EAU GUIDELINES ON RENAL TRANSPLANTATION

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Introduction

The European Association of Urology (EAU) Renal Transplantation Guidelines aim to provide a comprehensive overview of the medical and technical aspects relating to renal transplantation.

Organ retrieval and transplantation surgery

Living-donor nephrectomy

Recommendations	Strength rating
Offer pure or hand-assisted laparoscopic/ retroperitoneoscopic surgery as the preferential technique for living-donor nephrectomy.	Strong
Perform open living-donor nephrectomy in centres where endoscopic techniques are not implemented.	Strong
Perform laparo-endoscopic single site surgery, robotic and natural orifice transluminal endoscopic surgery-assisted living-donor nephrectomy in highly-specialised centres only.	Strong

Organ preservation

Recommendations for kidney storage solutions	Strength rating
Use either University of Wisconsin or histidine tryptophane ketoglutarate preservation solutions for cold storage.	Strong
Use Celsior or Marshall's solution for cold storage if University of Wisconsin or histidine tryptophane ketoglutarate solutions are not available.	Strong

Recommendations for kidney preservation: static and dynamic preservation	Strength rating
Minimise ischaemia times.	Strong
Use hypothermic machine-perfusion (where available) in deceased donor kidneys to reduce delayed graft function.	Strong
Hypothermic machine-perfusion may be used in standard criteria deceased donor kidneys.	Strong
Use low pressure values in hypothermic machine perfusion preservation.	Strong
Hypothermic machine-perfusion must be continuous and controlled by pressure and not flow.	Strong
Do not discard grafts due to only increased vascular resistance and high perfusate injury marker concentrations during hypothermic machine perfusion preservation.	Weak

Donor kidney biopsies

Recommendations	Strength rating
Do not base decisions on the acceptance of a donor organ on histological findings alone, since this might lead to an unnecessary high rate of discarded grafts. Interpret histology in context with clinical parameters of donor and recipient, including perfusion parameters where available.	Strong
Use paraffin histology for histomorphology as it is superior to frozen sections, however, its diagnostic value has to be balanced against a potential delay of transplantation.	Strong
Submit 14 or 16 G needle core biopsies, wedge biopsies or skin punch biopsies for histopathology.	Weak
Procurement biopsies should be read by a renal pathologist or a general pathologist with specific training in kidney pathology.	Strong

Living and deceased donor implantation surgery

Recommendations	Strength rating
Immediate pre-op haemodialysis	
Use dialysis or conservative measures to manage fluid and electrolyte imbalance prior to transplant surgery taking into consideration the likelihood of immediate graft function.	Weak

Operating on patients taking anti-platelet and anticoagulation agents	
Consider continuing anti-platelet therapy in patients on the transplant waiting list.	Weak
Discuss patients who take anti-platelet and anti-coagulation agents prior to transplant surgery with relevant cardiologist/ haematologist /nephrologist.	Weak
Prevention of venous thrombosis including deep vein thrombosis during and after renal transplant	
Do not routinely give post-operative prophylactic unfractionated or low-molecular-weight heparin to low-risk living donor transplant recipients.	Weak
Peri-operative antibiotics in renal transplant	
Use single-dose, rather than multi-dose, peri-operative prophylactic antibiotics in routine renal transplant recipients.	Strong
Specific fluid regimes during renal transplantation	
Optimise pre-, peri- and post-operative hydration to improve renal graft function.	Strong
Use balanced crystalloid solutions for intra-operative intravenous fluid therapy.	Weak
Use target directed intra-operative hydration to decrease delayed graft function rates and optimise early graft function.	Strong
Dopaminergic drugs in renal transplantation	
Do not routinely use low-dose dopaminergic agents in the early post-operative period.	Weak

Surgical approaches for first, second, third and further transplants

Single kidney transplant – living and deceased donors

Recommendations	Strength rating
Assess the utility (including inspection) of the kidney for transplantation before commencement of immunosuppression and induction of anaesthesia for deceased donor kidney transplantation.	Strong
Choose either iliac fossa for placement of a first or second single kidney transplant.	Weak
Ligate peri-iliac vessel lymphatics (lymphostasis) to reduce post-operative lymphocele.	Weak
Assess the length of the donor renal vein and if it is short consider one of a variety of surgical techniques to optimise the venous anastomosis.	Weak
Use the external or common iliac arteries for an end-to-side arterial anastomosis to donor renal artery.	Weak
Use an end-to-end anastomosis to the internal iliac artery as an alternative to external or common iliac arteries.	Weak
Check the intima of the donor and recipient arteries prior to commencing the arterial anastomosis to ensure that there is no intimal rupture/flap. If this is found it must be repaired prior to/as part of the arterial anastomosis.	Strong

