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Renal Transplant Recipient Workup; Obstacles and Challenges

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ABSTRACT

Renal transplant, undoubtedly, is the best available approach for selected patients with end-stage kidney disease. It enhances life quality and improves life expectancy when compared with dialysis therapy. It is very pertinent to carefully assess patients who are referred for transplantation to identify factors that may limit patient and graft survival, and thereby, saving those patients who are likely to be harmed by transplantation. Presence of multiple comorbidities in patients contemplating renal transplant such as elderly recipients, obese patients, candidates with cardiovascular, pulmonary, concomitant psychiatric diseases, peripheral vascular diseases, thromboembolic disease and candidates with high calculated reaction frequency cRF level (Also called cPRA level, calculated panel reacting antibodies) and heavy smokers are not an absolute contraindication for surgery. Decision making for assessment of patient's suitability for a renal transplant can be complicated. This process of evaluation requires a multidisciplinary approach. A robust process would facilitate careful planning to reduce peri- and post-operative complications.

Keywords: Renal transplant, Recipient, Work up, Cardiovascular disease, Coronary artery disease, Peripheral vascular disease, Sensitisation

INTRODUCTION

Renal transplant, undoubtedly, is the best available approach for suitable patients with end-stage kidney disease. It enhances patients' quality of life and improves life expectancy when compared with dialysis. Nonetheless, not all patients are suitable for kidney transplantation due to the inherent risks of the surgical procedure and the long-term side effects of immunosuppression. Therefore, all potential transplant recipients should have an extensive assessment to identify any co-morbidities and contra-indications that might lead to a sub-optimal outcome [1-3].

Pre-transplant evaluation

The decision making for assessment of patient's suitability for a renal transplant can be complicated. A plethora of guidelines has been developed to help clinicians assess patients appropriately. The objectives of these guidelines are to identify and to treat all concomitant medical issues that may accelerate morbidity and mortality of the transplant surgery. A careful assessment would identify any pre-existing illness that may be aggravated by transplantation. A robust process would facilitate careful planning to reduce

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peri- and postoperative complications. This step-wise approach becomes a part of an effective informed consent process for counselling potential recipients in regard to their potential risks and benefits of transplantation [1,2,4].

The pre-transplant assessments can vary from centre to another, but generally, include:

- Laboratory tests for transplant recipients such as blood chemistries, full blood count, coagulation profile, liver function tests, virology studies (including CMV, varicella zoster, EBV, hepatitis B, C and HIV), bone profile (PTH, calcium, phosphate) and prostatic specific antigen (for men above 50-60 years old) [1-4].
- Additionally, chest radiograph, electrocardiogram, breast ultrasound or mammogram (for women aged 50 years and older and for those with a family history of breast cancer) and Pap smear.
- Immunological evaluation: Recipients of renal allograft should have an immunological assessment to evade any risk of having antibody-mediated rejections. The immunological evaluation consists of 4 following components:
    1. Human leukocyte antigen (HLA) typing
    2. Antibody screening to HLA antibodies
    3. ABO blood group identification.
    4. Cross-matching
- Special procedures might be considered in a number of patients based on relevant history and physical assessment, such as aetiology of kidney disease and risk of recurrence, history of sensitization (pregnancy, transfusion history, former transplant), old and active infections (hepatitis, TB), cardiovascular risks (smoking, diabetes, hypertension), pulmonary, genitourinary disease, gastrointestinal disease, malignancy, psychiatric and surgical issues (such as obesity, iliac vessels disease, urine outflow and earlier abdominal surgery) [1,2,4].
- Pre-transplant surgical interventions: Occasionally, a medical check-up may disclose circumstances that demand surgical interventions to prepare patients for transplantation. Such interventions may consist of the following:

Native kidney nephrectomy or nephron-ureterectomy for certain diseases; such as chronic reflux disease, recurrent infections, persistent pain, intractable hypertension, large polycystic kidneys, or significant proteinuria.

Cholecystectomy: For patients with gallstones

There are currently few absolute contraindications to transplant, such as active infections, non-compliance or substances abuse, malignancy and any illness that might limit life expectancy to less than 1-2 years [1-4].

Evaluation of patients with multiple comorbidities:

Patients with multiple comorbidities are increasingly referred to transplant physicians since the boundaries for acceptance into transplant programs broadened. Each individual problem in itself might not be an absolute contraindication, but cumulatively, they may indicate significantly reduced overall survival prospects.

COMORBIDITIES THAT INCREASE RISK OF TRANSPLANT SURGERY

Age

Age is not a contra-indication to transplant surgery as per most of the international guidelines; yet age related co-morbidities is a significant restrictive factor [3,5-7]. Patients aged 60 years and older are reported to have longer hospitalizations during the early post-transplant period. They have a greater mortality risk secondary to cardiovascular events and more infectious episodes in the first few months after transplantation [7,8]. However, they tend to have fewer acute rejection episodes. Though Meier-Kriesche et al. in his data analysis of USRDS registry demonstrated that elderly recipients are more prone to develop chronic allograft nephropathy.

Despite the fact that patient survival decreases with advancing age, transplanted patients above the age of 60 have a survival advantage when compared to maintenance dialysis. The annual death rate for patients older than 60 years was reported at 10% while on waiting list for transplant, versus 7.4% for those who get a transplant [8]. Older candidates with no medical contraindications should, therefore, be considered fit for kidney transplant, though a comprehensive assessment with careful accentuation on CVD risk and screening for malignancy are of great importance among elderly population [7,9].

