET-CT caused to screen for hepatocellular carcinoma in candidates with cirrhosis prior to transplantation.
4. Screening for bowel cancer in candidates with inflammatory bowel disease or age >60 years with upper and lower GI endoscopy or as per local protocol.
5. Potential kidney transplant candidates with cancer:
   a. Candidates with active malignancy are excluded from kidney transplantation Exceptions (indolent and low-grade cancers)
      i. Prostate cancer (Gleason score ≤6)
      ii. Superficial nonmelanoma skin cancer
      iii. Incidentally detected renal tumours (≤1 cm in maximum diameter)
      iv. Curatively treated (surgically or otherwise)
         - Non-metastatic basal cell and squamous cell carcinoma of the skin
         - Melanoma *in situ*
         - Small renal cell carcinoma (<3 cm)
         - Prostate cancer (Gleason score ≤6)
         - Carcinoma *in situ* (ductal carcinoma *in situ*, cervical, others)
         - Thyroid cancer (follicular/papillary <2 cm of low-grade histology)
         - Superficial bladder cancer

      Decisions about transplantation for candidates in remission from cancer is made after discussion in a tumor board collaboratively with oncologists, transplant nephrologists, patients, and their caregivers.

      Patients with a history of metastatic cancer are not excluded provided that potentially curative therapy has been administered and complete remission achieved but the risk of recurrence should be borne in mind.

      Hematologic malignancy management and candidacy for transplantation is a complex situation and requires a discussion between the hematologist, patient and transplant team. Usual yardstick is to approve patients for kidney transplantation with estimated survival comparable to national standards.

   Its recommend preemptive transplantation with a living kidney donor as the preferred treatment for transplant-eligible CKD patients.

COMORBID CONDITIONS

Cardiovascular Disease (CVD) and Management of Cardiovascular Risk Factors[72–78]

Leading cause of death in CKD patients. Aggressive management of hypertension, dyslipidaemia, and diabetes is essential through lifestyle modifications and medications. All candidates require assessment for the presence and severity of cardiac disease with history, physical examination, and electrocardiogram (ECG). Symptomatic patients with cardiac disease will require treatment of underlying cardiac disease and have acceptable risk for noncardiac surgery and estimated survival of minimum of 10 years before being considered for renal transplantation. Risk stratification is done for asymptomatic candidates with high-risk for coronary artery disease (CAD) (e.g. diabetes, previous CAD) or with poor functional capacity using undergo noninvasive CAD screening like echocardiography and stresstests. Asymptomatic candidates with known CAD should not be revascularized exclusively to reduce perioperative cardiac events.

Patients with asymptomatic, advanced triple vessel coronary disease be excluded from kidney transplantation unless they have an estimated survival comparable to national standards. Pulmonary vascular disease assessed using echocardiography: Asymptomatic candidates with dialysis vintage of 2 years and patients with portal hypertension, connective tissue disease, congenital heart disease, chronic obstructive pulmonary disease who have an estimated pulmonary systolic pressure greater than 45 mm Hg should be assessed by a cardiologist for surgical fitness and long-term prognosis. Uncorrectable pulmonary artery systolic pressure greater than 60 mm Hg (obtained from right heart catheterization), severe valvular heart disease, uncorrectable symptomatic New York Heart Association (NYHA) functional Class III/IV heart disease [severe CAD; left ventricular dysfunction (ejection fraction <30%); severe valvular disease] require indepth cardiac management and optimisation before considering for kidney transplantation.

Candidates with coronary artery disease who have a myocardial infarction require treatment of CAD by cardiologist and appropriate time for transplant surgery. Transplantation may be delayed after placement of a coronary stent due to use of strong antiplatelet agents till such time as recommended by the patient's cardiologist.

Peripheral Vascular Disease

Candidates without clinically apparent PAD, but at high-risk for PAD, undergo noninvasive vascular testing like Doppler, duplex and CT angiographies. Candidates with clinically apparent PAD should undergo imaging and management of their PAD in consultation with a vascular surgeon prior to transplantation. Candidates with nonhealing extremity wounds with active infection are not transplanted until the infection is resolved and critical limb ischemia addressed. Patients with severe aortoiliac disease or distal vascular disease, prior aortoiliac procedures including iliac artery stent placement can be considered for kidney transplantation provided there is sufficient native artery available for vascular anastomosis and patients explained the risk of progression after transplantation.[4,79]

Diabetes Mellitus

Strict glycaemic control reduces the risk of posttransplant infections and complications. Candidates with ESRD and type 1 DM should be considered for simultaneous pancreas-

kidney transplantation wherever feasible. Testing for abnormal glucose metabolism by oral glucose tolerance test is done in all candidates who are not known to have diabetes. Its good practise of achieving targeted blood glucose levels of 80–130 mg/dl in fasting state and post meals 2 hours of 100–200 mg/dl prior to surgery. HbA1c levels can be erroneous in CKD patients. It is prudent to utilise rapid short-acting insulins to achieve this purpose. Only oral hypoglycemics like linagliptin, repaglinides and GLP1 receptor agonists can be used in CKD 5 state. It is important to note that patient on GLP 1 receptor agonists should be stopped at least 1 week prior to surgery as they can cause chronic gastroparesis and aspiration hazard. They may also interfere with absorption of immunosuppressant medications. Perioperative management shall involve transition to Insulin infusion pump use with continuous blood glucose monitoring to maintain euglycemia.[80–83]