Pre-operatively plan the surgical approach in third or further transplants, to ensure that appropriate arterial inflow and venous outflow exists with adequate space to implant the new kidney.	Strong

Emerging surgical technologies

Robot-assisted kidney transplant (RAKT) surgery is being evaluated in prospective non-randomised trials (using IDEAL consortium principles). Whilst potential advantages may exist (decreased post-operative pain, length of hospital stay, incision length and lymphocele rate), evidence is too premature to recommend RAKT.

Dual kidney transplants

Dual kidney transplant is performed when the quality of a single deceased donor kidney is thought to be insufficient for appropriate long-term graft function and that the outcome with both kidneys would be better. A variety of surgical techniques have been described to implant a pair of donor kidneys these include: unilateral extra-peritoneal or intra-peritoneal and bilateral extra-peritoneal or intra-peritoneal that can be via a midline or two lateral incisions. No randomised controlled trials exist to recommend one technique for all patients or situations.

Ureteric implantation in normal urinary tract

Ureteric anastomotic techniques described for renal transplant recipients with no underlying urological abnormality include: extra (Lich-Gregoir) or intra (Ledbetter-Politano) vesical uretero-neo-cystotomy and uretero-ureterostomy using native ureter.

Recommendations	Strength rating
Perform Lich-Gregoir-like extra-vesical ureteric anastomosis technique to minimise urinary tract complications in renal transplant recipients with normal urological anatomy.	Strong
Pyelo/uretero-ureteral anastomosis is an alternative especially for a very short or poorly vascularised transplant ureter.	Strong
Use transplant ureteric stents prophylactically to prevent major urinary complications.	Strong
Use the same surgical principals for single ureters to manage duplex ureters and anastomose them either separately or combined.	Strong

Transplantation/ureteric implantation in abnormal urogenital tract

The following points should be considered when performing kidney transplantation in the abnormal urogenital tract:

- In patients with an ileal conduit, a kidney transplant may be placed upside down to align the ureter to the conduit and avoid a redundant ureter.
- The technique used to implant transplant ureter(s) into an ileal conduit is the same as the method used with native ureter(s) (Bricker; Wallace).
- In bladder augmentation or continent pouches, ureters should be implanted with a tunnel technique or extravesically (Lich-Gregoir). The latter is favoured in most patients.
- In patients with a Mitrofanoff catheterisable stoma or continent ileo-caecal pouch with catheterisable stoma, consideration should be given to the positioning of the

catheterisable stoma (umbilical or iliac fossa - usually right-side) with clear communication with the transplant surgeons so that the position of any future transplant kidney is not compromised. If an intraperitoneal placement of a future kidney transplant is likely, then placement of a Mitrofanoff exiting in the iliac fossa is preferable at the umbilicus. If a future kidney transplant is likely in the right iliac fossa then placement of a Mitrofanoff exiting at the umbilicus or left iliac fossa may be preferable.

Donor complications

Living-donor nephrectomy, like any other intervention, is potentially associated with complications and mortality. However, the fact that the operation is performed on a healthy individual amplifies the relevance of any complications. Intraoperative complications occur in 2.2% (the most common being bleeding in 1.5% and injury to other organs in 0.8%) and post-operative complications occur in 7% (infectious complications in 2.6% and bleeding in 1%). Potential complications should be included in the process of informed consent. Long term complications are mostly related to the single-kidney condition. Health related quality of life, including mental condition, remains on average better than the general population after donation.

Recommendations	Strength rating
Restrict living donor nephrectomy to specialised centres.	Strong
Offer long-term follow-up to all living kidney donors.	Strong

Recipient complications

Surgical complications during and after kidney transplantation may expose the recipient to an increased risk of morbidity and mortality. The incidence and management of such

complications is therefore of primary importance. The most common surgical complications in renal transplantation are summarised below.

Haemorrhage

The incidence of haematomas is reported to be between 0.2-25%. Small and asymptomatic haematomas do not usually require any intervention. In case of larger haematomas, clinical signs and symptoms due to external pressure with graft dysfunction and/or thrombotic graft vessels complications can be present. These cases may be treated by percutaneous drainage under computed tomography or ultrasound guidance or may require surgical treatment.

Arterial thrombosis

Transplant renal artery thrombosis is a rare complication (prevalence 0.5-3.5%).

Recommendations	Strength rating
Perform ultrasound-colour-doppler in case of suspected graft thrombosis.	Strong
Perform surgical exploration in case of ultrasound finding of poor graft perfusion.	Strong
Perform a surgical thrombectomy in case of a salvageable graft if arterial thrombosis is confirmed intra-operatively.	Weak
Perform an allograft nephrectomy in case of a non-viable graft.	Strong

Venous thrombosis

Transplant renal vein thrombosis is an early complication (prevalence 0.5-4%) and one of the most important causes of graft loss during the first post-operative month.

Recommendations	Strength rating
Perform ultrasound-colour-doppler in case of suspected graft thrombosis.	Strong
Perform surgical exploration in case of ultrasound finding of poor graft perfusion.	Weak
If venous thrombosis is confirmed intra-operatively, perform a surgical thrombectomy in case of a salvageable graft or an allograft nephrectomy in case of a non-viable graft.	Weak
Do not routinely use pharmacologic prophylaxis to prevent transplant renal vein thrombosis.	Strong

Transplant renal artery stenosis

The incidence of transplant renal artery stenosis is 1-25%. Risk factors include small calibre and atherosclerosis of the donor artery, trauma to donor artery at procurement, absence of arterial patch, suturing technique (interrupted versus continuous), and damage to the iliac artery during transplantation.

Recommendations	Strength rating
Perform ultrasound-colour-doppler to diagnose an arterial stenosis, in case of undetermined results on ultrasound consider a magnetic resonance or computed tomography angiogram.	Strong
Perform percutaneous transluminal angioplasty/stent, if feasible, as first-line treatment for an arterial stenosis.	Strong
Offer surgical treatment in case of recent transplant, multiple, long and narrow stenosis, or after failure of angioplasty.	Strong

Arteriovenous fistulae and pseudo-aneurysms after renal biopsy

Percutaneous biopsy may result in arteriovenous fistulae and/or intrarenal pseudo-aneurysms in 1-18% of cases.

Recommendations	Strength rating
Perform a ultrasound-colour-doppler if a arteriovenous fistulae or pseudo-aneurysm is suspected.	Strong
Perform angiographic embolisation as first-line treatment in symptomatic cases of arteriovenous fistulae or pseudo-aneurysm.	Strong

Lymphocele

Lymphocele is a relatively common complication (prevalence 1-26%). There is a significant aetiological association with diabetes, m-TOR inhibitors (i.e sirolimus) therapy, and acute rejection.

Recommendations	Strength rating
Perform percutaneous drainage placement as the first treatment for large and symptomatic lymphocele.	Strong
Perform fenestration when percutaneous treatments fail.	Strong

Urinary leak

Urinary leakage occurs in 0-9.3% of cases.

Recommendations	Strength rating
Manage urine leak by JJ-stent and bladder catheter and/or percutaneous nephrostomy tube.	Strong
Perform surgical repair in cases of failure of conservative management.	Strong

Ureteral stenosis

Ureteral stenosis is a common complication in recipients, with an incidence of 0.6-10.5%. Early stenosis (within three months of surgery) is usually caused by surgical technique or compromised ureteral blood supply during surgery. Late stenosis (after six months) is provoked by infection, fibrosis, progressive vascular disease and/or rejection.

Recommendations	Strength rating
In case of ureteral stricture, place a nephrostomy tube for both kidney decompression and stricture diagnosis via an antegrade pyelogram.	Strong
Manage strictures < 3 cm in length either with surgical reconstruction or endoscopically (percutaneous balloon dilation or antegrade flexible ureteroscopy and holmium laser incision).	Strong
Treat late stricture recurrence and/or stricture > 3 cm in length with surgical reconstruction in appropriate recipients.	Strong

Haematuria

The incidence of haematuria ranges from 1-34%. The Lich-Gregoire technique provides the lowest incidence of haematuria. Bladder irrigation is the first line of treatment. Some cases require cystoscopy with evacuation of clots and/or fulguration of bleeding sites.

Reflux and acute pyelonephritis

The frequency of vesicoureteral reflux is between 1-86%. Acute graft pyelonephritis occurs in 13% of graft recipients. Patients with lower tract urinary infections and cytomegalovirus (CMV) infection present a higher risk of acute graft pyelonephritis.