Cardiovascular risk

Cardiovascular diseases are common in patients with end stage kidney disease and considered a fundamental risk for morbidity and mortality. Therefore, cardiovascular evaluation is crucial in the assessment of potential transplant candidates. The role of cardiovascular screening for all pre-transplant patients with coronary intervention is controversial and there is variation among different guidelines. Nevertheless, given the high occurrence of cardiac events at peri-transplant and post-transplant period and its real impact on increased mortality; an aggressive screening with possible intervention is required for high risk patients while evading excessive tests and invasive techniques in low-risk recipients [3,6,10-12]. Number of traditional risk factors as diabetes mellitus, hypercholesterolemia, family history of coronary disease in first degree relatives, BMI greater than 30 and smoking, are

well recognized risk factors for ischaemic heart disease in healthy people as well as in renal transplant recipients. Indeed, transplant recipients have additional numbers of those traditional risk factors such as male gender patients, age above 50 years, prolonged duration on dialysis >2 years, history of peripheral vascular disease or ischaemic cerebrovascular disease, previous deceased donor renal transplant and smoking which all can aggravate the risk of coronary artery disease and require detailed cardiac assessment [3,6,10-12].

Different scoring systems are available to calculate cardiovascular risks in transplant candidates. PROCAM score for cardiovascular risk calculation includes age, lipids, smoking, diabetes, family history of CAD and systolic blood pressure while Framingham score does not consider family history, diabetes, triglycerides or differentiation of cholesterol. ESC-SCORE relies on age, gender, systolic blood pressure, smoking and total cholesterol. The Muenster cardiovascular risk stratification scoring on the other hand includes age, diabetes and history of CAD/cardiac intervention or heart insufficiency. All of these scoring systems use cardiovascular disease as end point.

European Best Practice Guideline and American Heart Association/American College of Cardiology Foundation: endorsed by the American Society of Transplant Surgeons, American Society of Transplantation and National Kidney Foundation all had recommended risk stratification for CVD screening in transplant candidates, however, the evidence for the suggested risk classifications is low and all the recommendations should be regarded as an expert opinion [13-15]. Currently, there are no clear and uniform guidelines in regard to the CVD-screening (risk stratification, tests performed, or frequency of reassessment) of waiting list candidates are present.

The following screening measures are indicated [1-3,6,10,11,13]:

12-leads ECG: Chest radiography

Exercise/dobutamine stress echocardiography or myocardial perfusion scintigraphy with exercise/dipyridamole (Exercise ECG has a poor predictive value in dialysis patients, while stress echo and cardiac scintigraphy can both have moderate sensitivity and specificity among dialysis population).

Finally, a coronary arteriography (can be indicated based on above findings).

Where possible these investigations must be done without concomitant B-blockers use. Patients diagnosed to have positive cardiac stress test will be labelled as a high risk for cardiac events and must avoid transplant surgery till further cardiac evaluation and intervention are started [6,11,13,16]. Whether intervention in this group is beneficial in precluding future cardiac events or decreasing post-transplant mortality; still remains indeterminate [11].

Lifestyle modifications are frequently an initial step. Kawachi et al. [17] had shown in his study of 117,006 middle aged women; that smoking cessation had excluded the risk of coronary artery disease by one third during the first 2 years of smoking cessation. Treatment of hypercholesterolemia with statins is broadly acknowledged to play vital role for cardiovascular risk management **(Figure 1)**.

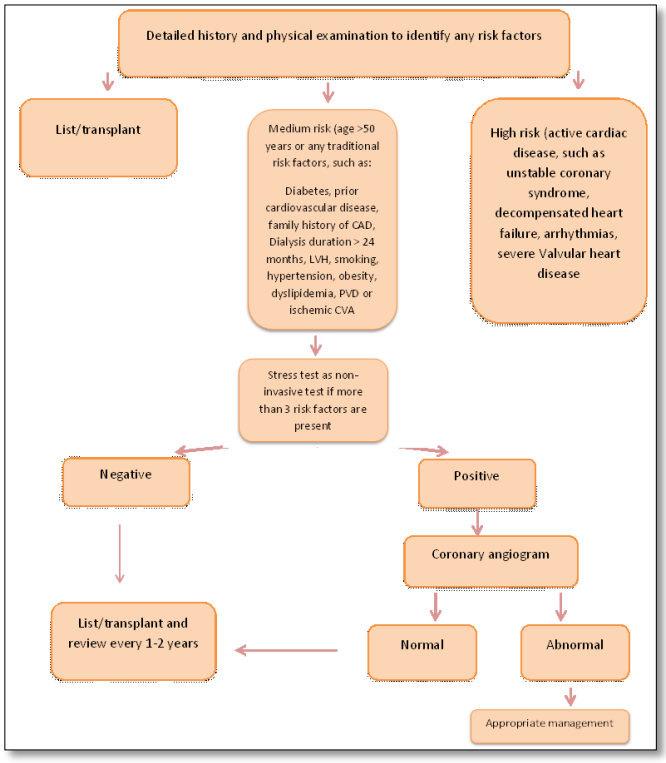

Figure 1. Pre-operative cardiovascular assessment
CAD: Coronary Artery Disease; LVH: Left Ventricular Hypertrophy; PVD: Peripheral Vascular Disease; CVA: Cerebrovascular Disease

Smoking

Cigarette smoking does adversely influence kidney transplant recipients, leading to cardiovascular disease, impairment in allograft function and increased risk of malignancies. Though published studies are small, the results consistently showed a strong relationship between cigarette smoking and reduced patient and graft survival [4,10,18]. Tobacco and cigarette smoke might cause micro-vascular alterations in the transplant vasculature leading to decreased renal plasma flow, enhance platelet aggregation, reduced the vasodilator endothelial nitric oxide generation, increased synthesis of endothelin-1, increased free radical production and accelerates atherosclerosis. Chronic cigarette smoke also increases proteinuria. Moreover, nicotine potentiates the sympathetic nervous system, leading to acute renal vasoconstriction, which is reported to be permanent in smokers [18]. Zitt et al. [19] in their analysis of allograft

biopsies of different chronic transplant smokers had demonstrated histological changes in kidney allografts when smoking had persisted after transplantation, in the form of vascular fibrous intimal thickening, which may act as a possible factor for the development of chronic allograft nephropathy.