Anemia and Blood Disorders

Erythropoietin-stimulating agents (ESAs) and iron therapy (oral and parenteral) can address anemia and improve overall well-being. It is prudent to target a minimum haemoglobin level of 10 g/dl before transplant surgery. This is important in some patients who have increased risk of perioperative blood like plasmapheresis requirement, on antiplatelets, poor vascular health. In case blood transfusion are required, use of irradiated packed cell volume, leukocyte depleted fractionated red cell volume are recommended. Leukocyte filter use may mitigate but not eliminate the risk of alloreaction. Nutritional anemias and blood loss due to GI lesions will require targeted management.

Patients who have experienced a venous thromboembolic event need to be screened for thrombophilia. A history of recurrent arteriovenous access thromboses, non-atherosclerotic arterial thrombosis, or family history of venous thromboembolism are at high risk of graft thrombosis. Single antiplatelet agents (e.g. aspirin, clopidogrel, ticagrelor) can be continued while wait-listed for deceased donor transplant. Elective kidney transplantation should be delayed for the mandated period of treatment with dual antiplatelet therapy (e.g. aspirin plus clopidogrel) when the risk of stopping medication (e.g., stent thrombosis) or operating while on treatment (e.g. surgical bleeding) exceeds the anticipated benefit of transplantation. Antiplatelet agents (except aspirin) should be stopped 5 days prior to living donor transplantation (unless cessation is contraindicated) and during the perioperative period for deceased donor transplantation. Patients on direct-acting oral anticoagulants (DOACs, e.g. apixaban, rivaroxaban) should not undergo renal transplantation surgery unless centre has specific expertise using DOACs perioperatively and access to DOAC reversal agents. It is prudent to switch to an alternative anticoagulant (e.g. warfarin) when waitlisted for a deceased or living donor transplantation. Nonheparin based agents like fondaparinaux and bivalirudin are utilised for perioperative anticoagulation in candidates with a history of HIT.[84–88]

Mineral and Bone Disorders

Disorders of mineral and bone metabolism are prevalent in CKD patients and can adversely impact transplant outcomes. Severe hyperparathyroidism will require treatment before considering kidney transplantation. If the cause is tertiary or rarely primary hyperparathyroidism with significant bone disease like bone pains,

cystic lesions, fractures and tendon avulsions then selective adenoma surgery/ parathyroidectomy (surgical or medical using cinacalcet/calcimimetics) followed by use of vitamin d analogues and oral calcium supplements may be required until blood corrected ionised calcium levels have normalised and PTH levels decrease to 2–7 times upper limit of local laboratory for at least 2 weeks. Patients with osteoporotic fractures of vertebrae and long bones may require denosumab/ teriparatide therapy undertaken 1 month before surgery so as to achieve stable ionised serum calcium levels 2 weeks prior to surgery.[89–94]

Stroke Management

A waiting time of at least 6 months after a stroke or 3 months after a transient ischemic attack (TIA) is recommended before kidney transplantation. Screening symptomatic candidates for carotid artery disease with 4 vessel MR angiogram/carotid Doppler is recommended. Candidates with autosomal dominant polycystic kidney (ADPKD) disease should be screened for intracranial aneurysms only if they are at high risk due to prior history of or a family history of subarachnoid hemorrhage. Presence of progressive neurodegenerative disease of brain or spinal cord should exclude patients from a transplantation. In contrast, patients with uremic progressive peripheral neuropathy should be considered for urgent kidney transplantation.[95–99]

Gastrointestinal and Liver Disease

Patients with symptoms suggestive of active peptic ulcer disease undergo esophagogastroscopy and *H. pylori* testing prior to kidney transplantation and delay kidney transplantation in candidates with endoscopically-proven peptic ulcer disease until symptoms have resolved. Active diverticulitis is treated till until symptoms have resolved. Prophylactic colectomy in patients with asymptomatic diverticulosis or a history of diverticulitis is not recommended. Kidney transplantation is delayed in patients with acute pancreatitis for a minimum of three months after symptoms have resolved. Candidates with a history of cholecystitis should undergo cholecystectomy before kidney transplantation. Same time it's not recommended to screen asymptomatic candidates for cholelithiasis. Kidney transplantation should be delayed in patients with active symptomatic inflammatory bowel disease and they should undergo screening for bowel cancer prior to transplantation.[100–105]

Medication Management

Optimizing medication therapy pre transplantation is crucial to ensure the safety and efficacy of immunosuppressive regimens posttransplantation. This involves strategies for minimizing drug interactions and adverse effects. Moreover, the importance of medication adherence and patient education is integral to successful transplant outcomes Assessment of adherence and medication discussion pretransplantation allows for appropriate education, counselling and posttransplant surveillance. Its important to refer candidates with a history of health-compromising nonadherent behaviour, medication abuse issues, teenagers and substance abusers and h/o addictions or identified adherence barriers for adherence-based education and counselling pre-transplant. More so in candidates with a history of graft loss due to missed