EAU Guidelines on Renal Transplantation

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1. INTRODUCTION

1.1 Aim and objectives

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. It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel Composition

The EAU Renal Transplantation Guidelines panel consists of an international multidisciplinary group of urological surgeons, a nephrologist and a pathologist. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guideline/renal-transplantation/.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is available in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. All are available through the EAU website: http://www.uroweb.org/guideline/renal-transplantation/.

1.4 Publication history

The EAU published the first Renal Transplantation Guidelines in 2003 with updates in 2004 and 2009. This document is a comprehensive update of the 2009 Renal Transplantation Guidelines. Additional chapters will be added in the coming year to address ethical issues surrounding kidney transplantation as well as the issue of prior malignancy in kidney transplantation.

2. METHODS

2.1 Introduction

For the 2017 Renal Transplantation Guidelines, new and relevant evidence was identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Renal Transplantation Guidelines was performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between January 1st 2007 and May 31st 2016. A total of 2,601 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: http://www.uroweb.org/guideline/renal-transplantation/. The next update of the Renal Transplantation Guidelines will be published in 2019.

For the 2018 edition of the EAU Guidelines the Guidelines Office have transitioned to a modified GRADE methodology across all 20 guidelines [1, 2]. For each recommendation within the guidelines there is an accompanying online strength rating form which addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [3];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words ‘strong’ or ‘weak’ [4]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review and future goals

This document was subject to independent peer review prior to publication in 2017.

The results of completed and ongoing systematic reviews will be included in the 2019 update of the Renal Transplantation Guidelines. Ongoing systematic reviews include:

- What are the effectiveness and harms of using kidneys with small renal tumours from deceased or living donors as a source for renal transplantation [5]?

Completed systematic reviews include:

- The risk of tumor recurrence in patients undergoing renal transplantation for end-stage renal disease after previous treatment for a urological cancer [6].

Brief summary: The systematic review included 32 studies (four retrospective comparative studies, 21 retrospective non-comparative studies and seven case reports) and a total of 2,519 patients suffering from: renal cell carcinoma (RCC) (72%); prostate cancer (PCa) (8%); upper urinary tract carcinoma/bladder cancer (UUTUC/BC) (18%) and testicular cancer (TC) (2%). Although the level of evidence was poor, the risk of recurrence was similar between transplantation and dialysis for RCC and PCa, especially for low grade/stage PCa, for which the risk of recurrence was low and consistent with monograms. For low stage/grade RCC the recurrence rate was significant for both dialysis and renal transplantation; however, recurrences were mainly contralateral RCC with no impact on patient and graft survival. This implies that a kidney transplant candidate with a history of low stage/grade PCa or RCC could be proposed for a renal transplantation without any additional delay compared to a cancer-free patient. Testicular cancer had a low risk of recurrence but case reports highlighted the possibility of late recurrence even for stage I tumours.

For urothelial carcinoma, studies were mainly related to upper urinary tract carcinomas in the context of aristolochic acid nephropathy. Considering the 10-16 % risk of synchronous bilateral involvement and the 31-39 % risk of contralateral recurrence, the following two strategies seem justified for candidates for renal transplantation with a history of UUTUC/BC :

1. Systematic treatment of the contralateral upper urinary tract and/or the bladder by nephroureterectomy and/or cystectomy;
2. Close monitoring of the bladder and the contralateral upper urinary tract.

3. THE GUIDELINE

3.1 Organ retrieval and transplantation surgery

*3.1.1 **Living-donor nephrectomy***

The endoscopic (laparoscopic) approach is the preferred technique for living-donor nephrectomy in established kidney transplant programmes [7]. Nevertheless, open surgery, preferably by a mini-incision approach, can still be considered a valid option, despite increased pain in the post-operative period [8].

Endoscopic living-donor nephrectomy (ELDN) includes:

- Pure or hand-assisted transperitoneal laparoscopy;
- Pure or hand-assisted retroperitoneal approach;
- Laparo-Endoscopic Single Site Surgery (LESS);
- Natural orifice transluminal endoscopic surgery-assisted (NOTES);
- Laparo-Endoscopic Single Site Surgery and robotic-assisted transperitoneal or retroperitoneal approach.

There is strong evidence in support of laparoscopic living-donor nephrectomy (LLDN), including several systematic reviews and meta-analysis, which have compared its safety and efficacy to open donor nephrectomy. Laparoscopic living-donor nephrectomy is associated with similar rates of graft function and rejection, urological complications and patient and graft survival. However, measures related to analgesic requirements, pain, hospital stay, and time to return to work are significantly better for laparoscopic procedures [9-11].

Standard LLDN is usually done through 5 and 12 mm ports, but has also been done with 3 or 3.5 mm ports [12]. Laparoscopic living-donor nephrectomy can also be performed with robotic assistance, with equivalent results according to a recent systematic review [13]. However, the numbers are still low and a recent paper found a higher complication rate for this approach [14].

Laparo-endoscopic single site surgery nephrectomy allows the surgeon to work through a single incision (usually the umbilicus) with a multi-entry port. The same or a separate incision is then used for kidney withdrawal. Several retrospective and at least three prospective randomised trials demonstrated equivalent safety and results, with a trend towards less pain and better cosmetic results [15]. However, LESS is considered a more technically demanding procedure when compared with classic LLDN and its role is yet to be defined.

Natural orifice transluminal endoscopic surgery-assisted transvaginal nephrectomy avoids the abdominal incision needed for kidney extraction, aimed at minimising scaring and pain. Initial reports suggest that this approach is safe, however experience with this technique is still highly limited [16].

Right LLDN has been considered more difficult, yielding inferior results. However, according to a recent systematic review and meta-analysis right LLDN can be performed with equivalent safety and efficacy [17].

Laparoscopic living-donor nephrectomy has brought attention to potential failures of different devices such as, endoscopic staplers and locking and non-locking clips, used to secure the renal hilum [17]. There is no scientific evidence that one device is safer than another for securing the renal artery [18-20]. However, the U.S. Food and Drug Administration (FDA) and the manufacturers of locking clips have issued a contraindication against their use in securing the artery during LLDN.

Summary of evidence	**LE**
Laparoscopic living-donor nephrectomy is associated with similar rates of graft function and rejection, urological complications and patient and graft survival to open nephrectomy.	1a
Measures related to analgesic requirements, pain, hospital stay, and time to return to work are significantly better for laparoscopic procedures.	1a

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

*3.1.2 **Organ preservation***

3.1.2.1 Kidney storage solutions and cold storage

There are two main sources for kidney graft injury: ischaemia (warm and cold), and reperfusion injury. The aims of modern kidney storage solutions include: control of cell-swelling during hypothermic ischaemia; maintenance of intra- and extra-cellular electrolyte gradient during ischaemia; buffering of acidosis; provision of energy reserve; and minimisation of oxidative reperfusion injury. There is no agreement on which of the mechanisms is most important for post-ischaemic renal graft function [21]. No storage solution seems to combine all mechanisms. Previously, Euro-Collins was widely used, but is no longer recommended.

Presently, University of Wisconsin (UW), and histidine-tryptophan-ketoglutarate (HTK) solution are equally effective and are standard for multi-organ or single kidney harvesting procedures. The characteristics of HTK are its low viscosity, low potassium concentration and low cost. University of Wisconsin solution has been the standard static cold preservation solution for the procurement of liver, kidney, pancreas, and intestine [22]. University of Wisconsin, HTK, and Celsior solutions have provided similar allograft outcomes in most clinical trials, however, some differences have become apparent in recent studies and registry reports [23, 24]. Marshall's hypertonic citrate solution (MHCS) is also suitable for use in the preservation of human kidneys before transplantation [25]. In experimental studies of kidney preservation, HTK and UW retained a greater capacity to preserve endothelial structure and pH buffering function during warm ischaemia in comparison to MHCS and Celsior, especially in uncontrolled donors after cardiac death (DCD) [26]. In the absence of a cost-utility analysis, the results of the meta-analysis from the randomised controlled trials (RCTs) comparing

UW with Celsior and MHSC in standard cadaver donors, indicate that these cold storage solutions are equivalent [27].

For living donors, in whom immediate kidney transplantation is planned, perfusion with crystalloid solution is sufficient. Kidneys coming from DCD, especially those uncontrolled are high-risk marginal organs due to prolonged warm ischaemia periods, and require specific measures in order to diminish the rate of non-function or delayed graft function (DGF). More than 60% of kidney grafts currently come from Expanded Criteria Donors (ECD) (any donor aged > 65 years and/or donor aged > 55 years with any of the following: acute renal dysfunction, stroke or arterial hypertension) [28].

Summary of evidence	**LE**
University of Wisconsin and HTK solution are equally effective and are standard for multi-organ or single kidney harvesting procedures.	1b
A meta-analysis of RCTs indicated that UW and Celsior solution are equivalent in standard cadaver donors.	1a

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

3.1.2.2 Duration of organ preservation

Cold ischaemia time should be as short as possible. Kidneys from elderly (> 55 years) and marginal donors are more sensitive to ischaemia than young kidneys. Organ preservation relies mainly on hypothermia, which lowers the metabolic rate, conserves stores of adenosine triphosphate (ATP), and prevents formation of oxygen-free radicals during the reperfusion phase. Kidneys from deceased donors should ideally be transplanted within 18 hours. Within this 18 hour window, ischaemia time has no significant influence on graft survival [29].

3.1.2.3 Methods of kidney preservation: static and dynamic preservation

Whichever method is used, cold storage is critical. The use of cold preservation as a therapeutic window to deliver pharmacological or gene therapy treatments could, from an investigational point of view, improve both short- and long-term graft outcomes [30]. Cooling reduces the metabolic rate of biological tissue minimising continuous cellular processes that lead to depletion of ATP and accumulation of metabolic products. Reperfusion with oxygenated blood invokes ischaemia-reperfusion injury. Hypothermic perfusion does not enable normal cellular metabolic function or prevent depletion of energy stores [31]. However, it prevents the deleterious effects of simple cooling, especially in the setting of prolonged warm-ischaemic time in uncontrolled DCD. Hypothermic machine perfusion reduces DGF compared with static cold storage [32].

The increased demand for organs has led to the increased use of “higher risk” kidney grafts. Kidneys from DCD or grafts coming from ECDs are more susceptible to preservation injury and have a higher risk of unfavourable outcomes [33, 34].

Dynamic, instead of static, preservation could allow for organ optimisation, offering a platform for viability assessment, active organ repair and resuscitation. *Ex situ* machine perfusion and *in situ* regional perfusion in the donor are emerging as potential tools to preserve vulnerable grafts. Preclinical findings have driven clinical organ preservation research that investigates dynamic preservation, in various modes (continuous, pre-implantation) and temperatures (hypo-, sub-, or normothermic) [31].