Recommendation	Strength rating
Use an endoscopic approach as first-line treatment for symptomatic reflux.	Weak

Kidney stones

Urolithiasis occurs in 0.2-1.7% of recipients.

Recommendations	Strength rating
Evaluate the causes of urolithiasis in the recipient.	Strong
Treat ureteral obstruction due to a stone with a percutaneous nephrostomy tube or JJ-stent placement.	Strong
Perform shockwave lithotripsy or antegrade/retrograde ureteroscopy for stones < 15 mm.	Strong
Perform percutaneous nephrolithotomy for stones > 20 mm.	Weak

Wound infection

Wound infections occur in about 4% of cases. Subcutaneous sutures, pre-dialysis transplantation, sealing or ligation of lymphatic trunks, prophylactic fenestration, reducing corticosteroid load, and avoiding sirolimus/everolimus therapy can decrease wound complication rates.

Incisional hernia

Incisional hernia occurs in approximately 4% of open kidney transplantations. Mesh infection is a risk factor for incisional hernia recurrence. Open and laparoscopic repair approaches are safe and effective.

Malignancy prior to renal transplantation

Recommendations	Strength rating
In the recipient	
List for renal transplantation patients with a history of appropriately treated low stage/grade renal cell carcinoma or prostate cancer without additional delay.	Weak
In the potential donor kidney	
Do not discard a kidney for potential transplantation on the basis of a small renal mass alone.	Weak
Malignancy after renal transplantation	
Be aware of the presence of a kidney transplant in the pelvis and the possibility of subsequent transplants when planning treatment for prostate cancer.	Strong
Refer kidney transplant patients with prostate cancer to an integrated transplant urology centre.	Strong

Matching of donors and recipients

Histocompatibility antigens show remarkable polymorphism and human leukocyte antigen (HLA) matching is still very important in kidney transplantation as transplant outcome correlates with the number of HLA mismatches.

Recommendations	Strength rating
Determine the ABO blood group and the human leukocyte antigen A, B, C and DR phenotypes for all candidates awaiting kidney transplantation.	Strong

Test both the donor and recipient for human leukocyte antigen DQ. Human leukocyte antigen DP testing may be performed for sensitised patients.	Strong
Perform thorough testing for HLA antibodies before transplantation.	Strong
Perform adequate cross-match tests to avoid hyper-acute rejection, before each kidney and combined kidney/pancreas transplantation.	Strong

Immunosuppression after kidney transplantation

The principle underlying successful immunosuppression is 'the balance of survival'. Practitioners must prescribe a dosage of drug high enough to suppress rejection without endangering the recipient's health.

The currently recommended standard initial immunosuppression regime provides excellent efficacy with good tolerability.
It is given to most patients and consists of:

- calcineurin inhibitors (preferably tacrolimus, alternatively cyclosporine);
- mycophenolate (MMF or enteric-coated mycophenolate sodium;
- steroids (prednisolone or methylprednisolon);
- induction therapy (preferably basiliximab in low and standard risk patients and anti-thymocyte globulin (ATG) in high risk patients).

Recommendations	Strength rating
General immunosuppression after kidney transplantation	
Perform initial rejection prophylaxis with a combination therapy of a calcineurin inhibitor (preferably tacrolimus), mycophenolate, steroids and an induction agent (either basiliximab or anti-thymocyte globulin).	Strong
Calcineurin inhibitors	
Use calcineurin inhibitors for rejection prophylaxis as they represent current best practice pending publication of long-term results using newer agents.	Strong
Use tacrolimus as first-line calcineurin inhibitor due to its higher efficacy.	Strong
Monitor blood-levels of both cyclosporine and tacrolimus to allow appropriate dose adjustment of calcineurin inhibitors.	Strong
Mycophenolates	
Administer mycophenolate as part of the initial immunosuppressive regimen.	Strong
Azathioprine	
Azathioprine may be used in a low-risk population as an immunosuppressive drug, especially for those intolerant to mycophenolate formulations.	Weak
Steroids	
Initial steroid therapy should be part of immunosuppression in the peri-operative and early post-transplant period.	Strong

Consider steroid withdrawal in standard immunological risk patients on combination therapy with calcineurin inhibitors and mycophenolic acid after the early post-transplant period.	Weak
Inhibitors of the mammalian target of rapamycin (m-TOR)	
The m-TOR inhibitors may be used to prevent rejection in patients who are intolerant to standard therapy.	Weak
Significantly reduce calcineurin inhibitor dosage in a combination regimen with m-TOR inhibitors to prevent aggravated nephrotoxicity.	Strong
Do not convert patients with proteinuria and poor renal function to m-TOR inhibitors.	Strong
Monitor blood-levels of both sirolimus and everolimus to allow for appropriate dose adjustment.	Strong
Induction with Interleukin-2 receptor antibodies	
Use interleukin-2 receptor antibodies for induction in patients with normal immunological risk in order to reduce incidence of acute rejection.	Weak
T-cell depleting induction therapy	
T-cell depleting antibodies may be used for induction therapy in immunologically high risk patients.	Weak
Belatacept	
Belatacept may be used for immunosuppressive therapy in immunologically low-risk patients, who have a positive Epstein-Barr virus serology.	Weak

Immunological complications

Immunological rejection is a common cause of early and late transplant dysfunction. There is great variation in the timing and severity of rejection episodes and how they respond to treatment. Two main types of immunological reactions are distinguished: T-cell mediated rejections (TCMR) and antibody-mediated rejections (ABMR). Antibody-mediated rejection and TCMR may be diagnosed together, called mixed acute rejection. Antibody-mediated rejection may occur as hyperacute rejection, acute rejection or chronic rejection. Chronic ABMR is considered as one of the leading causes of late graft loss.

Recommendations	Strength rating
Monitor transplant recipients for signs of acute rejection, particularly during the first six months post-transplant.	Strong
Take regular blood samples in addition to regular monitoring of urine output and ultrasound examinations in order to detect graft dysfunction during hospitalisation.	Strong
Immediately rule out other potential causes of graft dysfunction in cases of suspected acute rejection. An ultrasound of the kidney transplant should be performed.	Strong
Perform a renal biopsy, graded according to the most recent Banff criteria, in patients with suspected acute rejection episodes.	Strong
Only if contraindications to renal biopsy are present, can 'blind' steroid bolus therapy be given.	Strong
Test patients who suffer acute rejection as soon as possible for anti-HLA antibodies against the graft.	Strong

Reassess the immunosuppressive therapy of all patients with rejection, including patient adherence to the medication, which is of particular importance in late rejections.	Strong

Hyper-acute rejection

Hyper-acute rejection is the most dramatic and destructive immunological attack on the graft. It results from circulating, complement-fixing IgG antibodies, specifically reactive against incompatible donor antigen, which engages with and destroys the vascular endothelium within minutes or hours after vascularisation.

Recommendation	Strength rating
Prevent hyper-acute rejection by adequate ABO blood group and HLA matching of donor and recipients.	Strong

Treatment of T-cell mediated acute rejection

Recommendations	Strength rating
Use steroid bolus therapy as first-line treatment for T-cell mediated rejection in addition to ensuring adequate baseline immunosuppression.	Strong
In severe or steroid-resistant rejection, use intensified immunosuppression, high-dose steroid treatment, and eventually T-cell depleting agents.	Strong

Treatment of antibody mediated rejection

Recommendation	Strength rating
Treatment of antibody mediated rejection should include antibody elimination.	Strong

Follow-up after transplantation

Long-term graft function is of critical importance for the success of a transplant. Therefore, regular long-term follow-up by experienced transplant physicians is essential in order to detect complications or graft dysfunction early and reassure adherence to the immunosuppressive regimen.

Recommendations	Strength rating
Provide lifelong regular post-transplant follow-up by an experienced and trained transplant specialist at least every six to twelve months.	Strong
Advise patients on appropriate lifestyle changes, potential complications, and the importance of adherence to their immunosuppressive regimen.	Strong
Regularly monitor (approximately every four to eight weeks) serum creatinine, estimated glomerular filtration rate, blood pressure, urinary protein excretion, immunosuppression and complications after renal transplantation. Changes in these parameters over time should trigger further diagnostic work-up including renal biopsy, a search for infectious causes and anti-HLA antibodies.	Strong

Perform an ultrasound of the graft, in case of graft dysfunction, to rule out obstruction and renal artery stenosis.	Strong
In patients with interstitial fibrosis and tubular atrophy undergoing calcineurin inhibitor therapy and/or with histological signs suggestive for calcineurin inhibitor toxicity (e.g. arteriolar hyalinosis, striped fibrosis) consider calcineurin inhibitor reduction or withdrawal.	Strong
Initiate appropriate medical treatment, e.g. tight control of hypertension, diabetes, proteinuria, cardiac risk factors, infections, and other complications according to current guidelines.	Strong

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-23-3) available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines.