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	LE	GR
Offer pure or hand-assisted laparoscopic/ retroperitoneoscopic surgery as the preferential technique for living-donor nephrectomy.	1a	A
Perform laparo-endoscopic single site surgery, robotic and natural orifice transluminal endoscopic surgery-assisted living-donor nephrectomy in highly specialised centres only.	2a	B
Perform open living-donor nephrectomy in centres where endoscopic techniques are not implemented.	1a	B

Organ preservation

Recommendations for kidney storage solutions	LE	GR
Use either University of Wisconsin or histidine tryptophane ketoglutarate preservation solutions for cold storage.	1a	A
Use Celsior or Soltran solution for cold storage if University of Wisconsin or histidine tryptophane ketoglutarate solutions are not available.	1b	B

Recommendations for kidney preservation: static and dynamic preservation	LE	GR
Use cold and warm ischaemia time as predictors of delayed graft function.	1a	A
Use hypothermic machine-perfusion in type III kidneys from donors after cardiac death, kidneys with prolonged simple cold storage and expanded criteria donor kidneys.	1a	A
Hypothermic machine-perfusion may be used in standard criteria cadaver donor kidneys.	2a	B
Use low pressure values in hypothermic machine-perfusion preservation.	2a	B
Hypothermic machine-perfusion must be continuous and controlled by pressure and not flow.	1b	B
Do not discard grafts due to only increased vascular resistance and high perfusate injury marker concentrations during hypothermic machine-perfusion preservation.	1b	B

Donor kidney biopsies

Recommendations	LE	GR
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.	3	B
For frozen sections preferably submit 16 G needle core biopsies, wedge biopsies or skin punch biopsies since adequate work-up of very thin specimens in frozen sections is technically difficult.	4	C
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.	3	B
Procurement biopsies should be read by a renal pathologist or a general pathologist with specific training in kidney pathology.	3	B

Living and deceased donor implantation surgery

Recommendation for immediate pre-op haemodialysis	LE	GR
Manage fluid and electrolyte imbalance prior to transplant surgery with conservative measures where possible.	2	B

Recommendations for operating on patients taking anti-platelet and anti-coagulation agents	LE	GR
Consider continuing anti-platelet therapy in patients on the transplant waiting list.	3	C
Discuss patients who take anti-platelet and anti-coagulation agents prior to transplant surgery with relevant cardiologist/haematologist/ nephrologist.	4	C

Recommendation for prevention of venous thrombosis including deep vein thrombosis during and after renal transplant?	LE	GR
Post-operative prophylactic unfractionated or low-molecular-weight heparin should not be routinely given to low-risk living donor transplant recipients.	1b	B*

**Downgraded due to low power of the RCT.*

Recommendation for peri-operative antibiotics in renal transplant	LE	GR
Use single-dose, rather than multi-dose, peri-operative prophylactic antibiotics in routine renal transplant recipients.	1b	A

Recommendations for specific fluid regimes during renal transplantation	LE	GR
Optimise pre-, peri- and post-operative hydration to improve renal graft function.	1b	B*
Use balanced crystalloid solutions for intra-operative intravenous fluid therapy.	1b	B*
Use target directed intra-operative hydration to decrease delayed graft function rates and optimise early graft function.	1b	B*

**Downgraded due to low power of the RCT.*

Recommendation for dopaminergic drugs in renal transplantation	LE	GR
Do not routinely use low-dose dopaminergic agents in the early post-operative period.	2b	C

Surgical approaches for first, second, third and further transplants

Single kidney transplant – living and deceased donors

Recommendation	LE	GR
Inspect the kidney to be implanted on the back table before or at the commencement of transplant surgery.	4	A*
Choose either iliac fossa for placement of a first or second single kidney transplant.	2	B
Ligate peri-iliac vessel lymphatics (lymphostasis) to reduce post-operative lymphocele.	3	C
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.	3	C
Use the external or common iliac arteries for an end-to-side arterial anastomosis to donor renal artery.	2	B
An end-to-end anastomosis to the internal iliac artery is an alternative to external or common iliac arteries.	1b	B**
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.	4	A*
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.	3	B