There are several methods of kidney preservation including:

- Initial flushing with cold preservation solution followed by ice storage. However, the limitations of static cold storage (CS) in preserving marginal organs such as ECD kidneys has led to the increased use of dynamic methods.
- Current dynamic preservation strategies entering clinical practice and the different modalities of their use are: hypothermic machine perfusion, hypothermic regional perfusion, normothermic machine perfusion, normothermic regional perfusion, sub-normothermic machine perfusion and sub-normothermic regional perfusion [31].
- Continuous pulsatile hypothermic machine-perfusion (HMP) seems to be a good preservation method for marginal organs, either initially or after a period of simple CS (shipping of suboptimal kidneys) [35].

- Some evidence shows that hypothermic dynamic preservation should be controlled by pressure and not flow, using low pressures to avoid pressure-related injury. The perfusion solutions used are specific, and are qualitatively different to CS solution [24].
- Nonoxygenated HMP of the kidney at low perfusion pressures (20-30 mmHg) has been shown to reduce DGF [32]. The largest RCT comparing simple CS with HMP of deceased donor kidneys showed an overall reduced risk of DGF and a survival benefit, most pronounced in ECD kidneys [36]. Hypothermic machine perfusion of kidneys from type III DCD decreased DGF with no impact on graft survival [33].
- Hypothermic machine-perfusion reduces the risk of DGF in standard cadaver donor kidneys regardless of cold ischaemia time [37].
- Increased vascular resistance and high perfusate injury marker concentrations are risk factors for DGF; however, they do not justify discarding the kidney. The flow perfusion value seems to be an indicator of graft viability in uncontrolled DCD, particularly donors with high creatinine level [38]. However, research is required to identify a strong and reliable measure for predicting kidney viability from machine perfusion [27]. Perfusion parameters (renal flow and renal vascular resistance) have low predictive values and should not be used as the sole criterion to assess viability of kidney grafts [39].
- Oxygenation during HMP appears to be beneficial, improving early kidney graft function [40]. The effect of oxygenated HMP is being investigated in two RCTs initiated by the Consortium on Organ Preservation in Europe (COPE), on type III DCD kidneys and ECD kidneys [31].
- A short period of normothermic machine perfusion (NMP) immediately prior to implantation has been shown to improve kidney graft function, replenish ATP and reduce injury in experimental models [41, 42].
- Active research is being developed on preservation of prolonged warm-ischaemically damaged human kidneys (types I and II DCD) by *in situ* normothermic extracorporal hemoperfusion with oxygenation and leukocyte depletion before procurement [43]. Oxygen carriage is achieved by using blood depleted of leukocytes. Potential advantages of this preservation technique are reduction in ischaemia-reperfusion injury as well as the possibility of assessing organ viability.
- Currently there are no registered ongoing RCTs on pre-implantation NMP using an oxygenated, sanguineous normothermic perfusion solution. However, kidney function can be evaluated during NMP by assessing macroscopic appearance of blood perfusion, renal blood flow and urine output [44].
- Continuous subnormothermic MP and controlled oxygenated rewarming has demonstrated improved creatinine clearance and preservation of structural integrity compared with continuous oxygenated HMP in a research setting [45].

Summary of evidence	**LE**
A RCT comparing simple CS with HMP of deceased donor kidneys showed an overall reduced risk of DGF and a survival benefit, most pronounced in ECD kidneys.	1b
Hypothermic machine-perfusion reduces the risk of DGF in standard cadaver donor kidneys regardless of cold ischaemia time.	2a
Hypothermic dynamic preservation should be controlled by pressure and not flow, using low pressures to avoid pressure-related injury.	2a
Perfusion parameters (renal flow and renal vascular resistance) have low predictive values and should not be used as the sole criterion to assess viability of kidney grafts.	2b

Recommendations	**Strength rating**
Use cold and warm ischemia time as predictors of delayed graft function.	Strong
Use hypothermic machine-perfusion in type III kidneys from donors after cardiac death, kidneys with prolonged simple cold storage and expanded criteria donor kidneys.	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

*3.1.3 **Donor Kidney biopsies***

Donor kidney biopsies can serve different purposes including:

- histological assessment of organ quality prior to transplantation (often referred to as procurement or harvest biopsies);
- histological analysis of focal lesions, especially if there is a suspicion of neoplasia;

- detection of donor derived lesions as reference for subsequent post-transplant biopsies (often referred to as baseline, zero-time or implantation biopsies).

3.1.3.1 Procurement Biopsies

3.1.3.1.1 Background and prognostic value

Procurement biopsies are used for the detection of tissue injury to aid the decision of whether or not a deceased donor kidney is suitable for transplantation. These biopsies are most commonly performed in donors with clinical suspicion of chronic kidney injury (ECDs).

Kidney discard in Europe is rarely based on histology findings, as procurement biopsies are not regularly performed for graft allocation in the Eurotransplant region [46]. However, since biopsy findings are the most frequent cause for discarding donor organs in the United States [47-49], their prognostic value has been analysed in numerous studies. A recently published systematic review of studies on donor kidney biopsies revealed a lack of prospective studies and marked heterogeneity regarding the type of lesions being assessed, their scoring, the definitions of post-transplant outcomes and the statistical methods employed [50]. Therefore, the published evidence suggests that the use of procurement biopsies for deciding on suitability for transplantation of donor kidneys may have some important limitations including the following [46, 50, 51]:

- *There is no consistent association between histological lesions observed in donor kidney biopsies and post-transplant outcomes.*

The concept of procurement biopsies in elderly donors was introduced by a study from Gaber *et al.* in 1995. This study observed significantly worse outcomes in recipients of kidneys with > 20% globally sclerotic glomeruli [52]. However, subsequent studies yielded highly variable results and it cannot be concluded that glomerulosclerosis is independently associated with graft outcomes [50]. A similar variability was also observed for other potentially relevant lesions like arterial injury, interstitial fibrosis and tubular atrophy which did show predictive value in some studies but not in others [50].

- *There is no agreement on prognostically relevant lesions and how they should be scored.*

Specific grading systems for donor kidney biopsies have not yet been developed. Lesion scoring in pre-transplant biopsies is mostly based on the Banff consensus for post-transplant renal allograft pathology, which is supported by the 2007 Banff Conference report [53].

Many attempts have been made to use composite semi-quantitative scoring systems to express the global extent of tissue injury in donor kidney biopsies. These scoring systems are mostly based on simple addition of the Banff scores for individual lesions, most commonly glomerulosclerosis, arteriolar hyalinosis, arterial intimal fibrosis, interstitial fibrosis and tubular atrophy and rarely include clinical parameters like donor age [54], serum creatinine values and donor hypertension [55].

A limited number of histological scoring systems are based on modelling analysis [54-58]. Only the Maryland Aggregate Pathology Index (MAPI) [58] scoring system and the Leuven donor risk score [54], use graft failure as their endpoint and have been independently validated in a second cohort. Other studies used surrogate clinical endpoints like DGF [56] and estimated glomerular filtration rate (eGFR) at three months [57] to calculate histological models. In addition, these models were not validated in independent cohorts. The variation in how the components are weighted to achieve the composite score and the different endpoints used may explain the conflicting conclusions in the literature [46, 50, 51].

- *Due to the time constraints of organ allocation procurement biopsies are mostly read on frozen sections by on-call pathologists, which might affect the diagnostic reliability of reported findings.*

This may have substantial impact on the diagnostic reliability of the procedure since frozen sections are prone to morphological artefacts that can impair the detection and scoring of potentially important lesions such as arteriolar hyalinosis and interstitial fibrosis [59, 60]. There is strong evidence that dedicated renal pathologists should examine formalin-fixed paraffin-embedded (FFPE) core-needle biopsies. Paraffin histology employing special stains is technically superior to frozen sections since morphological details are better preserved on paraffin sections than on frozen sections and potentially confounding artefacts can be avoided. Rapid processing of tissue for paraffin histology is technically feasible but the respective protocols are not universally implemented and are not available on a 24/7 basis in most departments. Another source of variability is the professional experience of the pathologist in charge. Procurement biopsies are commonly read by the on-call general pathologist who frequently has no specific training in renal pathology. A recent study specifically addressing this issue found that the on-call pathologists tended to overestimate chronic injury in biopsies [61].

3.1.3.2 Type and size of biopsy

Many transplant centres obtain wedge biopsies of donor kidneys rather than needle biopsies due to the presumed higher risk of bleeding complications with the latter. Wedge biopsies sample the cortex superficially

whereas needle biopsies reach deeper aspects of the cortex. Needle biopsies also allow sampling from different areas of the kidney. Several studies comparing wedge with needle biopsies concluded that needle biopsies perform much better in the evaluation of vascular lesions because interlobular arteries are rarely sampled in wedge biopsies. Both methods were comparable for glomerular or tubulointerstitial lesions [62-65]. It was also demonstrated that glomerulosclerosis is significantly more pronounced in the subcapsular zone compared with deeper areas of the cortex [66]. The problem of insufficient sampling of arteries and over representation of (subcapsular) glomerular scars in wedge biopsies, can only be avoided if particular attention is paid to the correct performance of the biopsy, with a minimal depth of 5 mm [67]. The predictive value of glomerulosclerosis increases significantly with higher numbers of glomeruli in the wedge biopsy, with ideally, at least 25 glomeruli required for evaluation [64].

For surgeons who are reluctant to take needle biopsies, the use of a skin punch biopsy device might be an attractive alternative. Skin punch biopsies measure 3 mm in diameter. They have a shorter length than needle biopsies therefore avoiding injury to large calibre arteries at the corticomedullary junction whilst still sampling tissue from deeper areas of the cortex [68].

3.1.3.3 Summary of evidence and recommendations

Summary of evidence	**LE**
Individual histologic lesions like glomerulosclerosis, arterial luminal narrowing or tubulointerstitial injury observed in donor kidney biopsies have limited prognostic value for long-term allograft survival.	3
Composite histological scoring systems provide a more comprehensive measure of overall organ damage. Published scoring systems, however, still lack independent validation and robust thresholds.	3
Size of the biopsy is of critical importance for its diagnostic value. An adequate biopsy reaches beyond the immediate subcapsular area (≥ 5 mm) and contains ≥ 25 glomeruli and ≥ one artery. Needle biopsies, wedge biopsies or specimens obtained with a skin punch biopsy device will result in equally adequate biopsies if sampling is properly performed. Obtaining adequate biopsies with 18 G needles is difficult and requires multiple cores.	3

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

3.1.3.4 Implantation biopsies

Implantation biopsies are used to provide baseline information on donor kidney injury for comparison with subsequent post-transplant kidney biopsies. Baseline biopsies can be essential for clear distinction between pre-existing damage and acquired lesions. They are particularly valuable in cases of thrombotic microangiopathy, arteriolar hyalinosis or acute tubular injury. In contrast to procurement biopsies that are obtained at the time of organ harvesting, implantation biopsies are usually taken before implantation in order to cover potential effects of cold ischaemia time. Their diagnostic contribution has not been formally quantified in the literature which might be due to the difficulties of measuring the value of implantation biopsies for improving diagnoses. Despite the lack of formal studies investigating their value it seems very reasonable to perform implantation biopsies in deceased donor kidneys.

*3.1.4 **Living and deceased donor implantation surgery***

3.1.4.1 Anaesthetic and peri-operative aspects

Good communication between nephrologists, anaesthetists and surgeons is required for optimal anaesthetic and peri-operative care of the renal transplant patient. Anaesthetic care of the living kidney donor [69] and renal transplant recipient [70] have been reviewed and recent guidelines from the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA) [71] are cross referenced.

3.1.4.2 Immediate pre-op haemodialysis

Routine use of haemodialysis immediately prior to renal transplantation is not indicated [71]. Hyperkalaemia is the most common indication for haemodialysis pre-operatively. The risks of haemodialysis compared with medical therapy must be considered along with the risks of intra-operative fluid overload, electrolyte and acid-base disturbances, particularly where a deceased donor kidney is transplanted with a significant risk of DGF. Pre-operative haemodialysis may initiate a pro-inflammatory state, delay surgery, increase the cold ischaemia time and increase the risk of DGF [72].

Summary of evidence	LE
Pre-operative haemodialysis has the potential to delay transplantation, increase cold ischaemia time and increase the risk of DGF.	2

Recommendation	Strength rating
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

3.1.4.3 Operating on patients taking anti-platelet and anti-coagulation agents

Many patients active on the transplant waiting list have vascular disease and/or a pro-thrombotic condition that should be risk-assessed prior to transplantation. Dual anti-platelet therapy is commonly given to patients with coronary artery stents for six to twelve months; peri-operative management plans for these patients should be discussed with a cardiologist so that the risks of withdrawal of the anti-platelet agent can be fully considered. Options for reversal of anti-coagulation and post-operative anti-coagulation should be discussed with a haematologist prior to patient listing.

Some patients will be active on a transplant waiting list whilst continuing to take anti-platelet and/or anti-coagulation agents. The indication for anti-platelet or anti-coagulation agents should be clearly documented for each individual. Potential increased risk of peri-operative bleeding needs to be weighed against potential harm from arterial or venous thrombosis. In accordance with the American College of Chest Physicians and the European Society of Cardiology guidelines [73, 74], the literature suggests that continuing anti-platelet therapy with aspirin, ticlopidine or clopidogrel does not confer a significantly greater risk of peri/post-operative complications [75], however, the number of patients studied was low. If needed, the effect of anti-platelet agents can be reduced with intra-operative platelet infusions.

Summary of evidence	LE
A retrospective single-centre case-control study in patients undergoing kidney transplantation concluded that continuing anti-platelet therapy with aspirin, ticlopidine or clopidogrel does not confer a significantly greater risk of peri/post-operative complications.	3

Recommendations	Strength rating
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

3.1.4.4 What measures should be taken to prevent venous thrombosis including deep vein thrombosis during and after renal transplant?

Peri-operative administration of short-acting anti-coagulation agents reduces peri-operative risk of venous thrombosis (including in ileo-femoral and renal veins), however, due to associated increased blood loss administration requires knowledge of individual patient risk factors. None of the current major thrombosis prevention guidelines directly address thromboprophylaxis in the renal transplant peri-operative period. A small RCT [76] showed no difference in early post-operative graft loss or thromboembolic complications with or without prophylactic anti-coagulation. Those administered prophylactic anti-coagulation had significantly lower haemoglobin whilst those administered prophylactic unfractionated heparin had prolonged lymph drainage. Based on this study, routine pharmacological prophylaxis is not recommended in low-risk living donor recipients. Mechanical measures to decrease ileo-femoral deep vein thrombosis (DVT) can be used where there is no contraindication due to peripheral vascular disease particularly where there are concerns about bleeding risks with pharmacological prophylaxis.

Summary of evidence	LE
A small RCT (n=75) showed no difference in early post-operative graft loss or thromboembolic complications with or without prophylactic anti-coagulation.	1b

Recommendation	Strength rating
Do not routinely give post-operative prophylactic unfractionated or low-molecular-weight heparin to low-risk living donor transplant recipients.	Weak

3.1.4.5 Is there a role for peri-operative antibiotics in renal transplant?

Prophylactic peri-operative antibiotics are generally used in renal transplant surgery but the optimal antibiotic regimen is not known and increasing antibiotic resistance may hamper their effectiveness in this setting. A multicentre, prospective RCT showed no difference at one month in surgical site, bacterial, fungal or viral infection between those receiving a single dose broad spectrum antibiotic at induction of anaesthesia compared to those receiving antibiotic 12 hourly for 3-5 days [77]. A retrospective comparison of peri-operative intravenous cefazolin prophylaxis compared to no antibiotic showed no difference in infectious complications (surgical site, urinary tract, bacteraemia or central catheter-related infection) in the first month after renal transplantation [78].

Summary of evidence	LE
A multicentre, prospective RCT showed that the incidents of surgical site infection and urinary tract infection were similar in those receiving a single dose broad spectrum antibiotic at induction of anaesthesia and those receiving antibiotic 12 hourly for 3-5 days.	1b

Recommendation	Strength rating
Use single-dose, rather than multi-dose, peri-operative prophylactic antibiotics in routine renal transplant recipients.	Strong

3.1.4.6 Is there a role for specific fluid regimes during renal transplantation and central venous pressure measurement in kidney transplant recipients?

Careful peri- and post-operative fluid balance is essential for optimal renal graft function. There is no evidence determining if crystalloids or colloids are better for intravenous fluid management during renal transplant surgery, however colloids may be immunogenic. If normal saline (0.9%) is used, monitoring for metabolic acidosis is recommended in the peri-operative period. A prospective double-blind RCT compared normal saline to lactated Ringer's solution as intra-operative intravenous fluid therapy. Serum creatinine at day three post-surgery did not differ between the two groups. However, Ringer's lactate caused less hyperkalaemia and metabolic acidosis than normal saline. Balanced solutions may be the optimal and safer option for intra-operative intravenous fluid therapy [79].

Central venous pressure (CVP) measurement helps anaesthetists guide fluid management. A small prospective non-blinded RCT compared two normal (0.9%) saline regimens: constant infusion (10-12 $mL/kg^{-1}/h^{-1}$ from start of surgery until reperfusion) and central venous pressure-based infusion (target CVP appropriate to stage of operation) [80]. Central venous pressure directed infusion produced a more stable haemodynamic profile, better diuresis and early graft function. Directed hydration may decrease DGF rates and CVP measurement may help optimise early graft function.

Summary of evidence	LE
A small (n=51) prospective RCT found that use of Ringer's lactate solution was associated with less hyperkalaemia and acidosis compared with normal saline in patients undergoing kidney transplantation.	1b
A small (n=40) prospective RCT comparing constant infusion vs. CVP found that CVP produced a more stable haemodynamic profile, better diuresis and early graft function.	1b

Recommendations	Strength rating
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

3.1.4.7 Is there a role for dopaminergic drugs, furosemide or mannitol in renal transplantation?

Low-dose dopamine (LDD) has been used in renal transplantation due to a perceived improvement in urine output and early graft function. Use of LDD in kidney donors is outside of the scope of this section. Conflicting results prevent a consensus statement on routine use of LDD in transplant recipients. A small (n=20) prospective randomised cross-over study in deceased donor renal transplantation suggested significant improvements in urine output and creatinine clearance in the first nine hours post-surgery without adverse events [81]. By contrast, a retrospective comparison of LDD in the first twelve hours post-deceased donor renal transplantation showed no difference in diuresis or kidney function but those administered LDD (n=57) had increased heart rates, longer intensive therapy unit stay and higher six-month mortality than those not treated with LDD (n=48) [82].

Considerable variation exists in the use of diuretics during renal transplant recipient surgery and there is little evidence to suggest any benefit from their use [83]. No evidence on the use of mannitol during renal transplant recipient surgery was found during the panels literature search. Use of mannitol in kidney donors is outside of the scope of this section.

Summary of evidence	LE
A retrospective comparison study of LDD treated vs. non-treated renal transplantation patients concluded that LDD administration did not improved kidney function in the first twelve hours post renal transplantation but did result in increased heart rates, longer intensive therapy unit stay and higher six-month mortality in those receiving LDD.	2b

Recommendation	Strength rating
Do not routinely use low-dose dopaminergic agents in the early post-operative period.	Weak

3.1.5 ***Surgical approaches for first, second, third and further transplants***

Transplant (bench/back-table) preparation is a crucial step in the transplantation process. The kidney must be inspected whilst on a sterile iced slush, removing peri-nephric fat when possible to permit inspection of the quality of the organ and to exclude exophytic renal tumours. Biopsy of the kidney on the back-table may be performed to help in the multifactorial decision making process regarding the quality and usage of the kidney for both single and/or dual transplantation. Suspicious parenchymal lesions also require biopsy. Techniques for intra-operative kidney biopsy are discussed in section 3.1.3.

The number, quality and integrity of renal vessels and ureter(s) should be established and lymphatics at the renal hilum ligated. The quality of the intima of the donor renal artery should be evaluated. Branches of the renal artery not going to the kidney or ureter(s) should be tied.

In deceased donor kidney transplantation the quality of the aortic patch should be determined. If severe atheroma of the patch, ostium or distal renal artery is seen then the aortic patch and/or distal renal artery can be removed to provide a better quality donor renal artery for implantation. Back table reconstruction of multiple donor arteries is discussed in section 3.1.5.1.

The length of the renal vein should be evaluated. Renal vein branches should be secured/tied. For a deceased donor right kidney, lengthening the renal vein on the back table may be performed if needed with donor inferior vena cava [84]. Techniques for lengthening a short living donor right renal vein from donor gonadal vein or recipient saphenous vein require pre-operative planning and specific consent (discussed in section 3.1.5.1).

The length, quality and number of the ureter(s) should be established. The peri-pelvic and proximal peri-ureteral tissue in the ‘golden triangle’ should be preserved.

Recommendation	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

3.1.5.1 Single kidney transplant - living and deceased donors

An extra-peritoneal approach to either iliac fossa should be used as the operative approach in most first or second single kidney transplant (SKT) operations. There is no evidence to prefer placement of a left or right kidney into either iliac fossa [85]. Peri-iliac vessel lymphatics should be ligated to try and prevent

post-operative lymphocele. Appropriate segments of iliac artery and vein should be mobilised to facilitate appropriate tension free vascular anastomoses and the final positioning of the transplanted kidney.

Recommendations	Strength rating
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

A variety of techniques have been described to help with the anastomosis of a short renal vein. This is most commonly encountered with a right kidney especially from a living donor. To achieve equivalent outcomes with right kidneys appropriate surgical technical manoeuvres may be needed to optimise right kidney implantation.

Data from cohort studies [85, 86] and one registry study [87] suggest equivalent outcomes with either left or right deceased donor kidneys. By contrast, another registry study of 2,450 paired kidneys, donated after cardiac death, observed with right kidneys: more early surgical complications; an increased risk in DGF (Odds Ratio [OD] 1.46); and inferior one year graft survival (OD 1.62) but not at subsequent time points [88]. However, surgical techniques used to compensate for a right kidney, anastomosis time and surgeon experience were not recorded.

Data from at least two large registry studies demonstrate a slightly higher risk of early graft failure using right compared to left kidneys from living donors [87, 89, 90]. However, meta-analysis of data from one RCT and fourteen cohort studies suggested equivalent graft outcomes [91].

Techniques to manage a short renal vein can be addressed in the donor and/or recipient. Ligation of internal iliac vein(s) may be necessary to elevate the iliac vein and avoid tension on the renal vein anastomosis [85]. Transposition of the iliac artery and vein may enhance the position for the venous anastomosis [92]. The right renal vein may be lengthened. With deceased donor kidneys this is usually done with donor inferior vena cava (IVC) [86]. In living donors, lengthening of the renal vein may be achieved with donor gonadal vein retrieved at donor nephrectomy [93] or with recipient saphenous vein [94], although both require specific consent and in general the other aforementioned techniques are preferred.

Summary of evidence	LE
Prospective cohort studies demonstrated that: • transposition of the recipient iliac vein is an appropriate technical solution to compensate for the short length of the renal vein in right-kidney LDN (n=43); • the living donor right kidney renal vein can be successfully lengthened using donor gonadal vein (n=17) or recipient saphenous vein (n=19).	3

Recommendation	Strength rating
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

A history suggesting previous iliac or femoral vein thrombosis should initiate pre-operative imaging to establish patency of one iliac vein and the IVC. An intra-operative finding of an unexpected iliac vein and/or vena cava thrombosis may lead to abandonment of implantation. With pre-operative planning, native renal (orthotopic) or superior mesenteric vein or gonadal vein collaterals can be used.

The external or common iliac arteries are equally good for arterial anastomosis. The internal iliac artery is more frequently affected by atherosclerosis than the external or common iliac arteries. End-to-side anastomosis of donor renal artery to recipient external and/or common iliac artery is recommended in general over an end-to-end anastomosis to the internal iliac artery. The only RCT comparing these techniques suggests no difference [95]. However, the study was limited by small numbers and a high (8%) overall renal artery thrombosis rate.

The sites of the vascular anastomosis should be chosen carefully according to the length of the renal artery and vein to avoid kinking of the vessels when the kidney is placed into its final location, usually in the iliac fossa. The site of the arterial anastomosis should avoid atheromatous plaques in the iliac artery to decrease the risk of iliac artery dissection. The intima of the donor and recipient arteries should be checked 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 or as part of, the arterial anastomosis.

A Carrel patch is usually maintained on a deceased donor renal artery although it can be removed if there is either severe ostial atheroma/stenosis (with good quality proximal renal artery) or if the length of the

renal artery is too long for the appropriate implantation site on the iliac artery (which is more common with the right renal artery).

Multiple renal arteries supplying a deceased donor kidney can be maintained on a Carrel patch (of appropriate length) and implanted as a single anastomosis. In living donor transplantation, multiple renal arteries require a variety of strategies to achieve optimum re-perfusion [83]. Two arteries can be implanted separately or to achieve a single anastomosis: a very small second artery (especially if supplying the upper pole) may be sacrificed; the two arteries may be joined together (as a trouser graft); or the smaller artery can be anastomosed onto the side of the main artery (end-to-side anastomoses). A lower polar artery may be re-vascularised via anastomosis to the inferior epigastric artery [96]. In living donor transplantation where three or more donor arteries exist consideration should be given to alternate kidney donors. In circumstances using a living donor kidney with three or more donor arteries, strategies include a combination of the above techniques or, after appropriate consent, use an explanted (recipient's own) internal iliac artery graft [97] or saphenous vein graft [98].

In cases where an iliac artery prosthetic replacement has previously been carried out because of severe symptomatic iliac atheroma, the renal artery should be implanted into the prosthesis. Administration of systemic heparin should be considered prior to clamping of a vascular prosthesis [99].

A variety of sutures and suturing techniques for the vascular anastomosis are described, but in general practice, a 5/0 and 6/0 non-absorbable mono-filament polypropylene suture(s) are used for the renal vein and renal artery anastomosis. Despite this, there is no evidence to recommend one suturing technique over another to prevent, for example, transplant artery stenosis. Use of an expanded polytetrafluroethylene (ePTFE) suture compared to standard polypropylene suture may reduce blood loss due to a better needle/thread ratio [100].

In third or further transplants the surgical approach must be planned pre-operatively so that appropriate arterial inflow and venous outflow exists with adequate space to implant the new kidney [101, 102]. Nephrectomy of an old transplant kidney may be required prior to transplantation or at the time of transplantation [101]. Mobilisation of the common or internal iliac artery, internal iliac vein or IVC may be required. An intra-peritoneal approach (via the iliac fossa or midline) may be required [103]. Rarely orthotopic transplantation is needed [101, 104].

Summary of evidence	**LE**
A small RCT (n=38) comparing end-to-end anastomosis to the internal iliac artery vs. end-to-side anastomosis to the external iliac artery found that both techniques showed similar results in the post-operative period and at three-years follow-up.	1b
Cohort studies have demonstrated third or further transplants are a valid therapeutic option with reasonable short- and long-term patient and graft survival.	3

Recommendations	**Strength rating**
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

3.1.5.1.1 Emerging surgical technologies

Robot-assisted kidney transplant (RAKT) surgery is being evaluated in prospective non-randomised trials (using IDEAL consortium principles) [105]. 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.

3.1.5.2 Dual kidney transplants

Dual kidney transplant (DKT) 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 the pair of donor kidneys [106]. These include unilateral extra-peritoneal (UEP) or intra-peritoneal (UIP) and bilateral extra-peritoneal (BEP) or intra-peritoneal (BIP) that can be via a midline [107] or two lateral incisions.

The aim of a unilateral approach is to leave the contralateral iliac fossa intact for future transplantation in the event of graft loss and to reduce cold ischaemia time (CIT) for the second kidney transplant [108]. The unilateral approach may require mobilisation and division of the internal iliac vein to facilitate the two renal veins to iliac vein anastomoses. Modifications of the unilateral technique include single renal artery and vein anastomoses (with bench reconstruction) to further reduce CIT for the second kidney [109-111]. Dual kidney transplant takes longer and has higher blood loss than SKT regardless of the technique used. Data suggest shorter operative time and hospital stay with UEP compared to BEP [112] but other data suggest similar outcomes from all DKT techniques. No RCT exist to recommend one technique for all patients or situations.

En-bloc retrieval is performed when kidneys are retrieved from children weighing < 15 kg. Depending on the size of the donor kidney and size and weight of the adult recipient(s), *en-bloc* transplantation of the two kidneys may be performed or, if appropriate, the aorta and IVC patch may be divided for SKT [113].

3.1.5.3 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. A meta-analysis [114] of two RCTs and 24 observational studies favoured the extra-vesical Lich-Gregoir technique for reduced overall complications (specifically urine leak, stricture and post-operative haematuria). Fewer urinary tract infections (UTIs) were observed with the extravesical approach when compared with the intra-vesical technique in one RCT [115].

The donor ureter should be kept as short as possible with peri-ureteric fat preserved to ensure adequate ureteric blood supply. The location on the bladder to position an extra-vesical anastomosis was shown in one small RCT to be advantageous at the posterior bladder rather than anterior position to facilitate future endoscopic manipulation if needed and reported less hydronephrosis post stent removal [116]. Pyelo- or uretero-ureterostomy to the ipsilateral native ureter has been described as a primary technique in recipients with non-refluxing native ureters [117]. In cases where donor ureter has been damaged at retrieval then pyelo-native-ureterostomy or pyelo-neo-cystotomy can be performed. Mono-filament absorbable sutures should be used for the urinary anastomosis to prevent stone formation around the suture material [118].

Summary of evidence	**LE**
A meta-analysis of two RCTs and 24 observational studies favoured the extra-vesical Lich-Gregoir technique for reduced overall complications.	1a
A multi-centre prospective comparison study found the incidence of overall complications was similar for pyelo- and uretero-ureteral anastomosis and that for both procedures no graft was lost due to urological complications.	2b

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

The transplant ureteric anastomosis can be performed with or without a ureteric stent. If a stent is placed a second procedure is generally required for removal. A Cochrane review [119] concluded that stents are recommended to reduce major urological complications, especially urinary leak. The optimal timing for stent removal has yet to be defined but if left over 30 days is associated with more UTIs [120].

Most commonly, stents are removed with local anaesthetic flexible cystoscopy unless there is a need to combine with another procedure warranting general anaesthetic. Various techniques to reduce the morbidity of a second procedure involve tying the stent to the catheter or percutaneous stents but evidence is not yet available as to whether this is beneficial.

Recommendation	**Strength rating**
Use transplant ureteric stents prophylactically to prevent major urinary complications.	Strong

Duplex ureters are not infrequently identified at organ retrieval/kidney benching or during work-up for living donor nephrectomy [121, 122]. Duplex ureters can be anastomosed together and then joined to the bladder as one unit (double pant) or kept as two separate anastomoses. This also applies to the two single ureters in DKT in adults or with *en-bloc* transplantation from paediatric donors. The arguments for two separate ureteric anastomoses to the bladder are that an already tenuous blood supply may be further compromised with added suturing and handling, and if there is an issue with one ureter the other should remain unaffected. The advantages to forming one single (two ureter) anastomosis to the bladder are that only one cystotomy is needed; it may be faster and complications may be reduced. There is a lack of high quality evidence relating to duplex ureters.

Recommendation	Strength rating
Use the same surgical principals for single ureters to manage duplex ureters and anastomose them either separately or combined.	Strong

3.1.5.4 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 [123].
- 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 intra-peritoneal 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.

3.1.6 ***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. Potential complications should be included in the process of informed consent.

Reported surgical mortality is 0.01% to 0.03% with no apparent alteration due to changes in surgical techniques or donor selection in recent years [124, 125]. According to a recent systematic review (190 studies) and meta-analysis (41 studies) on complications in minimally invasive LDN, reporting on a total of 32,308 LDNs, 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%) [124]. Conversion to open surgery was reported in 1.1%, half due to bleeding and half due to injury to other organs. Surgical re-interventions occurred in 0.6%; the majority due to bleeding or to evacuate a haematoma [124]. A low trigger for conversion or re-operation should be observed in order to minimise the risk of serious complications.

A recent review looked for complications in 14,964 LDNs performed in the U.S. from 2008-2012 and found an overall peri-operative complication rate of 16.8%, gastrointestinal (4.4%), bleeding (3.0%), respiratory (2.5%), surgical/anaesthesia-related injuries (2.4%), and “other” complications (6.6%). Among the sample, 2.4% required intensive care and in-hospital mortality was 0.007% [14].

Major Clavien Classification of Surgical Complications grade IV or higher affected 2.5% of donors. Risk factors for Clavien grade IV or higher events included obesity (adjusted odds ratio [aOR] 1.55, $p = 0.0005$), pre-donation haematologic (aOR 2.78, $p = 0.0002$), psychiatric conditions (aOR 1.45, $p = 0.04$) and robotic nephrectomy (aOR 2.07, $p = 0.002$). An annual centre volume > 50 (aOR 0.55, $p < 0.0001$) was associated with lower risk [14].

3.1.6.1 Long-term complications

Long-term complications are mostly related to the single-kidney condition. Renal function in living donors decreases after donation before improving for many years, however, in the long run it shows signs of slight deterioration [126, 127]. There is a steady increase in the incidence of proteinuria and hypertension, yet the incidence of end-stage renal disease (0.4-1.1%) does not differ from the general population [126-129]. Long-term risk of death is no higher than for an age- and co-morbidity-matched population [125, 128].

Health related quality of life (HRQoL), including mental condition, remains on average better than the general population after donation [128-130]. However, some donors experience significant deterioration in their perceived QoL [130]. While global HRQoL is comparable or superior to population normative data, some factors identifiable around time of donation including longer recovery, financial stressors, younger age, higher body mass index (BMI), lower education, smoking and higher expectations prior to donation, may identify donors more likely to develop poor HRQoL, providing an opportunity for intervention [128-130].

Summary of evidence	LE
A systematic review and meta-analysis on complications in minimally invasive LDN concluded that the techniques used for minimally invasive LDN are safe and associated with low complication rates.	1a
Survival rates and risk of end-stage renal disease are similar to those in the general population whilst donors HRQoL remains on average better than the general population.	2b

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

*3.1.7 **Recipient complications***

3.1.7.1 General 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 [114, 120, 131-143]. We herein describe in detail the most common surgical complications in renal transplantation.

3.1.7.2 Haemorrhage

Haematomas are usually a minor complication in renal transplantation. Their incidence is reported to be between 0.2-25% [144, 145]. Small and asymptomatic hematomas 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 (CT) or ultrasound (US) guidance or may require surgical treatment [144].

3.1.7.3 Arterial thrombosis

Transplant renal artery thrombosis is a rare complication with a prevalence ranging from 0.5-3.5% [146]. Usually, it is a consequence of a technical error during the anastomosis although other causes may be related to both the donor and recipient's artery condition (i.e. atherosclerosis), intimal rupture during kidney harvesting, acute rejection episodes, external compression by haematoma or lymphocele, hypercoagulative state, severe hypotension, and toxicity of immunosuppressive agents (cyclosporine or sirolimus) [147]. The clinical manifestations are acute reduction of urine output and the elevation of renal function tests, often resulting in graft loss [144]. The diagnosis is obtained with eco-colour-doppler [144]. Surgical exploration is usually recommended to evaluate the status of the graft. In the rare event the graft appears salvageable, a thrombectomy must be performed. In this situation, the iliac artery is clamped and an arteriotomy versus a dissection of the vascular anastomosis must be performed in order to remove the cloth. The graft can be flushed on site and re-vascularised [144]. Unfortunately, in the majority of the situations, the graft is not perfused and therefore an allograft nephrectomy must be performed [144]. Alternatively, thrombolytic agent administration through a catheter directly into the transplant renal artery can be an efficient treatment [144], after the first ten to fourteen post-transplantation days [144].

Summary of evidence	LE
The diagnosis of renal artery thrombosis depends on eco-colour-doppler followed by surgical exploration to assess the status of the graft.	2b
Thrombectomy in the case of a viable graft and allograft nephrectomy in the case a non-viable graft are the treatment options for renal artery thrombosis.	2b

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

3.1.7.4 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 [148]. The aetiology includes technical errors and/or difficulties during surgery [144] and the hypercoagulative state of the recipient [149, 150]. Colour-doppler-flow-ultrasonography shows absence of venous flow with an abnormal arterial signal (usually a plateau-like reversed diastolic flow). Furthermore, it is common to see an enlargement of the graft due to venous congestion [151]. Surgical exploration is usually recommended despite the fact that the majority of the cases will result in graft loss. In those cases where the venous thrombosis has not resulted in kidney loss at surgical exploration, a venotomy with surgical thrombectomy after clamping the iliac vein can be performed. Alternatively, an explantation and subsequent re-implantation can be considered [144]. Thrombolytic agents can also be used, however, their results have not been satisfactory [144, 152].

Summary of evidence	LE
The diagnosis of renal vein thrombosis depends on colour-doppler-flow-ultrasonography followed by surgical exploration to assess the status of the graft.	2b
Thrombectomy in the case of a viable graft and allograft nephrectomy in the case a non-viable graft are the treatment options for renal vein thrombosis.	2b

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

3.1.7.5 Transplant renal artery stenosis.

The incidence of transplant renal artery stenosis is 1-25% [153, 154]. 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 [155, 156]. It is more common at the site of the anastomosis [155, 156]. It can be suspected in case of arterial hypertension refractory to medical treatment and/or an increase in serum creatinine without hydronephrosis or urinary infection (30). The diagnosis is performed by US-colour-doppler, showing a peak systolic velocity (PSV) of > 200 cm/s in the graft renal artery [155]. In cases of doubt a magnetic resonance angiogram (MRA) or a CT angiogram (CTA) can be performed [157]. It is important to determine whether the stenosis is haemodynamically significant or not. Usually, a stenosis of over 50% is considered a risk for kidney impairment [158]. In case of mild stenosis (< 50%) and absence of symptoms with no deterioration of the allograft, the management is normally conservative although a strict follow-up with US-colour-doppler and clinical parameters has to be adopted due to the possible risk of graft failure [155]. In cases of clinically significant stenosis and/or > 50% on US-colour-doppler, a confirmatory angiogram should be performed. If confirmed and a decision to treat is taken, treatments include percutaneous transluminal angioplasty/stent or surgical intervention. Interventional radiology is typically the first choice although patients considered unsuitable for radiological angioplasty due to recent transplant, multiple, long and narrow stenosis, or after failure of angioplasty may benefit from surgical treatment [155, 156].

Summary of evidence	LE
Suspect transplant renal artery stenosis in case of refractory arterial hypertension and/or increasing serum creatinine without hydronephrosis/infections.	3
The diagnosis for transplant renal artery stenosis is by US-colour-doppler, showing a peak systolic velocity (PSV) of > 200 cm/s in the graft renal artery.	2a
Interventional radiology is the first-line treatment option for transplant renal artery stenosis; however, in patients considered unsuitable for radiological angioplasty surgical treatment may be considered.	3

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

3.1.7.6 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 [159]. The aetiology of the AV fistula is related to the simultaneous injury of adjacent arterial and venous branches. A pseudo-aneurysm occurs when only the arterial branch is damaged. Both conditions are diagnosed with US-colour-doppler [144]. The majority of AV fistulae are asymptomatic, resolving in one to two years spontaneously, whilst approximately 30% of them persist and become symptomatic. Typically, the symptoms are hypertension, haematuria, and graft dysfunction due to shunting between arterial and venous vessels. There is an increased risk of spontaneous rupture in case of enlarging pseudo-aneurysms. For both AV fistulae and pseudo-aneurysm, angiographic selective or super selective embolisation represents the treatment of choice [160]. Partial or radical allograft nephrectomy is currently considered the last option [144].

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

3.1.7.7 Lymphocele

Lymphocele is a relatively common (1-26%) complication [161]. There is a significant aetiological association with diabetes, m-TOR inhibitors (i.e sirolimus) therapy, and acute rejection [162]. For large and symptomatic lymphocele, laparoscopic fenestration is associated with the lowest overall recurrence (8%) and complication (14%) rate compared to open surgery and aspiration therapy [163]. Placement of a percutaneous drain (i.e.Fr Pig-Tail) is an option with a success rate as high as 50% [163]. Percutaneous aspiration can be performed although the recurrence rate can be as high as 95% [163], with an increased risk of local infection (6% - 17%) [163]. Furthermore, sclerosant agents such as ethanol, fibrin sealant, gentamicin, or octreotide reduce the recurrence rate compared to simple aspiration [163, 164].

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

3.1.7.8 Urinary leak

Urinary leakage occurs in 0-9.3% of cases [165]. Anastomotic urine leaks can be ureteral or vesical [166]. Ureteral necrosis and/or suture failure are the most important causes [167, 168]. Non-technical risk factors include recipient age, number of renal arteries, site of arterial anastomosis, occurrence of acute rejection episodes, bladder problems, and immunosuppressive regimen [169]. Urinary leak can be suspected by the urine output and the creatinine level in the drain fluid [167]. In order to decrease the risk of ureteral necrosis, it is important to preserve vascularisation of the distal ureter [167]. Furthermore, the routine use of JJ-stent is recommended [168, 170]. The management of urinary leak depends on the location (renal pelvis, proximal or distal ureter, and bladder), the time of appearance and the volume of the leak. For early and low volume urine leaks the treatment may be conservative (i.e. urethral catheter, percutaneous nephrostomy and JJ-stent) [171]. In case of failure of the conservative management, or massive leak, surgical repair must be undertaken. Ureteral re-implantation directly to the bladder or to the native ureter provide similar results [171, 172].

Summary of evidence	LE
Suspect urinary leakage based on the urine output and the creatinine level in the drain fluid.	3
For early and low volume urine leaks conservative management may be considered.	3
Surgical repair should be undertaken when conservative management fails or massive urine leak occurs.	2b

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

3.1.7.9 Ureteral stenosis

Ureteral stenosis is a common complication in recipients, with an incidence of 0.6-10.5% [173]. 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 [167, 174]. Clinically significant ureteral stricture should be considered when persistent hydronephrosis on US occurs in association with impaired renal function. The first approach in the management of stricture is the placement of a percutaneous nephrostomy tube with an antegrade pyelogram [173]. The following treatment options depend mainly on the timing, recoverable kidney function, anatomy of the stricture, patient body habitus/comorbidities, and surgeon preference. Strictures < 3 cm in length may be treated endoscopically either with percutaneous balloon dilation or antegrade flexible ureteroscopy and holmium laser incision. In this scenario the success rate approaches 50% [175-177]. In case of a recurrence after a primary endourological approach and/or stricture > 3 cm in length, surgical reconstruction should be performed [174] including ureteral direct re-implantation, pyelo-vesical re-implantation (with or without psoas hitch and/or Boari Flap) or in cases with a normal native ureter, uretero-ureterostomy [178, 179].

Summary of evidence	LE
Clinically significant ureteral stricture should be considered when persistent hydronephrosis on US occurs in association with impaired renal function.	3
The first approach in the management of stricture is the placement of a percutaneous nephrostomy tube with an antegrade pyelogram.	2b
Strictures < 3 cm in length may be treated endoscopically.	3
For strictures > 3 cm in length or those which have reoccurred following a primary endourological approach surgical reconstruction should be performed.	2b

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

3.1.7.10 Haematuria

The incidence of haematuria ranges from 1-34% [165]. According to the literature, the Lich-Gregoire technique provides the lowest incidence of haematuria (9). Furthermore, meticulous haemostasis during re-implantation results in minimal bleeding [114, 165, 166]. Bladder irrigation is the first line of treatment. Some cases require cystoscopy with evacuation of clots and/or fulguration of bleeding sites [165].

3.1.7.11 Reflux and acute pyelonephritis

The frequency of vesicoureteral reflux is between 1-86% [165, 180]. 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 [181]. Endoscopic injection of dextranomer/hyaluronic acid copolymer may be the first approach for treatment of vesicoureteral reflux associated with acute pyelonephritis, with a success rate ranging from 57.9% after the first injection to 78.9% after the second injection [182]. Ureteral re-implantation or pyelo-ureterostomy with the native ureter is a viable second treatment option [178].

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

3.1.7.12 Kidney stones

Urolithiasis occurs in 0.2-1.7% of recipients [183, 184]. The most frequent causes are hyper filtration, renal tubular acidosis, recurrent UTIs, hypocitraturia, hyperoxaluria, hyperuricemia, excessive alkaline urine,

persistent tertiary hyperparathyroidism and ureteral strictures [185, 186]. Another risk factor can be urinary anastomosis, with the lowest stone rate using Lich-Gregoir technique [184]. The most frequent clinical signs are fever, increased serum creatinine level, decreased urine output, and haematuria. Pain is usually not referred to due to impaired innervation. A US examination usually provides the diagnosis although a CT of the kidneys, ureters and bladder may be needed to confirm the location and size of the stone [185]. The management depends on the location and size of the stone, and the presence of obstruction. In case of obstructive stones first-line treatment includes placement of a nephrostomy tube, or in some occasions a JJ-stent [187]. Extracorporeal shock wave lithotripsy (ESWL) is usually considered the first approach for stones < 15 mm with stone-free rate varying between 40 and 80% depending on the location of the stone [187]. Ureteroscopy, including antegrade and retrograde approaches, can be considered for stones < 20 mm, with a success rate of up to 67% [117, 184, 188]. For larger stones (> 20 mm), percutaneous nephrolithotomy (PNL) can be offered with a high overall effective stone-free rate. In cases of large impacted stones, uretero-ureteral anastomosis, pyelo-ureteral anastomosis, or uretero-vesical re-implantation may provide excellent results for both stone and ureteral obstruction [184].

Summary of evidence	LE
Extracorporeal shockwave lithotripsy should be considered as the first-line treatment option for stones < 15 mm.	2b
Antegrade/retrograde ureteroscopy and percutaneous nephrolithotomy may be considered as first- or second-line treatment options as they provide high stone-free rates.	2b
For larger stones (> 20 mm), PNL can be offered with a high overall effective stone-free rate.	2b

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

3.1.7.13 Wound infection

Wound infections occur in about 4% of the cases. Risk factors include recipients > 60 years, high BMI, anaemia, hypoalbuminemia, long surgical times (> 200 min) [189]. Bacteria commonly involved are *Enterobacteriaceae, Staphylococcus aureus* and *Pseudomonas* [178]. 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 [189].

3.1.7.14 Incisional hernia

Incisional hernia occurs in approximately 4% of open kidney transplantations. Risk factors include age, obesity, diabetes, haematoma, rejection, re-operation through the same transplant incision and use of m-TOR inhibitors. Mesh infection is a risk factor for incisional hernia recurrence [190]. Open and laparoscopic repair approaches are safe and effective [190].

*3.1.8 **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 [191-194]. Human leukocyte antigen incompatibility can result in proliferation and activation of the recipient's CD4+ and CD8+ T-cells with concomitant activation of B-cell allo-antibody production. This may lead to cellular and humoral graft rejection. Matching should concentrate on HLA antigens, which impact outcome. Human leukocyte antigens A, B, C as well as DR must be determined in all potential recipients and donors according to current guidelines and national allocation rules [191-196]. Additionally, it is recommended to determine HLA-DQ antigens of donor and recipient. Furthermore, HLA-DP antigen characterisation may be performed, especially for sensitised recipients [191-196].

All patients registered for renal transplantation must have their serum screened for anti-HLA antibodies, which are particularly common after pregnancy, previous transplant, transplant rejection, and blood transfusions [191-196]. Thorough pre-transplant testing for HLA antibodies must be performed according to current recommendations [191-196]. Sera from potential organ recipients should be screened for HLA-specific antibodies every three months or as stipulated by the national and/or international organ exchange

organisations [191-196]. In addition, screening for HLA-specific antibodies should be carried out at two and four weeks after every immunising event, e.g. blood transfusion, transplantation, pregnancy, and graft explantation [191-196]. Highly sensitised patients should have prioritised access to special allocation programs [193, 194, 196], such as the acceptable mismatch (AM) programme of Eurotransplant [197]. A careful analysis of HLA antibody specificities must be carried out to avoid unacceptable HLA antigens and to determine acceptable HLA antigens in potential donors, who are expected to give a negative cross-match result. The definition of unacceptable HLA antigens should be implemented according to local allocation rules and international recommendations [191-195, 198]. The information on unacceptable HLA antigens should be highlighted with the patient's details in the database of the national kidney-sharing programme, preventing the unnecessary transport of kidneys to recipients with high antibody sensitivity.

To avoid hyper-acute rejection (HAR), adequate (e.g. CDC, virtual) cross-match tests must be performed before each kidney and combined kidney/pancreas transplantation in accordance with national and international recommendations [191-194, 196].

Laboratories which provide HLA-testing, HLA antibody testing and cross-matching for transplant centres must have valid accreditation to ensure accuracy and reliability [189-193]. They must follow the standards of national and international organisations, such as the European Federation for Immunogenetics [196].

Previously, compatibility for ABO blood group antigens and HLA antigens was of critical importance in kidney transplantation. This may change in the future, e.g. in the new U.S. allocation system A2 and A2B donors are transplanted into B recipients [194]. To avoid an increasing imbalance between demand and supply in deceased-donor kidney transplantation in O recipients, ABO identity is demanded by several organ allocation organisations with a few exceptions, e.g. as in zero HLA-A+B+DR-mismatch kidneys [194, 195]. With the introduction of antibody elimination methods, potent immunosuppression and novel agents (e.g. anti B-cell drugs), successful ABO-incompatible living donor transplantations, with good long-term outcomes are possible [199, 200]. However, higher costs and infection rates have been described.

Even the barrier of a positive cross-match due to preformed HLA antibodies is under discussion with newer "desensitisation" techniques available in cases with available living donors [201, 202]. Success rates are lower, antibody-mediated rejections are frequent, but survival may be better compared to waiting list survival on dialysis. While this is a rapidly evolving field, further research is needed to define standard protocols. Until then such "desensitisation" protocols are experimental and patients undergoing "desensitisation" should be treated in specialised centres, where outcomes are documented. Patients should be informed adequately of the risks and limitations and alternative strategies (e.g. acceptable mismatch programmes, cross-over transplantation and donor chains) should be discussed.

Summary of evidence	**LE**
Human leukocyte antigen (HLA) matching is very important in kidney transplantation as transplant outcome correlates with the number of HLA mismatches. Matching should concentrate on HLA antigens, which impact outcome.	3
In accordance with national and international recommendations adequate (e.g. CDC, virtual) cross-match tests must be performed before each kidney and combined kidney/pancreas transplantation to avoid hyper-acute rejection.	3

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

3.1.9 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. Increased understanding of immune rejection has led to the development of safe modern immune suppression agents [203, 204], which suppress sensitised lymphocyte activity against a transplant. Immunosuppression

is particularly important during the initial post-transplant period when there is a high incidence of early post-transplant rejection.

In later post-operative stages, 'graft adaptation' occurs, resulting in the very low rejection rates seen in maintenance patients. Rejection prophylaxis should therefore be reduced over time by steroid tapering and gradual lowering of calcineurin inhibitor (CNI) [203-205].

Non-specific side effects of immunosuppression include a higher risk of malignancy and infection, particularly opportunistic infections [203-205]. All immunosuppressants also have dose-dependent specific side effects. Current immunosuppressive protocols aim to reduce drug-specific side effects using a synergistic regimen. A truly synergistic regimen allows profound dose reductions of immunosuppressive drugs; therefore, reducing side effects whilst still maintaining efficacy due to the synergistic effects of the immunosuppressants.

The currently recommended standard initial immunosuppression regime provides excellent efficacy with good tolerability [203-206]. 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).

This multidrug regimen reflects the current standard of care for the majority of transplant recipients worldwide [203-205] and may be modified according to local needs and immunological risk. This standard regimen is likely to change as new immunosuppressive drugs and new treatment regimens are developed [203-205]. In addition, any initial drug regimen will need to be tailored to the individual needs of a patient as suggested by the appearance of side effects, lack of efficacy or protocol-driven requirements.

Recommendation	Strength rating
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

3.1.9.1 Calcineurin inhibitors

Both cyclosporine and tacrolimus have significant side effects that are hazardous to the graft and patient [203-209]. Most importantly, both are nephrotoxic, and long-term use is an important cause of chronic allograft dysfunction, eventually leading to graft loss or severe chronic kidney disease in recipients of non-renal organs. Both CNIs are considered to be 'critical-dose' drugs, so that any deviations from exposure can lead to severe toxicity or failure of efficacy. Because of the narrow therapeutic window and the potential for drug-to-drug interaction, CNIs should be monitored using trough levels, which provide a reasonable estimate for exposure.

Meta-analysis of tacrolimus and cyclosporine has demonstrated similar outcomes with respect to overall patient and graft survival [203-209]. Tacrolimus provided better rejection prophylaxis and were associated with better graft survival, when censored for death in some analyses. Renal function was favourable for tacrolimus treated patients, but did not reach statistical significance in most analyses. Therefore, both CNIs can be used for the effective prevention of acute rejection, but due to higher efficacy tacrolimus is recommended by current guidelines as first-line CNI [204].

For both CNIs several different formulations are available. Precautions (e.g. close surveillance and determination of drug levels) should be instituted after conversion from one formulation to another [210-214]. In case of specific side effects of a CNI (e.g. hirsutism, alopecia, gingival hyperplasia, diabetes, polyoma nephropathy) conversion to the other CNI can be a successful strategy to reduce side effects [203-205]. Due to differences in the efficacy and safety profile, the choice of CNI should include the individual risks and benefits for each patient.

Despite their side effects, CNIs have been a cornerstone of modern immunosuppressive regimens for more than twenty years as they have resulted in an exemplary improvement in kidney graft survival [203, 204]. Future protocols aim to minimise or even eliminate CNIs [205, 208, 215, 216]. However, until such strategies provide superior outcomes, CNIs remain the standard of care [203, 204, 217]. For severe CNI-related side effects, CNI withdrawal, replacement, or profound reduction may be needed [203, 205, 208, 215, 216]. Special attention should be paid to maintenance patients, who may need less CNIs than previously thought [203, 205, 216].

Summary of evidence	LE
Meta-analysis of tacrolimus and cyclosporine has demonstrated similar outcomes with respect to overall patient and graft survival however, tacrolimus provided better rejection prophylaxis.	1a
Due to differences in the efficacy and safety profile, the choice of CNI should take into account the immunological risk, characteristics, concomitant immunosuppression, and socio-economic factors of the recipient.	1

Recommendations	Strength rating
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

3.1.9.2 Mycophenolates (MPA)

The mycophenolates, MMF and EC-MPS, are based on mycophenolic acid, which inhibits inosine monophosphate dehydrogenase (IMPDH) [218-222]. This is the rate-limiting step for the synthesis of guanosine monophosphate in the *de novo* purine pathway. As the function and proliferation of lymphocytes is more dependent on *de novo* purine nucleotide synthesis compared to other cell types, IMPDH inhibitors may provide more specific lymphocyte-targeted immunosuppression. The co-administration of mycophenolate with prednisolone and CNI has resulted in a profound reduction of biopsy-proven rejections [203, 206, 218-222]. Mycophenolic acid is not nephrotoxic; however, it inhibits bone marrow function and may cause CMV infections and gastrointestinal side effects, particularly diarrhoea [203, 206, 218-222]. There is also a higher incidence of polyoma nephropathy, especially when mycophenolate is combined with tacrolimus [223].

Both MPA formulations are equally effective with an almost identical safety profile [201, 216-220], though some prospective studies suggest a better gastrointestinal side-effect profile for EC-MPS in patients who have suffered from MMF-related gastrointestinal complaints, although firm evidence from prospective randomised studies is lacking [218-222].

Standard doses in combination with cyclosporine are MMF 1 g or EC-MPS 720 mg twice daily, although higher initial doses have been suggested [203, 204, 218-222]. Mycophenolic acid is not formally approved for use with tacrolimus, though this is the most frequently used drug combination in many countries worldwide and recommended by guidelines [204]. Despite its frequent use with tacrolimus, there is insufficient evidence to support the optimal dosage for this combination [203, 218, 220]. Tacrolimus has no influence on MPA exposure and leads to approximately 30% higher MPA exposure compared to cyclosporine. Most transplant centres use the same starting dose as in cyclosporine-treated patients, however dose reductions are frequent, especially because of gastrointestinal side effects. Due to the high incidence of side effects, some centres perform a protocol-driven MPA dose reduction in tacrolimus treated patients [218, 220]. Regular monitoring for polyoma is recommended in patients given MPA combined with tacrolimus [203, 223].

Due to a higher incidence of CMV disease with MPA [222], either CMV prophylaxis or a pre-emptive strategy with regular screening for CMV viraemia should be instituted [203, 224]. Cytomegalovirus prophylaxis with antiviral medications (e.g. valganciclovir) should be used routinely in CMV positive recipients and in CMV negative recipients of CMV positive organ transplants, because prophylaxis has recently been shown to reduce CMV disease, CMV-associated mortality in solid organ transplant recipients, and leads to better long-term graft survival in kidney allograft recipients.

The benefit for MPA drug monitoring is uncertain and currently not recommended for the majority of patients [218, 220, 221, 225].

In maintenance patients, the potency of MPA can be used for successful steroid withdrawal in most patients [226] or for substantial dose reductions of nephrotoxic CNIs, which may lead to better renal function [203-206, 208, 216]. Although there have been several studies of the potential for CNI-free protocols with MPA and steroids, complete CNI avoidance or withdrawal over the first three years has been associated with a substantially increased rejection risk and even worse outcomes in prospective randomised studies [203, 205, 216]. In contrast, CNI withdrawal under MPA and steroids appeared to be safe in long-term maintenance patients beyond five years post-transplant and resulted in improved renal function [203, 205, 208, 216, 227].

Summary of evidence	LE
The co-administration of MPA with prednisolone and CNI has resulted in a profound reduction of biopsy-proven rejections.	1
Both MPA formulations, MMF and EC-MPS, are equally effective with an almost identical safety profile.	1
Due to a higher incidence of CMV disease with MPA either CMV prophylaxis or a pre-emptive strategy with regular screening for CMV viraemia should be instituted.	1

Recommendation	Strength rating
Administer mycophenolate as part of the initial immunosuppressive regimen.	Strong

3.1.9.3 Azathioprine

Mycophenolate is now routinely used as a primary therapy in place of azathioprine in most units worldwide. In comparison to azathioprine, MPA reduced rejection rates significantly in prospective randomised trials [203, 204, 206, 218-222]. Although a large, prospective study found that azathioprine may give acceptable results in a low-risk population [228], azathioprine is usually reserved for patients who cannot tolerate MPA [203, 204, 218, 219, 221]. When added to dual therapy with cyclosporine and steroids, a meta-analysis found no significant benefit for azathioprine with respect to major outcome parameters [229].

Recommendation	Strength rating
Azathioprine may be used in a low-risk population as an immunosuppressive drug, especially for those intolerant to mycophenolate formulations.	Weak

3.1.9.4 Steroids

Steroids have a large number of side effects [203-205, 226], especially with long-term use. Most practitioners still consider steroids (either prednisolone or methylprednisolone) to be a fundamental adjunct to primary immunosuppression, even though successful steroid withdrawal has been achieved in the vast majority of patients in many prospective, randomised trials [203, 205, 206, 226]. These trials suggest the risk of steroid withdrawal depends on the use of concomitant immuno-suppressive medication, immunological risk, ethnicity, and time after transplantation. Although the risk of rejection diminishes over time, potential benefits may be less prominent after a prolonged steroid treatment period [203-206, 226].

Recommendations	Strength rating
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

3.1.9.5 Inhibitors of the mammalian target of rapamycin

The immunosuppressants, sirolimus and everolimus, inhibit the mammalian target of rapamycin (m-TOR) and suppress lymphocyte proliferation and differentiation [203, 215, 230-232]. They inhibit multiple intracellular pathways and block cytokine signals for T-cell proliferation. Similar effects are seen on B-cells, endothelial cells, fibroblasts, and tumour cells. Inhibitors of m-TOR are as effective as MPA when combined with CNIs in preventing rejection [203, 206, 215, 230-232]. However, m-TOR inhibitors exhibit dose-dependent bone marrow toxicity [203, 215, 230-232]. Other potential side effects include hyperlipidaemia, oedema, development of lymphoceles, wound-healing problems, pneumonitis, proteinuria, and impaired fertility.

To date, no prospective comparative studies have been carried out on the m-TOR inhibitors sirolimus and everolimus. Both m-TOR inhibitors have an almost identical side effect profile and mainly differ in their pharmacokinetic properties [203, 215, 230-233]. Sirolimus has a half-life of about 60 hours, is given once a day and is licensed for prophylaxis in kidney recipients only. Everolimus has a half-life of about 24 hours, is licensed for kidney, liver and heart recipients and is given twice a day. Everolimus is licenced for use with cyclosporine and can be given simultaneously with cyclosporine, while sirolimus should be given four hours after cyclosporine. Sirolimus is also licensed in combination therapy with steroids for cyclosporine withdrawal from combination therapy with cyclosporine.

Therapeutic monitoring of trough levels is recommended because of the narrow therapeutic window and the risk of drug-to-drug interactions [203, 215, 230-233].

When combined with CNIs, antimicrobial prophylaxis for *Pneumocystis jirovecii* pneumonia should be administered for one year following transplantation, e.g. low-dose cotrimoxazole [203, 230-232]. Most importantly, combination therapy with CNIs aggravates CNI-induced nephrotoxicity, although m-TOR inhibitors themselves are non-nephrotoxic [203]. Several studies suggest less favourable outcomes for this combination, especially if CNIs are maintained at standard dosages [203, 206, 208]. Calcineurin inhibitor dosage should therefore be substantially reduced in combination therapy with m-TOR inhibitors, which seems to have no impact on efficacy, due to the highly synergistic potential of this combination therapy [215, 230-234].

Several studies suggest m-TOR inhibitors cannot replace CNIs in the initial phase after transplantation due to lower efficacy and a less favourable side effect profile, particularly wound healing problems and lymphoceles [201, 203, 204, 213, 228-230, 232]. Other trials suggest that m-TOR inhibitors may replace CNI at later stages, e.g. three months after transplantation, with improvements in renal function [203, 205, 206, 208, 215, 230-232, 234]. However, there is an increased risk of rejection and development of HLA antibodies [203, 205, 215, 235], which may be offset by the benefit of the non-nephrotoxic immunosuppression. To date, limited data on long-term follow-up of m-TOR-treated patients have been reported.

Proteinuria and poor renal function at conversion are associated with inferior outcomes [203, 205, 215, 230-232]. Conversion from CNIs is not advisable in patients with proteinuria > 800 mg/day, and a cautious and individual approach should be followed in patients with GFR < 30 mL/min.

Due to an anti-proliferative effect and a lower incidence of malignancy in m-TOR inhibitor treated patients, conversion from CNIs to m-TOR inhibitors may be beneficial for patients, who develop malignancy after transplantation, or who are at a high risk for the development of post-transplant malignancy or skin cancer [203, 205, 215, 230-232, 234, 236, 237]. Several studies and case reports have suggested that patients with Kaposi sarcoma under CNI therapy benefit from conversion to an m-TOR inhibitor [237].

In summary, m-TOR inhibitors are not recommended as initial immunosuppressive therapy due to their side effect profile and higher discontinuation rates [204]. However, m-TOR inhibitors are a well-studied alternative treatment option.

Summary of evidence	**LE**
Combination therapy with CNIs aggravates CNI-induced nephrotoxicity, calcineurin inhibitor dosage should therefore be substantially reduced in combination therapy with m-TOR inhibitors, which seems to have no impact on efficacy, due to the highly synergistic potential of this combination therapy.	1
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
When combined with CNIs, antimicrobial prophylaxis for *Pneumocystis jirovecii* pneumonia should be administered for one year following transplantation.	1
Conversion from CNIs is not advisable in patients with proteinuria > 800 mg/day, and a cautious and individual approach should be followed in patients with GFR < 30 mL/min.	1

Recommendations	**Strength rating**
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

3.1.9.6 Induction with Interleukin-2 receptor antibodies

Basiliximab, a high-affinity anti-interleukin-2 (IL-2) receptor monoclonal antibody is approved for rejection prophylaxis following organ transplantation [203, 204, 206, 238-240]. Basiliximab is given before transplantation and on day four post-transplant. The drug is safe, and IL-2 receptor antibodies have been shown in RCTs to reduce the prevalence of acute cellular rejection by approximately 40% [203, 204, 206, 238-240]. Meta-analyses [206, 238-240] have confirmed the efficacy, although no positive effect on patient or graft survival could be demonstrated, large retrospective cohort studies and recent large prospective studies

suggest such a benefit [203, 204]. Several large controlled trials support the efficacy and safety of quadruple therapy with tacrolimus, mycophenolate and steroids. Interleukin-2 receptor antibodies may allow early steroid withdrawal [226], although higher rejection rates were described. Most importantly, IL-2 receptor antibodies allow a substantial reduction in CNIs, while maintaining excellent efficacy and renal function [203-206, 238-240]. Therefore, this regimen is proposed as first line immunosuppression in patients with low to normal immunological risk [204].

Recommendation	Strength rating
Use interleukin-2 receptor antibodies for induction in patients with normal immunological risk in order to reduce incidence of acute rejection.	Weak

3.1.9.7 T-cell depleting induction therapy

Prophylactic immunosuppression regimens in many countries, particularly the U.S., use potent T-cell depleting 'induction' treatments [203, 204, 206, 238, 241, 242]. Most frequently, ATG is used for prevention of rejection in immunological high risk patients, as recommended by guidelines [204]. In addition these potent biological agents are used for the treatment of severe, steroid resistant rejection episodes [241].

Use of T-cell depleting antibodies in immunological low-risk patients has not been associated with improved long-term outcomes but with an increased risk of severe opportunistic infections and malignancy, particularly post-transplant lymphoproliferative disease [203, 204, 206, 238, 241, 242]. Graft rejection rates are initially lower with induction treatment, however, some studies suggest an increased rejection rate after cessation of lymphocyte depletion [241]. Some centres use these agents to provide effective rejection prophylaxis while initiating CNIs after recovery of the graft from ischaemic injury, although evidence supporting this hypothesis is lacking [241].

Recommendation	Strength rating
T-cell depleting antibodies may be used for induction therapy in immunologically high-risk patients.	Weak

3.1.9.8 Belatacept

Belatacept is a fusion protein, which effectively blocks the CD28 co-stimulatory pathway and thereby prevents T-cell activation [215, 243, 244]. Belatacept is intravenously administered and indicated for use as part of a CNI-free regimen together with basiliximab induction, mycophenolate, and corticosteroids. Long-term data from three randomised studies of *de novo* kidney transplant recipients demonstrated better renal function versus cyclosporine-based immunosuppression, although rates and grades of acute rejection were higher for belatacept in the first year post-transplant [203, 206, 215, 243-246]. In patients receiving a standard deceased or living donor kidney, better graft survival was observed, while similar graft survival rates were found with ECDs. Interestingly, belatacept-treated patients had better preserved histology and developed less donor specific antibodies (DSA) compared to cyclosporine. The long-term safety profile of belatacept treated patients was similar to cyclosporine controls, less belatacept treated patients discontinued due to adverse events. In addition, the option of converting patients (either stable patients or due to CNI or m-TOR associated toxicity) was explored with promising initial results [246, 247]. Specific safety signals include a higher rate of post-transplant lymphoproliferative disorder (PTLD) (especially in Epstein-Barr virus (EBV) negative patients), more herpes infections, and tuberculosis in patients from endemic areas [215, 243, 244]. Belatacept was approved in the U.S. and in Europe for EBV positive patients, but is not yet available in many countries. Additional studies are ongoing to fully explore the value of this compound.

Recommendation	Strength rating
Belatacept may be used for immunosuppressive therapy in immunologically low-risk patients, who have a positive Epstein-Barr virus serology.	Weak

*3.1.10 **Immunological complications***

Immunological rejection is a common cause of early and late transplant dysfunction [204, 248-250]. There is great variation in the timing and severity of rejection episodes and how they respond to treatment. Today two main types of immunological reactions are distinguished, T-cell mediated rejections (TCMR) and antibody-mediated rejections (ABMR) [204, 248-250]. 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.

The ultimate standard for the diagnosis of rejection is transplant biopsy [204], because it is impossible to differentiate acute rejection solely on clinical indicators from other causes of renal dysfunction (e.g. acute tubular necrosis, infection, disease recurrence or CNI nephrotoxicity). Therefore, all rejections should be verified by renal biopsy and biopsies should be classified according to the most recent Banff criteria [251], which are the basis for prognosis and treatment [202, 246]. Renal transplant biopsy should be conducted preferably under US control, using an automated needle biopsy system (e.g. tru-cut, biopsy gun) [204, 248] with a 16 G needle to assure specimen adequacy. The biopsy procedure is considered safe but complications such as bleeding and AV fistulas may occur [204, 252, 253]. The reported risk of major complications (including substantial bleeding, macroscopic haematuria with ureteric obstruction, peritonitis or graft loss) is approximately 1%. Most important contraindications are anti-coagulant therapy including anti-platelet agents and uncontrolled hypertension.

Summary of evidence	LE
There must be routine access to US-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
Steroid treatment for rejection may start before the renal biopsy is performed.	2

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

3.1.10.1 Hyper-acute rejection

Hyper-acute rejection is the most dramatic and destructive immunological attack on the graft [191, 204, 248, 249]. 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. It occurs in ABO-incompatible grafts due to the presence of high titres of pre-existing iso-antibodies against blood group antigens. In ABO-matched grafts, HAR is mediated by anti-donor HLA IgG antibodies. With the development of the cross-match test before transplantation, HAR has become an extremely uncommon complication [191]. Imaging and histology reveals generalised infarction of the graft, which has to be treated by graft nephrectomy. Therefore, prevention is crucial, either by avoidance of high iso-antibodies against incompatible blood group antigens in case of an ABO-incompatible renal transplant and/or by performing a regular cross-match before transplantation (see section 3.1.8).

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

3.1.10.2 Treatment of T-cell mediated acute rejection

As only a few randomised trials have investigated different treatment options for this clinical problem, therapy is mainly based on empirical experience rather than on clinical evidence [204, 248]. Parenteral methylprednisolone (500 mg to 1 g) should be given intravenously as one pulse per day for three days. Anuria or a steep rise in the serum creatinine may indicate steroid-refractory rejection and the need for another three day course of pulsed methylprednisolone therapy [204, 248]. In addition, baseline immunosuppression should be optimised to ensure adequate drug exposure [204, 248]. In severe rejection, a conversion from cyclosporine to tacrolimus and/or from azathioprine to mycophenolate is recommended [204, 248].

T-cell depleting biological agents, such as ATG may be given in severe steroid-refractory cases [204, 241, 248]. If biological agents are used, other immunological suppression should be adapted and daily T-cell monitoring should be considered to minimise the dose of the biological agent [241]. Before immunosuppression is intensified, especially before the use of T-cell depleting agents, the prognosis of the graft should be critically assessed against the risks of the aggravated immunosuppression. The patient should be counselled adequately.

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

3.1.10.3 Treatment of antibody mediated rejection

Antibody mediated rejection is treated in a similar way as T-cell mediated rejection [204, 241, 248, 254-257]. Treatment relies on retrospective studies and empirical treatment guidelines. Treatment with a steroid bolus (at least three days of 500 mg/day) and adequate maintenance therapy with mycophenolate and tacrolimus and sufficient tacrolimus trough levels are common in acute ABMR [204, 248, 254-257]. Although T-cell depleting agents such as ATG appear to have limited value they are frequently used during mixed acute rejection [241]. There are controversial data on the utility of the anti-CD20 antibody, rituximab [204, 248, 254-258]. A retrospective series suggests aggravated toxicity, when rituximab is combined with ATG [259]. In order to target the antibody producing plasma cell, several centres have advocated the use of bortezomib, a proteasome inhibitor approved for the treatment of multiple myeloma [260]. So far, no prospective, randomised trials on bortezomib or other novel agents have been published and neither dose, side effects nor efficacy parameters have been evaluated in a larger cohort of patients with acute ABMR with adequate follow-up.

Some centres advocate intravenous immunoglobulin (IVIG) [204, 248, 254-258], which may modulate and/or suppress antibody production. Intravenous immunoglobulin alone seems insufficient for effective treatment and IVIG is used today in a multimodal regimen. Dosages vary widely from 0.2-2.0 g/kg bodyweight, and no comparative studies (e.g. on the dose or optimal concomitant immunosuppression) have been published.

In addition, to drug therapy most centres also try to remove antibodies using plasmapheresis or immune-adsorption columns. Retrospective and prospective case series clearly suggest efficacy [204, 248, 254-258], although details of the procedures vary widely.

Treatment recommendations for chronic ABMR lack firm evidence, and treatment appears to be less successful [248, 254, 256]. Treatment relies on the same principles as for acute ABMR [204, 241, 248, 254-257]. Most centres have similar treatment algorithms and perform antibody elimination together with IVIG and eventually add anti-CD20 and/or bortezomib. Unfortunately, prospective trials on efficacy and side effects are lacking.

In summary, several regimens have proven some efficacy in ABMR. However, except for a beneficial effect of early antibody removal, the lack of firm evidence does not permit evidence-based recommendations for treatment.

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

3.1.11 ***Follow-up after transplantation***

Long-term graft function is of critical importance for the success of a transplant [204, 205]. 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. Complications of immunosuppression occur frequently including specific complications of the different drugs as well as over immunosuppression (namely opportunistic infections and malignancy) [204, 205]. The risk of cancer and cardiac disease is several-fold higher in transplanted patients than in the general population. Cancer is a cause of significant morbidity and mortality in the transplanted population [204, 261, 262]. Cardiovascular disease is the most frequent cause of death in renal allograft recipients [204, 263, 264]. Other important long-term problems are non-adherence, the development of anti-HLA antibodies, recurrence of the original disease and CNI associated nephrotoxicity [204, 205].

3.1.11.1 Chronic allograft dysfunction/interstitial fibrosis and tubular atrophy

Many patients lose their grafts due to chronic allograft dysfunction [204, 205, 265]. Histology will usually reveal a chronic process of interstitial fibrosis and tubular atrophy (IF/TA) [266]. Some patients will have immunological chronic ABMR [267], as discussed in section 3.1.10.3. Interstitial fibrosis and tubular atrophy takes months or years to develop and is heralded by proteinuria and hypertension, with a simultaneous or delayed rise in serum creatinine level over months [204, 265, 266]. It is likely that IF/TA is more common in patients who have had early attacks of acute rejection or infection. The main differential diagnoses is chronic nephrotoxicity [268], which is common in patients receiving CNIs, and pre-existing and/or aggravated chronic kidney damage from a marginal donor kidney [204, 265, 266].

Diagnosis is by renal biopsy [204, 265]. In patients diagnosed early, particularly if there is evidence for CNI toxicity, disease progression may be slowed by conversion to a CNI-free regimen [201-203, 263, 264]. Conversion to m-TOR inhibitors is an option for patients without significant proteinuria (< 800 mg/day) but moderate renal function [203-205]. Alternatively, successful conversion to a MPA-based regimen has been described, especially in patients beyond the first three years post-transplant [203, 205, 216]. If there is intolerance to m-TOR inhibitors or MPA, conversion to belatacept or an azathioprine-based regimen may be successful, though the higher risk of rejection warrants close surveillance [47, 247]. If the risk of rejection seems too high, another option is substantial reduction of CNI under the protection of MPA [205, 216].

In patients with proteinuria, intervention with an angiotensin converting enzyme inhibitor, or angiotensin II receptor blocker [204, 265] together with tight blood pressure control may slow down renal progression. Other supportive measures include the treatment of hypertension, hyperlipidaemia, diabetes, anaemia, acidosis, and bone disease [204]. However, ultimately, the patient will require another transplant (if fit enough to go on the transplant waiting list) or dialysis therapy.

Summary of evidence	**LE**
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.	4
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 US, including US 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
In patients diagnosed early with IF/TA, particularly if there is evidence for CNI toxicity, disease progression may be slowed by conversion to a CNI-free regimen. If the risk of rejection seems too high, another option is substantial reduction of CNI under the protection of MPA.	1
Supportive measures should aim to adequately treat the consequences of chronic kidney disease (e.g. anaemia, acidosis, bone disease).	4

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

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5. CONFLICT OF INTEREST

All members of the EAU Renal Transplantation Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the EAU website: http://www.uroweb.org/guidelines/. These Guidelines were developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

6. CITATION INFORMATION

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