The overall quantity of cigarettes packs smoked annually at the time of transplantation remained a better prognostic factor for graft loss; since smoking of 25 pack/years or more (in comparison to a lesser amount or no smoking at all) was concurrent with an increased risk of graft failure by 30% [4,18,20]. It is quite possible that smoking affects graft survival through an increase in mortality due to cardiovascular disease, while there was no association was found concerning smoking and the rate of acute rejection episodes at post-transplant which appears similar to non-smokers [8,18,20].

Lastly, having abandoned smoking more than 5 years preceding kidney transplantation had shown to decrease the relative risk of graft failure by 34%. Proper smoking suspension programmes ought to be offered with an easy access in primary centres [3,4,18,21]. Smoking cessation exhibits encouraging lifestyle behavior and high compliance. However, there is no agreement in the guidelines to deliberate active smoking as a contraindication for transplantation, and regardless if the patient quits smoking before transplantation, there is a tendency to relapse after transplantation [21].

Pulmonary disease

A preliminary evaluation by physical examination and chest radiograph is required for all candidates. Further tests such as pulmonary function tests or computed tomographic examination are conducted based on relevant findings [2,4].

Obesity

Weight gain in dialysis patients has been associated with decreased cardiovascular mortality (probably denoting a better nutritional status) compared to weight loss which is associated with increased mortality risk; a phenomenon known as the obesity paradox. Nonetheless, an elevated BMI above 35 kg/m^2 limits access to transplantation. Morbid obesity was associated with an increased risk of delayed graft function (DGF), prolonged hospitalisation, wound complications, acute rejection and decreased overall graft survival compared with normal weight patients [22,23]. USRDS registry analysis of 51,927 adult kidney transplant patients found a U-shaped association between BMI and death with functioning graft; a J-shaped association between BMI and allograft survival and a graded correlation between BMI and DGF [24].

Though morbid obesity was associated with worse outcomes when compared to ideal body weight recipients, obese patients who received a transplant have better outcomes compared to remaining on dialysis [24]. Furthermore, pre-transplant weight loss was noted to be transient in those patients and associated with rapid weight gain post-transplantation and this has been associated with an increased incidence of post-transplant diabetes mellitus, hypertension, ischemic heart disease and worse patient and graft survival [25].

Patients listed for transplant should be encouraged to lose weight. If a live donor is not available, wait-listing for transplantation should be deferred in patients with a BMI above 40 kg/m^2 and individual assessment should be made on a case-by-case basis for those with a BMI between 30 and 40 kg/m^2. A multidisciplinary approach involving dietary support and supervised exercise programs is ideal to ensure that weight loss is achieved in a healthy manner and to prevent muscle mass loss (sarcopenia), particularly in the dialysis population. For those unable to reach target weight via these means, particularly in the presence of other comorbidities such as hypertension, diabetes mellitus and sleep apnea, bariatric surgery should be considered. However, the risks associated with bariatric surgery need to be weighed up against the increased mortality risk associated with remaining on dialysis [26].

Screening for underlying cardiovascular disease in obese patients is essential. Local surgical expertise, previous experience, dialysis waiting time and presence of other comorbidities determine if a particular transplant candidate can be put forward for transplantation [26].

History of claudication

Peripheral pulses need to be examined carefully in patients with a history of claudication while considering vascular surgeon referral. Vascular assessment should begin with Doppler ultrasound and accordingly, CT angiography/MRA may be required with possible vascular intervention. Significant disease of peripheral vasculatures including iliac vessels might make transplant surgery difficult or impossible and can aggravate distal leg ischemia due to vascular steal syndrome.

Even though it is not an absolute contraindication to transplant, peripheral vascular diseases are accompanied by allograft ischemia, reduced patient survival and higher mortality risk [2-4,10].

Patients with increased risk of disease recurrence

Recurrent glomerulonephritis (GN) remains challenging and can be a challenge to be communicated to patients effectively. GN that occurs in the transplanted kidney can be caused by either recurrent or a de novo disease [27] **(Table 1)**.

Table 1. Recurrent glomerulonephritis following renal transplantation and recurrence related graft loss, modified from Floege [28,29].

	Clinical recurrence rate (% of transplanted patients)	Graft loss after 5-10 years (% of transplanted patients)
IgA nephropathy	10-25% (>50 histologically)	2-16%
FSGS	20-40%	10-20%
MPGN type I	20-50%	10-30%
MPGN type II (DDD)	>80% (histologically)	10-25%
Membranous GN	5-30%	5-20%
ANCA vasculitis	20%	Unknown
SLE	5-30%	<10%

Recurrence of glomerulonephritis (GN) and newly occurring GN (de novo GN) in the transplanted kidney are a frequent cause of allograft loss at 10 years. The prevalence of recurrent GN varies in different literatures from 2.9 to 19.4% and is inversely proportional to recipient age and directly proportional to the duration of follow-up [27-32].

The overall impact of recurrent GN on graft survival is controversial. Those who have recurrence have a higher risk of allograft loss, with recurrence being reported as the cause of graft loss in 1.1 to 4.4% of transplant recipients. Post-transplant proteinuria and/or hematuria remain the hallmark findings suggesting a recurrent GN. Allograft renal biopsy remains the gold diagnostic standard in cases of recurrent GN, and clinicians rely on renal histological findings to diagnose and to prognosticate recurrent GN. Light microscopy, immunofluorescence, and electron microscopy (EM) should be performed in all transplant recipients suspected with disease recurrence [27-32]. Histologic classification can be categorised into four types, according to the type of disease: 1) Recurrence of primary GN: Recurrent FSGS, membranoproliferative GN (MPGN), IgA nephropathy (IgAN), HenochSchonlein purpura, membranous nephropathy (MN). 2) Recurrence of secondary GN; such as systemic lupus erythematosus (SLE), hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS-TTP), rapidly progressive-crescentic GN, anti-glomerular basement membrane (anti-GBM) disease. 3) Recurrence of metabolic or systemic disease: Diabetic nephropathy, amyloidosis, cystinosis, oxalosis, Fabry disease, scleroderma, fibrillary GN. 4) Finally, *de novo* diseases can occur. Early recognition of disease recurrence in patients at-risk can provide great intervention opportunity at early stages of the disease to optimise long-term graft survival [2,27].

As compared with the average for all recipients with a primary diagnosis of glomerulonephritis, the incidence of allograft loss due to recurrence was significantly higher among recipients with focal segmental glomerulosclerosis (adjusted hazard ratio, 2.03 (95% confidence interval, 1.19 to 3.44); P=0.009) and with MPGN type I (adjusted hazard ratio, 2.91 (95% confidence interval, 1.53 to 5.55); P=0.001), as well as among male recipients (adjusted hazard ratio, 2.24 (95% confidence interval, 1.10 to 4.53); P=0.03) and among recipients with higher peak panel-reactive antibody titres (adjusted hazard ratio for each increment of 10%, 1.10 (95% confidence interval, 1.00 to 1.21); P=0.05) [30,31].

Primary FSGS has an overall relapse rate of 30% (34%-56%) for the first transplant which results in accelerated graft loss and 75% in the second transplant if already had recurred once [2,4,6,21,32]. Risk factors related to the high recurrences rate includes; FSGS at younger age, fast progression from initial diagnosis to development of ESRD (≤ 3 years), reappearance in the old transplant during the first post-transplant year (in this condition the risk might be as high as 80%) and diffuse mesangial proliferation on original kidney biopsy. Caucasians might have a higher recurrence risk compared with non-Caucasian candidates [4,6,21]. Whether recipients with living-donors are at high risk of recurrence than the recipients of deceased donors remains uncertain [32].

Transplantation might be contraindicated in light of the high risk of recurrent disease, for instance in recipients who had lost their first transplant early from recurrent disease [32]. ERBP Guidelines development group refereed that re-grafting must be discouraged in such patients [21], while Bertram et al. had expressed in the Clinical Practice Guidelines that recurrent FSGS is a relative contraindication to living donor transplant because of the high probabilities of disease recurrence up to 80% [6].

High risk of recurrent disease should be explained as a major aspect of the informed consent. Both the candidate with their potential donor ought to be cautioned of the significant risk of disease recurrence and the possible need for aggressive post-transplant interventions before scheduled for living

donation [4,6,21]. If the candidate decided to proceed with the transplant after counseling, then it is imperative that patients with FSGS should have negligible proteinuria at the time of the transplantation to discover any new proteinuria at an earlier time. Therefore, patients with pre-transplant significant proteinuria ought to have a trial of NSAID medications with or without angiotensin blockers to ablate any residual native kidney function. If such maneuvers failed, then renal ablation or native nephrectomy might be necessary [32].

A few investigators have proposed that the high risk for recurrent FSGS might decrease by using prophylactic plasma exchange, though no satisfactory data to support this, while others have encouraged beginning CsA at pre-transplant in candidates with FSGS to lessen the recurrence probabilities [6,32]. Treating recurrent post-transplant FSGS can be challenging. Aggressive treatment practices with cyclosporine/tacrolimus, steroids and plasmapheresis have been promoted with debatable success [21].

On the other hand, MPGN recurrence is probable and is seen in 20-33% of transplant recipients and graft loss has been accounted in up to 40% of those with disease recurrence, while the risk of recurrence in subsequent allografts can reach 80% [33,34]. Recurrence can be higher among living-related-donors, particularly among HLA-identical recipients. No treatment is proved to be efficient, and the primary disease for MCGN type I must be considered in each case [33,34]. MCGN Type II (Dense Deposit Disease, DDD) was reported to recur in 50-100% of renal grafts [35]. Clinically, it manifests with proteinuria and haematuria amid the first year post-transplantation, with gradual deteriorating renal function. Proteinuria is variable, but usually over 1 g/day. Hypocomplementemia is commonly observed in recurrent MPGN cases and might precede renal manifestations of recurrence. Graft losses have been described in 10-25% of cases, with predominance male gender, overt proteinuria, and crescents on biopsy indicating a higher risk of graft loss [36].

No successful therapy is known to attenuate the progression of DDD. Plasma exchange and immunosuppression have been depicted in case reports with some success; however, plasmapheresis has not been consistently beneficial [34,36]. There are no reports of the impact of mycophenolate mofetil, rituximab or bortezomib (proteasome inhibitor causing plasma cell depletion) in DDD [34]. Eculizumab therapy appears to have a promising role, yet the long-term effects of are not known yet [33-36]. The patient needs to be explained about the high risk of recurrence.

Patients on anticoagulation therapy for thromboembolic disease

Hereditary and acquired causes of hypercoagulable states predispose patients to thromboembolic diseases. Furthermore, these are associated with high morbidity and mortality rate in renal transplant recipients [37-39]. Risk factors for the development of thromboembolic disease are: protein C or S deficiency, the presence of factor V Leiden mutation, anti-phospholipid antibody, lupus, shortened activated partial thromboplastin time, anti-thrombin III deficiency, prothrombin 20210A gene mutation, thrombocytosis and polymorphism of plasminogen activator inhibitor-1 gene (4G/4G) in the kidney allograft. In contrast, heparin cofactor II deficiency was not associated with thrombosis in renal allograft recipients [6,37,40].

Other additional reported important risk factors for having thrombosis in transplant recipients are history of thrombosis, diabetes mellitus, ADPKD, peritoneal dialysis, donor aged under 6 or above 60 years or recipient aged beneath 5-6 years or >50 years, peri-op or post-operative hemodynamic variability, more than 24 h cold ischemic time or deceased donor, technical surgical problems and delayed graft function [6,37,41].

Female donors had duplicated the risk of thrombosis in the registry data obtained from Australian/New Zealand dialysis and transplant registry, possibly because of the small vessel diameters, though this has not been confirmed in other studies [41].

Vascular thrombosis represents 30-33% of early graft failure causes. The reported incidence of arterial thrombosis varies in different literatures between 0.2-7.5% and venous thrombosis between 0.1-8.2%, with the greatest incidence in infants and children, and the lowermost with living donor recipients [6,37,38,41,42]. Venous thromboembolic events (VTEs), which include pulmonary embolism (PE) and deep vein thrombosis (DVT), are major causes of postoperative morbidity and mortality [38]. Lam et al. had demonstrated a sevenfold higher risk of VTE in kidney transplant recipients compared to the general population with VTE conferring an increased risk of death and graft loss. The mortality risk among those recipients who experienced a post-transplant VTE was 28.5 vs. 11.2%; (HR=4.1, 95% CI=2.9-5.8; $p<0.0001$) and death-censored graft loss (13.1 vs. 7.5%; HR=2.3, 95% CI=1.4-3.6; p=0.0006) compared to matched recipients who did not experience a post-transplant VTE [39]. Furthermore, there is considerably a greater frequency of early acute rejection episodes in transplanted recipients with genetic or acquired thrombophilic states. Adhesion and chemotaxis of lymphocytes in the allograft vascular bed in response to vascular clotting were thought to trigger the acute rejection episodes or aggravate the incipient rejection by a primary hemostasis defect [40].

High-risk patients need screening for coagulation defects while continuing prophylactic anticoagulation therapy. Whether prophylactic oral anticoagulation or heparin administration in such recipients can increase the allograft survival is still a debate [6,40,41]. As a preparation for a transplant; warfarin should be discontinued five days prior to planned surgery, with a desirable INR of ≤ 1.4 if a patient at

high thromboembolic risk and already being on anticoagulation therapy, then bridging with heparin is desired. Heparin has to be initiated three days prior intended surgery (i.e., two-days following warfarin discontinuation, when the PT/INR begins to drop beneath the therapeutic level). Unfractionated heparin might be administered as intravenous infusion till 4-5 h before surgery, or as subcutaneous injections (approximate dose of 250 iu/kg twice daily); the last dose to be taken in the night proceeding surgery. Thereafter, warfarin can be resumed 12-24 h post-surgery (provided no active surgical issues arise that may complicate the bleeding risk). INR needs to be closely followed up [43].

Another point of particular importance is the drug metabolism with warfarin therapy. Medications are known to reduce the liver enzyme cytochrome P450s (CYPs), i.e., CYP3A4/5 will induce an inhibitory effect on warfarin, reducing the level; and require careful INR monitoring with the escalation of warfarin doses. Cyclosporine, Tacrolimus, Sirolimus and Azathioprine are all CYP3A4 Inhibitors; hence INR monitoring is necessary with concomitant administration of such medications. Additionally, special attention to the therapeutic level of these immunosuppressant's medication is essential [1,8,44,45]. In spite of careful considerations to decrease thrombotic risk factors, thrombosis cannot be avoided and required an early diagnosis to salvage the kidney with prompt re-exploration [41].

Patients with high calculated reaction frequency cRF level

PRA% as an indication for patient's sensitisation has been replaced widely in UK by NHS Blood and Transplant (NHSBT-ODT) with a high cRF. The purpose of such test is to define the recipient immune profile caused by a prior HLA exposure and the obtained results are expressed as percentage. Accordingly, patients with a cRF>85% are considered as highly sensitised [46-48]. Patients with high PRA are not precluded from transplantation, and the use of single antigen beads to determine HLA specificity of antibodies has helped defined acceptable and unacceptable antibodies [49]. Nonetheless, it is an evolving field, and much research is being done to fine tune the risk of antibody mediated rejection and allograft outcome in patients with high PRA.

Highly sensitized patients are more prone to hyper-acute rejections with early graft loss, therefore and depending on cross-match results; several desensitisation protocols have been implemented (if the cross match with their potential donor turn to be positive), most of those based on either high dose intravenous immunoglobulin's (IVIG) or a plasma-exchange (PE)/Immunoadsorption (IA) with low dose IVIG [50-53]. Rituximab were included lately in most protocols to inhibit antibodies synthesis. The combinations of rituximab, PE and IVIGs had eased the access of sensitised patients to transplant list and improved graft survival [21,53]. On the other hand, bortezomib were utilised as a part of desensitisation protocols, though the results are indefinite. Alternatively, eculizumab (anti-C5 monoclonal antibody) were used to decrease injuries induced by DSA-complement activation.

Desensitisation protocols aim to attain a negative cross-match. Though the majority of these protocols can decreases HLA antibodies to a level permit transplantation, yet the results on the long term remains uncertain [21,50,52,53]. The ideal induction therapy for such patient remains indeterminate. Recent publications had suggested using biological antibodies in addition to conventional immunosuppressive agents [51,54]. Presently, the available antibodies are Anti-lymphocyte and interleukin-2 (IL-2) receptor antibodies. Anti-lymphocyte antibodies are divided into polyclonal and monoclonal antibodies. Thymoglobulin is a polyclonal immunosuppressive agent, denoted as rabbit anti-thymocyte globulin (rATG). Atgam is a different polyclonal purified gamma globulin antibody, acquired by immunisation of horses with human thymocytes. Monoclonal anti-lymphocyte antibodies include Alemtuzumab (Campath-1H) which is anti-CD52 pan-lymphocytic (both B and T cells), and OKT3 (anti-CD3 antigen) [54]. Rituximab, on the other hand, is an anti CD20 monoclonal antibody that deplete CD20-positive B cells; however, its use amongst transplant recipients is confined for treatment of post-transplant lymphoproliferative disease and desensitisation of HLA and ABO-incompatible transplants, besides the treatment of antibody-meditated rejections. IL-2 receptor antagonists: currently the available one is Basiliximab.

KDIGO clinical practice guidelines in 2009 had necessities aggressive immunosuppressive administration in patients with considerably high rejection risk, for example those with: high PRA, patients with increase HLA mismatches, presence of DSA, Blood group incompatibility, younger recipient age and older donor, African-American ethnicity and patients with cold ischemic time more than 24 h. For those patients, the 2009 guidelines suggested to use the lymphocyte-depleting agents, which are potent immunosuppressive for patients at high immunologic risk, and to use IL-2 receptor antibodies for patients with low immunological risk of rejection [54]. There are significant proofs that rATG-Thymoglobulin is superior to IL-2 receptor antibodies amongst recipients at both; high plus the low immunological risk, moreover, it showed superiority compared to Atgam in lowering acute rejection episodes and improving graft survival [51,54,55].

rATG-Thymoglobulin should be avoided in patients with hypotension, leukopenia and/or thrombocytopenia at the time of presentation [54]. rATG-Thymoglobulin treatment has to be joined with maintenance immunosuppressive therapy. This begins pre-operatively with the administration

of mycophenolate 1000 mg on the operating room, followed with tacrolimus at day 1 postoperatively (0.05 mg/kg postoperatively twice daily, adjusted to achieve a 12 h trough level of 7-10 ng/mL for the first month and 5-7 ng/mL thereafter). Mycophenolate (1000 mg twice-daily, to be reduced to 500 mg twice-daily after five days) or its equivalent of mycophenolic acid (360 mg twice-daily); and prednisone (1 mg/kg orally for the first week, tapered gradually by fifth weeks).

Alemtuzumab (Campath-1H), is used as induction therapy in nearly 10% of kidney recipients in the USA. Usage of this medication had allowed some of the transplant patients to be maintained on less intense immunosuppressive therapy, including tacrolimus alone or very low-dose cyclosporine/sirolimus or steroid-free regimens in a randomised, controlled trials [54]. Though alemtuzumab had shown some superiority compared with basiliximab in reducing early acute rejection episodes, however, late rejections were more common in the alemtuzumab group. This supports earlier studies which demonstrated that alemtuzumab had less acute rejection rate at early post-transplant period amongst low-risk recipients, but then this effect attenuates over the long run; this attenuation is similar to the one observed in the high-risk population when comparing alemtuzumab with rATG-Thymoglobulin [49,54,56-59]. In a retrospective study of transplant recipients who were sustained on a steroid-free maintenance regimen, induction with rATG had shown superiority compared with alemtuzumab and IL-2 receptor blocker in term of graft survival [51].

Given the high risk of AMR, monitoring anti-HLA antibodies post-transplant, particularly DSA, is necessary and can determine the allograft outcome. Increasing DSA titer at early post-transplant period mandate an allograft biopsy (protocol or indication biopsies) and suggests intensified therapy, in the absence of allograft dysfunction; initiation of plasmapheresis/IVIG or other treatment will be decided according to biopsy results [48,51].

Donors and recipients with blood group incompatibility

Traditionally, to get transplanted through ABO blood group incompatibility were prohibited for the risk of hyper-acute rejections mediated by existing anti-A or anti B antibodies against carbohydrate blood group antigens. However, over the last two decades treatment modalities have improved impressively to overcome these barriers and ABO-incompatible living donor kidney transplantation has been performed widely [51,60-63].

Blood group A carried A1 or A2 antigen, A2 antigens is weakly presented in the cells compared with A1 antigens. The A2 subgroup represents roughly 20% of blood group A in Caucasians, whereas it is merely 0.15% in the Japanese populace.

Non-A recipients getting kidney allograft from A2 donors can receive transplant safely with no pre-conditioning, and such kidneys are less likely to have AMR in the presence of anti-A antibodies [61]. Anti-ABO antibodies are either immunoglobulin (IgM) or (IgG) type. Though the anti-ABO response was classically considered as T cell-independent IgM antibody response; latest publications suggested the importance of T cells or natural killer cells in the anti-ABO antibody reaction and demonstrated that anti-ABO IgG response is more critical than IgM response in AMR after ABOi renal transplant [61-63].

Monitoring anti-ABO antibodies level remains crucial for describing the effectiveness of desensitisation protocols besides determining the ideal period for performing ABOi Kidney transplant. Different methods exist to measure anti-ABO antibody levels, commonly used is the saline tube technique, though this technique has significant laboratory variations in the titer determined. New technologies, such as gel card and flow cytometry, may be better options than the saline tube test for their improved reproducibility. Flow cytometry would be suitable for an accurate measurement although it's not available in all centres for their high cost 51,61-63].

Natural and induced anti-ABO antibodies might cause AMR in ABOi renal transplant which may be evident as hyper acute rejection, acute AMR, or delayed AMR. Most AMRs occur between first and third week following ABOi renal transplantation, while it does not happen after the third week despite the presence of significant rebound high antibodies levels and C4d deposition due to accommodation.

Several desensitisation protocols were published to make ABO incompatible transplantation possible. All protocols strategies have two main principles: (1) pre-transplant antibody removal and (2) induction and maintenance of immunosuppression to inhibit the reappearance of further anti-ABO antibodies. Eradication of blood group Antibodies is carried via classical plasma-exchange or double-filtration plasmapheresis (DFPP) and antigen-specific or antigen-nonspecific IA (Immunoadsorption) for selective elimination of anti-A or anti B antibodies. Such sessions are usually performed daily till antibody titres are lowered to 1:8 or even lower. IA is safe and efficient with a minimum of four pre-operatives IAs are frequently required to attain a suitable titer. B-cell depletion is carried by pre-emptive splenectomy or by rituximab therapy; Rituximab to be given 1-4 weeks prior to transplantation to inhibit antibody production, and to avoid antibody rebound. Splenectomy was largely replaced by rituximab which has a long-acting B cell-depleting effect (up to 2 years) without inducing serious side effects [21,51,61-63].

Bortezomib (a proteasome inhibitor) on the other hand can control plasma cells, without suppressing either B-1 or B-2 cells.

Post-transplant antibody depletion by above therapy is used in some centres for patients with high risk of AMR, e.g. patients with a high initial titer (1:256), a rapidly increasing post-transplant titer (Z 8-fold) or a high post-transplant titer (Z 1:64). Intravenous IG (IVIG) is widely used to suppress both cell-mediated rejection and AMR, though the mode of action is still uncertain. IVIGs are typically given post plasmapheresis to rebuild the normal IgG levels. However, there is no uniform dose of IVIGs utilised as a part of the desensitisation protocol of ABOi renal transplant [61-63].

Maintenance immunosuppressive regimens included calcineurin inhibitors (preferably tacrolimus), antimetabolites (i.e., MMF) and steroids to be started 2 weeks before planned surgery to adequately inhibit antibody production [21]. Additionally, stronger induction agents, such as anti-thymocyte globulin (ATG), are often used for induction.

The target titres of anti-ABO antibodies immediately before the transplant is different in different countries protocols; e.g. in Japan are usually 1:16 to 1:32 or less, while in the Stockholm and Freiburg groups; The target titer of antibodies should be 1:4 or less. In the United States, the target is 1:8 to 1:16. Although strict target titres can achieve good transplant outcomes, yet 14-21% of patients failed to satisfy this criterion [21,51,61].

By utilisation of desensitisation protocols, patients and grafts outcomes seem to be similar compared with blood group compatible transplant for short to the medium period (equal to 9 years), though the long-term effects are still anticipated, nevertheless Japanese data had reported up to 20 years of successful outcomes [9,21,51,61-63].

The titer of anti-ABO antibodies should be monitored periodically especially in the first three weeks post-transplant to detect any rebound in antibody production that may indicate or induce AMR. In an ABO-incompatible transplant, it is common to find positive C4d on protocol biopsies as compared with HLA incompatible transplant. Therefore, re-initiation of plasmapheresis and IVIG should be suggested when graft dysfunction detected or with rising iso-agglutinin antibody titer, rather than with evidence of positive C4d staining alone. Acute AMR remained challengeable in ABOi renal transplant (with the incidence of 10-30%) and it can critically affect long-term graft outcomes and contributes to the development of chronic rejection [51].

Additionally, the infection rate in ABOi renal transplant was higher than that in ABOc renal transplantation (60% vs. 30%), particularly viral infections (cytomegalovirus, HSV, varicella-zoster and BK virus), Rituximab might be responsible for an increased infection risk [61-63], while the incidences of malignancies compared with ABOc renal transplant remained same [64].

Given the considerable chances of AMR, Paired/chains donor exchange is a better alternative if available; where a medically approved incompatible pair can exchange kidneys with one or more other incompatible pairs so that all recipients receive compatible organs from strangers. Such donors are arranged through regional/national programs. This practice evades the need for desensitisation in cases of ABO blood group incompatibility or pre-existing donor human leukocyte antigen (HLA) antibodies (DSA) and offers a living donor allograft to each recipient [65]. With Kidney Paired Donation (KPD) programs, Patient and graft outcomes were reported to be comparable with, or even better than, those with standard living-donor kidney transplantation **(Figure 2)** [51-53,66-68].

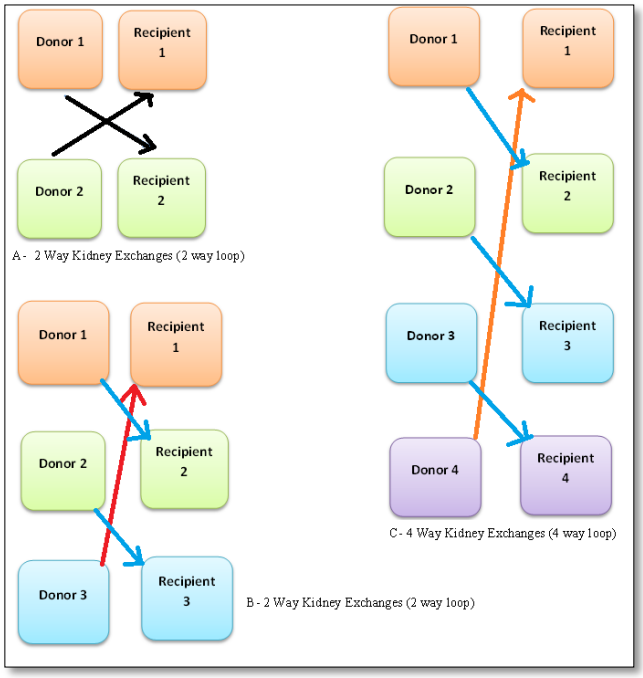

Figure 2. Exchange approaches in KPD: (A) Classical two-way loop exchange between two incompatible donor-ecipient pairs. (B and C) different way loop exchange amongst multiple incompatible donor-recipient pairs, which can be arranged with 3, 4, 5 or more pairs.

Patients with concurrent psychiatric illness

Patients awaiting solid organ transplant face a number of stressors that increase their risk of developing signs and symptoms of psychiatric illness. Frequently encountered psychological reactions while awaiting transplant surgery are complex, such as waiting tension to get a graft, tension of the procedure itself, fear that a donor can withdraw from the commitment to donate, panic attacks, severe depression and poor compliance with medication and diet, social phobia, personality disorders, generalized anxiety, substance use disorders and anti-social personality which may be caused by psychological stressors, medications or physiological disturbance. Different programs have different

requirements for psychological evaluation prior to transplant. For example, several kidney transplant programs have a social worker to evaluate patients prior to transplantation and occasionally refer patients to a psychiatrist or psychologist for further evaluation [69,70].

On the other hand, a transplant team might have candidates with well-known psychiatric disorders. The burden of psychiatric illness in patients awaiting transplant and following transplant is significant and associated with prospective morbidity and mortality. Therefore, if the patient has an active psychiatric disease, such as anxiety or affective disorder, it is prudent to treat them prior to intended transplant and to proceed with transplantation once remission ensues, though long-standing anxiety or affective disorders do not predict worse outcomes post-transplantation. A careful evaluation of past medical records and examination of the patient's behavior during the pre-transplant workup can provide important data to help assess if a patient will be able to comply following transplant [71,72].

A history of drug abuse is also a known risk factor for relapse, and these patients must be considered as high risk. Patients with a history of opioid dependence, methadone has been used successfully to prevent relapse to illicit use. Random urine toxicology screens should be used to evaluate abstinence [72]. Depression appears to be one of the most common psychiatric disorders in patients following organ transplantation with an incidence rate of 5-25% post-transplant. Depressed patients may experience a reduced quality of life, more somatic complaints and poor coping. These behaviors may lead to a sense of futility and subsequent impaired compliance, along with a return to unhealthy behaviors such as smoking. Depression following solid organ transplantation has been associated with increased morbidity and mortality.

Chronic psychiatric diseases such as schizophrenia may be more difficult to put into remission, but careful evaluation of the patient's history and compliance with treatment may lead to a careful selection of some schizophrenic patients with an acceptable outcome. Personality disorders, when severe, are felt by many programs to be a contraindication to transplant, however, one-time evaluation might be insufficient when trying to assess a personality disorder and a multidisciplinary evaluation in collaboration with patient psychiatric is warranted. Ultimately, decisions about listing patients with psychiatric illnesses should be as evidence-based as possible so that the biases of team members are minimized and patients are given every opportunity to have access to transplant [72].

The capacity of patients to consent to transplant should also be assessed prior to their being listed as candidates. Many patients listed for transplant suffer from cognitive impairment and may experience progressive difficulty with understanding the transplant process. Moreover, Patients with major psychiatric illness might not be in a position to give informed consent for the surgical procedure. Decisional capacity requires the ability to understand the basic facts involved in the medical decision, to assess all available information and to express a clear and consistent choice. If the patient is evaluated clinically and considered incapable of making a reasonable decision, a surrogate decision-maker must be identified. If the patient has not formally established a durable power of advocate for healthcare-related matters, then the treating physician should turn to the patient's family for a surrogate who either knows the patient sufficiently to represent the patient's values and goals or who is otherwise capable of making decisions based on the patient's best interests.

A term often confused with capacity is legal competency, which must be assessed by trained personnel within the legal system. Decision-making capacity in these situations is determined clinically rather than legally. Therefore, the treating physician must, based on his or her best clinical judgment, assess the patient's ability to complete cognitive tasks and make a determination regarding the patient's decisional capacity [71,72]. Poor compliance has been shown to impair both the patient's quality of life and life expectancy. Careful selection of candidates based on a number of evidence-based psychosocial criteria can improve outcomes and decisions about listing patients with psychiatric illnesses should be decided through a multidisciplinary approach in collaboration with patient psychiatric specialists [72].

The patient should be followed closely at post-transplant, and psychiatrist continues to play a vital role in post-operative care, as SUGG is often a stressful experience with associated psychiatric comorbidity. The treatment of psychiatric illness in patients following transplantation requires an understanding of the immunosuppressant medications that patients might be taking, coupled with the awareness of the associated risks of neuropsychiatric adverse effects and drug to drug interactions. Important drug interactions may occur when immunosuppressant are used together or co-administered with other medications used to treat comorbid illnesses. These medications often have a narrow therapeutic index and present the risk of ineffectiveness or drug toxicity [71,72].

Steroids as commonly used immunosuppressant in transplant patients have multiple, well-documented medical and neuropsychiatric adverse effects, that may include depression, psychosis, mania and delirium. The risk of psychiatric side effects appears related to dose, with higher doses presenting greater risk. Managing psychiatric complications of glucocorticoid treatment requires reducing the steroid to the lowest effective dose, coupled with symptomatic treatment with an antidepressant, mood stabilizer, or antipsychotic as appropriate.

Tacrolimus is associated with a significant risk of neurotoxicity. A minority of patients may experience severe neuropsychiatric toxicity in the form of delirium, psychosis, and seizures. Intentional overdoses of cyclosporine in transplant patients with psychiatric comorbidities have been associated with significant neurotoxicity compared to tacrolimus overdose which is well tolerated with minimal adverse sequels. Furthermore, cyclosporine and tacrolimus both utilise P450 3A4 hepatic metabolism, and many drug-drug interactions have been reported in the literature. Since both of these medications are metabolised by 3A4, inhibitors of this isoenzyme have been shown to increase the levels leading to toxicity. In addition, medications that induce 3A4 have been reported to decrease CNI blood level leading to graft rejection. This coupled with the narrow therapeutic index of antipsychotic medication, mandate monitoring levels of these medications regularly. Sirolimus, on the other hand, appears to have a much more benign neuropsychiatric side-effect profile than CNI therapy. Sirolimus is metabolised by the hepatic isoenzyme P450-3A4. As a result, caution must be employed whenever substances that either inhibit or induce this enzyme system are administered or withdrawn. However, since sirolimus is a reasonably well-tolerated medication, reports of drug interactions with it are minimal. Mycophenolate mofetil may cause some restlessness or anxiety, but these side effects appear to be less prevalent than with the calcineurin inhibitors. The clinician's ability to anticipate and avoid potential drug interactions when prescribing medications will significantly lower the chances of adverse outcomes relating to pharmacotherapy. Prompt treatment of identified neuropsychiatric complications and psychiatric comorbidity in transplant patients is essential to improve outcomes. Failure to treat these conditions would increase the risk of morbidity and mortality in these complex patients [72].

CONCLUSION

Living donors transplant ought to be a superior modality for CKD patients, whenever a suitable donor is available. However, the presence of multiple comorbidities in patients contemplating renal transplantation are not an absolute contraindication for surgery; but taking together all problems patient might have may significantly indicate reduced allograft survival. Determination of patient's suitability for renal transplant surgery requires input from a multidisciplinary medical and surgical specialty. The conclusion should be combined between patients and their clinicians after full explanation of the likely risks and advantages of the transplant.

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