**Upgraded based on panel consensus.*

***Downgraded due to low power of study.*

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: extra-peritoneal (UEP) or intraperitoneal (UIP) and bilateral extra-peritoneal (BEP) or intraperitoneal (BIP) 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

Recommendations	LE	GR
Perform Lich-Gregoir extra-vesical ureteric anastomosis technique to minimise urinary tract complications in renal transplant recipients with normal urological anatomy.	1a	A
Pyelo/uretero-ureteral anastomosis is an alternative especially for a very short or poorly vascularised transplant ureter.	2b	B
Use transplant ureteric stents prophylactically to prevent major urinary complications.	1a	A
Anastomose duplex ureters to the bladder either separately or as a combined single anastomosis.	3	C

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 extra-vesically (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. Intra-operative 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	LE	GR
Restrict living donor nephrectomy to specialised, preferably high volume, centres.	1	A
Offer long-term follow-up to all living kidney donors.	2a	A*

**Upgraded based on panel consensus.*

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 hematomas do not usually require any intervention. In case of larger hematomas, 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 (CT) or ultrasound (US) guidance or may require surgical treatment.

Arterial thrombosis

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

Recommendations	LE	GR
Perform ultrasound-colour-doppler in case of suspected graft thrombosis.	2b	B
Perform surgical exploration in case of ultrasound finding of poor graft perfusion.	2b	B
If arterial 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 .	2b	B
Do not perform directed injection of thrombolytic agents in the renal artery during the first ten to fourteen post-transplantation days due to the high risk of bleeding.	4	C

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	LE	GR
Perform ultrasound-colour-doppler in case of suspected graft thrombosis.	2b	B
Perform surgical exploration in case of ultrasound finding of poor graft perfusion.	2b	B
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.	2b	B
Pharmacologic prophylaxis to prevent transplant renal vein thrombosis is not currently recommended.	3	B

Transplant renal artery stenosis

The incidence of transplant renal artery stenosis is 1-25%, it is more common at the site of the anastomosis.

Recommendations	LE	GR
Suspect transplant renal artery stenosis in case of refractory arterial hypertension and/ or an increasing in serum creatinine without hydronephrosis/infections.	3	B
Perform ultrasound-colour-doppler to diagnose an arterial stenosis.	2a	B
Consider a magnetic resonance or computed tomography angiogram in case of undetermined results on ultrasound.	2a	B
Percutaneous transluminal angioplasty/stent should be the first-line treatment if feasible.	3	B
Offer surgical treatment in case of recent transplant, multiple, long and narrow stenosis, or after failure of angioplasty.	3	B

Arteriovenous fistulae and pseudo-aneurysms after renal biopsy

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

Recommendations	LE	GR
Perform a ultrasound-colour-doppler if a arteriovenous fistulae or pseudo-aneurysm is suspected.	2a	B
Perform angiographic embolisation as first-line treatment in symptomatic cases of arteriovenous fistulae or pseudo-aneurysm.	3	C

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	LE	GR
Perform percutaneous drainage placement as the first treatment option.	2a	A*
Perform laparoscopic fenestration when percutaneous treatments fail.	2a	A*
Simple aspiration and sclerosant agents are not recommended as first-line treatment due to the high risk of recurrence.	3	B

**Upgraded based on panel consensus.*

Urinary leak

Urinary leakage occurs in 0-9.3% of cases.

Recommendations	LE	GR
Initial management of a low volume urine leak should include percutaneous nephrostomy tube and/or JJ-stent placement and bladder catheter.	3	C
Perform surgical repair in cases of high volume leak and/or failure of conservative management.	2b	B

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	LE	GR
In case of ureteral stricture, place a nephrostomy tube for both kidney decompression and stricture diagnosis via an antegrade pyelogram.	2b	B
Endoscopic management (percutaneous balloon dilation or antegrade flexible ureteroscopy and holmium laser incision) should be considered for strictures < 3 cm in length.	3	B
Treat late stricture recurrence and/or stricture > 3 cm in length with surgical reconstruction in appropriate recipients.	2b	B

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.

Recommendations	LE	GR
An endoscopic approach may be the first option for the treatment of symptomatic reflux.	3	B
In case of recurrence (endoscopic failure), a surgical approach should be adopted.	3	B

Kidney stones

Urolithiasis occurs in 0.2-1.7% of recipients.

Recommendations	LE	GR
Evaluate the causes of urolithiasis in the recipient.	2b	B
Treat ureteral obstruction due to a stone with a percutaneous nephrostomy tube or JJ-stent placement.	2b	B
Extracorporeal shockwave lithotripsy should be considered as the first line treatment option for stones < 15 mm.	2b	B
Antegrade/retrograde ureteroscopy and percutaneous nephrolithotomy may be considered as first or second line treatment options as they provide high stone free rates.	2b	B

Wound infection

Wound infections occur in about 4% of the 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 the open kidney transplantations. Mesh infection is a risk factor for incisional hernia recurrence. Open and laparoscopic repair approaches are safe and effective.

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	LE	GR
Determine the ABO blood group and the human leukocyte antigen A, B, C and DR phenotypes for all candidates awaiting kidney transplantation.	3	A*
Testing of donor and recipient for human leukocyte antigen DQ is recommended and human leukocyte antigen DP testing may be performed for sensitised patients.	3	A*
Perform thorough testing for HLA antibodies before transplantation.	3	A*
Perform adequate cross-match tests to avoid hyper-acute rejection, before each kidney and combined kidney/pancreas transplantation.	3	A*

**Upgraded based on panel consensus.*

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 [EC-MPS]);
- steroids (prednisolone or methylprednisolone);
- induction therapy (preferably basiliximab in low and standard risk patients and anti-thymocyte globulin (ATG) in high risk patients).

Recommendation	LE	GR
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).	1	A

Calcineurin inhibitors

Recommendations	LE	GR
Use calcineurin inhibitors for rejection prophylaxis as they represent current best practice pending publication of long-term results using newer agents.	1	A
Choose a calcineurin inhibitor having taking in to account the immunological risk, characteristics, concomitant immunosuppression, and socio-economic factors of the recipient.	1	A
Use tacrolimus as first-line calcineurin inhibitor due to its higher efficacy.	1	A
Monitor blood-levels of both cyclosporine and tacrolimus to allow appropriate dose adjustment of calcineurin inhibitors.	3	A*

**Upgraded based on panel consensus.*

Mycophenolates

Recommendation	LE	GR
Administer mycophenolate as part of the initial immunosuppressive regimen.	1	A

Azathioprine

Recommendation	LE	GR
Azathioprine may be used in a low-risk population as a immunosuppressive drug, especially for those intolerant to mycophenolate formulations.	1	A

Steroids

Recommendations	LE	GR
Initial steroid therapy should be part of immunosuppression in the peri-operative and early post-transplant period.	1	A
Consider steroid withdrawal in standard immunological risk patients on combination therapy with calcineurin inhibitors and mycophenolic acid after the early post-transplant period.	1	A

Inhibitors of the mammalian target of rapamycin (m-TOR)

Recommendations	LE	GR
m-TOR inhibitors, such as sirolimus and everolimus, may be used to effectively prevent rejection.	1	A
Significantly reduce calcineurin inhibitor dosage in a combination regimen with m-TOR inhibitors to prevent aggravated nephrotoxicity.	1	A
Take into consideration impaired wound healing and prophylactic surgical measures when m-TOR inhibitors are used as part of the initial immunosuppressive regimen or when patients treated with m-TOR inhibitors undergo major surgery.	1	A
Conversion to m-TOR inhibitors is not recommended for patients with proteinuria and poor renal function.	1	A
Monitor blood-levels of both sirolimus and everolimus to allow for appropriate dose adjustment.	3	A

Induction with Interleukin-2 receptor antibodies

Recommendation	LE	GR
Use interleukin-2 receptor antibodies for induction in patients with normal immunological risk in order to reduce incidence of acute rejection.	1	A

T-cell depleting induction therapy

Recommendation	LE	GR
T-cell depleting antibodies may be used for induction therapy in immunologically high risk patients.	1	B

Belatacept

Recommendation	LE	GR
Belatacept may be used for immunosuppressive therapy in immunologically low risk patients, who have a positive Epstein-Barr virus serology.	1	B

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 (HAR), acute rejection or chronic rejection. Chronic ABMR is considered as one of the leading causes of late graft loss.

Recommendations	LE	GR
Monitor transplant recipients for signs of acute rejection, particularly during the first six months post-transplant.	3	C
Take regular blood samples in addition to regular monitoring of urine output and ultrasound examinations in order to detect graft dysfunction during hospitalisation.	3	B
Immediately rule out other potential causes of graft dysfunction in cases of suspected acute rejection. An ultrasound of the kidney transplant should be performed.	3	B
There must be routine access to ultrasound-guided biopsy of the transplant and sufficient expertise in the hospital pathology department to allow a rapid and clear-cut diagnosis of rejection or other type of allograft dysfunction.	2	B
Perform a renal biopsy, graded according to the most recent Banff criteria, in patients with suspected acute rejection episodes.	2	B
Only if contraindications to renal biopsy are present, can 'blind' steroid bolus therapy be given.	3	B
Steroid treatment for rejection may start before the renal biopsy is performed.	2	B
Test patients who suffer acute rejection as soon as possible for anti-HLA antibodies against the graft.	2	B
In all patients with rejection, the immuno-suppressive therapy should be re-assessed including patient adherence to the medication, which is of particular importance in late rejections.	2	B

Hyper-acute rejection

Recommendation	LE	GR
Prevent hyper-acute rejection by adequate ABO blood group and HLA matching of donor and recipients.	3	B

Treatment of T-cell mediated acute rejection

Recommendations	LE	GR
Use steroid bolus therapy as first-line treatment for T-cell mediated rejection in addition to ensuring adequate baseline immunosuppression.	3	B
In severe or steroid-resistant rejection, consider intensified immunosuppression, high-dose steroid treatment, and T-cell depleting agents.	3	B

Treatment of antibody mediated rejection

Recommendations	LE	GR
Treatment of antibody mediated rejection should include antibody elimination.	1	B
In addition, steroid bolus therapy, adequate maintenance immunosuppression with tacrolimus and mycophenolate, and intravenous immunoglobulin treatment may be used in patients with antibody-mediated rejection.	3	B

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	LE	GR
Provide lifelong regular post-transplant follow-up by an experienced and trained transplant specialist at least every six to twelve months.	4	C
Advise patients on appropriate lifestyle changes, potential complications, and the importance of adherence to their immunosuppressive regimen.	4	C
Annual screening should include a dermatological examination, cardiovascular history and exam, tumour screening (including a nodal examination, faecal occult screening, chest X-ray, gynaecological and urological examination), and an abdominal ultrasound, including ultrasound of the native and transplanted kidney. If appropriate, further diagnostic tests should be prompted to treat or slow down the progression of any identified complication.	4	C
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.	4	C
Perform an ultrasound of the graft, in case of graft dysfunction, to rule out obstruction and renal artery stenosis.	4	C
Changes in renal function, blood pressure and urinary protein excretion over time should trigger further diagnostic work-up including renal biopsy, a search for infectious causes and anti-HLA antibodies.	4	C

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.	1	A
Initiate appropriate medical treatment, e.g. tight control of hypertension, diabetes, proteinuria, cardiac risk factors, infections, and other complications according to current guidelines.	4	C
Supportive measures should aim to adequately treat the consequences of chronic kidney disease (e.g. anaemia, acidosis, bone disease).	4	C

This short booklet is based on the more comprehensive EAU Guidelines (ISBN 978-90-79754-91-5), available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines.