Supplement

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Practical Recommendations for Long-term Management of Modifiable Risks in Kidney and Liver Transplant Recipients: A Guidance Report and Clinical Checklist by the Consensus on Managing Modifiable Risk in Transplantation (COMMIT) Group

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Abstract: Short-term patient and graft outcomes continue to improve after kidney and liver transplantation, with 1-year survival rates over 80%; however, improving longer-term outcomes remains a challenge. Improving the function of grafts and health of recipients would not only enhance quality and length of life, but would also reduce the need for retransplantation, and thus increase the number of organs available for transplant. The clinical transplant community needs to identify and manage those patient modifiable factors, to decrease the risk of graft failure, and improve longer-term outcomes.

COMMIT was formed in 2015 and is composed of 20 leading kidney and liver transplant specialists from 9 countries across Europe. The group's remit is to provide expert guidance for the long-term management of kidney and liver transplant patients, with the aim of improving outcomes by minimizing modifiable risks associated with poor graft and patient survival posttransplant.

The objective of this supplement is to provide specific, practical recommendations, through the discussion of current evidence and best practice, for the management of modifiable risks in those kidney and liver transplant patients who have survived the first postoperative year. In addition, the provision of a checklist increases the clinical utility and accessibility of these recommendations, by offering a systematic and efficient way to implement screening and monitoring of modifiable risks in the clinical setting.

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COMMIT is an expert-led program. The authors formed a "consensus group" which met at various times over a period of approximately 1 year to discuss the development of a practical guidance document. Led by chairs, James Neuberger, Wolf Bechstein and Dirk Kuypers, the group developed their own content for their meetings, with editorial support from iS Health. Astellas had input into the selection of the program members and the appointment of iS Health to support the program. Astellas Pharma Europe Ltd has provided support in the form of funding for the meeting expenses, secretariat services by iS Health, and placement of the supplement (guidance report and checklist) in the journal selected by the authors.

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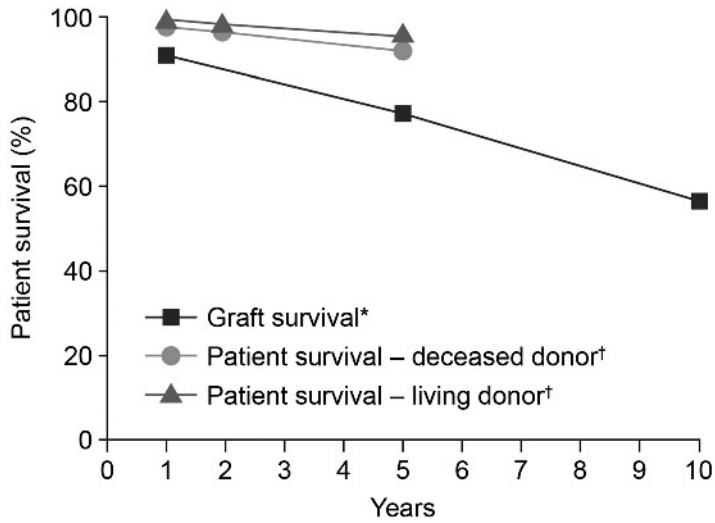
Solid organ transplantation has evolved from an experimental procedure to an established treatment option for many types of end-stage organ failure. Both patient and graft outcomes are continuing to improve, and 1-year patient and graft survival currently exceed 80%.[1,2] However, survival rates gradually decline over the long term. In kidney transplant, 5- and 10-year graft survival rates in Europe are 77% and 56%, and for liver transplant, 64% and 54% (Figures 1 and 2).[3,4]

Although most European countries have seen an increase in both living and deceased donation, transplantation is not available to all who would benefit from the procedure, and there is considerable morbidity and mortality for those listed for transplant.[6] Therefore, maximizing long-term graft survival and reducing the need for retransplantation is paramount, not only in improving outcomes for the recipients but also for those awaiting a graft. The improvement in outcomes is predominantly due to reduction in

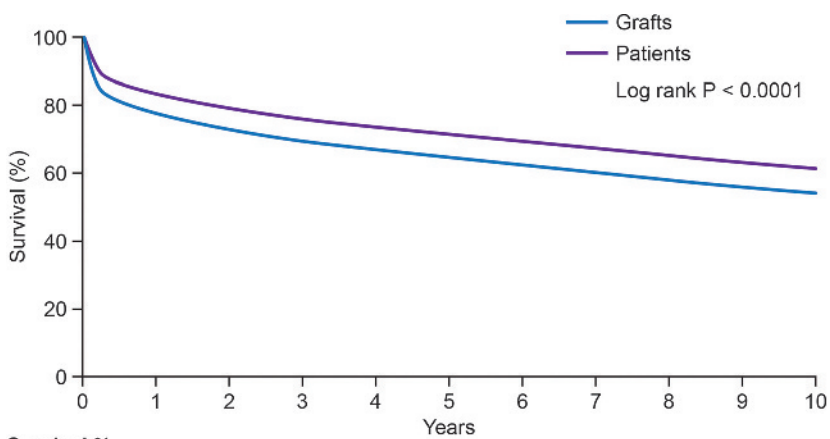


Population	Period	% Adjusted survival rates (standard error (SE) or 95% confidence interval)			
		One year	Two years	Five years	Ten years
Grafts	2005–2008	90.6 (SE 0.4)	–	77.0 (SE 0.6)	56.5 (SE 0.8)
Patient – deceased donor	2004–2008	97.4 (97.2–97.6)	96.1 (95.9–96.4)	91.8 (91.4–92.2)	–
	2007–2011‡	97.6 (97.4–97.8)	96.4 (96.1–96.6)	–	–
Patient living donor	2004–2008	98.7 (98.4–99.0)	98.1 (97.7–98.4)	95.6 (95.0–96.1)	–
	2007–2011‡	99.1 (98.9–99.3)	98.4 (98.2–98.7)	–	–

FIGURE 1. 1- to 10-year graft and patient survival rates after kidney transplantation.*1-year and cumulative 5- and 10-year age-adjusted kidney graft survival rates calculated for 2005 to 2008 by period analysis; †Survival probabilities were adjusted for age, sex and cause of end-stage renal disease (data shown in figure for period 2004-2008); ‡Data from 2007 to 2011 period not shown in figure. Figure based on data from Gondos 2013 and Kramer 2016.[3,5]

early graft loss and patient death, better surgical and anesthetic skills, technological innovations, improved donor and recipient management, and the advent of newer and more effective immunosuppressive agents.[7] Despite the improvement in survival rates, attention is now becoming more focused on improving longer-term outcomes beyond the first year posttransplant.

Posttransplantation care requires involvement from multidisciplinary healthcare professionals (HCPs) who must work collaboratively with the patient, their family, and the healthcare



Survival %

Population	1 year	3 years	5 years	8 years	10 years
Grafts	77%	69%	64%	58%	54%
Patients	83%	76%	71%	65%	61%

FIGURE 2. 1- to 10-year graft and patient survival rates in liver transplantation. Reprinted with permission of the European Liver Transplant Registry: www.eltr.org/Evolution-of-LTs-in-Europe.html[4] (Accessed July 2016).

provider. Maintaining a viable graft and healthy patient involves the consideration of many factors and balancing the need for immunosuppression with the associated risks. In addition to the direct and indirect consequences of immunosuppression, a multitude of risk factors influence patient and graft survival. Some risk factors may be present before transplantation (such as cardiovascular disease (CVD) seen especially in kidney transplant recipients), and other factors, such as donor age, cannot be modified.[8,9] However, some risk factors have the potential to be modified or mitigated posttransplantation to improve outcomes, including behavioral risk factors, such as medication adherence.[10-12]

The Consensus On Managing Modifiable risk In Transplantation (COMMIT) group was convened to provide practical recommendations for the identification and management of modifiable risk factors to maximize the life of the graft and patient after kidney and liver transplant.

Modifiable Risk Factors for Graft Loss Posttransplantation

Although solid organ transplantation improves both the quality and quantity of life of the recipient, the survival is less than an age-matched cohort from the general population. A study in the United Kingdom of adult liver allograft recipients, who had survived the first postoperative year, showed the average number of life-years lost was 7.7 years; those who had their transplants at a younger age (17-34 years) had a far greater loss of life-years than those who had their transplant later (≥35 years), and women had fewer life-years lost than men.[13,14] The main causes of death included cardiac problems, malignancy, and infection, and causes of graft failure included recurrent disease and chronic rejection.[15,16] In a retrospective review of 4483 adult primary liver transplant recipients, major causes of death were malignancy (30.6%), multisystem failure (10%), infection (9.8%), graft failure (9.8%), and CVD (8.7%).[17]

El-Agroudy et al[15] found the main causes of death in kidney allograft recipients were infections (35.6%), CVD (17.6%), liver disease (11.4%), and malignancy (6.1%). Of nearly 1600 kidney recipients in Japan, Shimmura et al[16] found the main causes of death with a functioning graft were infection (24%), stroke (17%), CVD (16%), malignancy (15%), and liver failure (12%).

Graft loss has been attributed to both immunological and nonimmunological factors in kidney and liver transplant recipients (Figures 3 and 4).

Preoperative, perioperative, and postoperative factors may impact long-term outcomes; these include donor and organ factors as well as logistic factors. For kidney transplantation, these include early ischemic injury, acute allograft rejection, and delayed graft function (DGF). For liver transplantation, early allograft dysfunction (EAD), prolonged cold ischemia times and use of steatotic livers and organs from donation after cardiac death (DCD) donors may contribute to reduced graft and patient survival.[32-34]

In both kidney and liver transplant recipients, modifiable risk factors for graft failure over the longer term include issues related to immunosuppression, such as nonadherence,[35] underimmunosuppression,[36] toxicity and adverse effects related to immunosuppression,[37] and high intrapatient variability (IPV) in immunosuppressive exposure.[38] The development of de novo donor-specific antibodies (DSAs) is also considered to be a modifiable risk factor, and has been strongly associated with nonadherence to immunosuppression in kidney transplant recipients.[20] However, knowledge of the pathological impact of DSAs is still evolving, particularly with regard to the impact of DSAs postliver transplantation.[39-41]

Furthermore, patient survival can be improved by attention to modifiable risk factors for CVD and cerebrovascular disease, some infections and some cancers.[34] The development of new-onset diabetes posttransplant (NODAT) is also associated with reduced patient and graft survival, as well as an increased risk of infections and CVD.[42] This list of risk factors is not exhaustive. Other factors that may have an impact on graft or patient survival include recurrence of initial disease.[34] Although there is little to be done regarding the nonmodifiable risk factors of graft failure, better screening and management of modifiable risk factors could improve long-term survival rates if integrated into routine clinical practice. Each section in this guidance document includes a review of the problem to be addressed, a summary of the literature and current clinical practice.

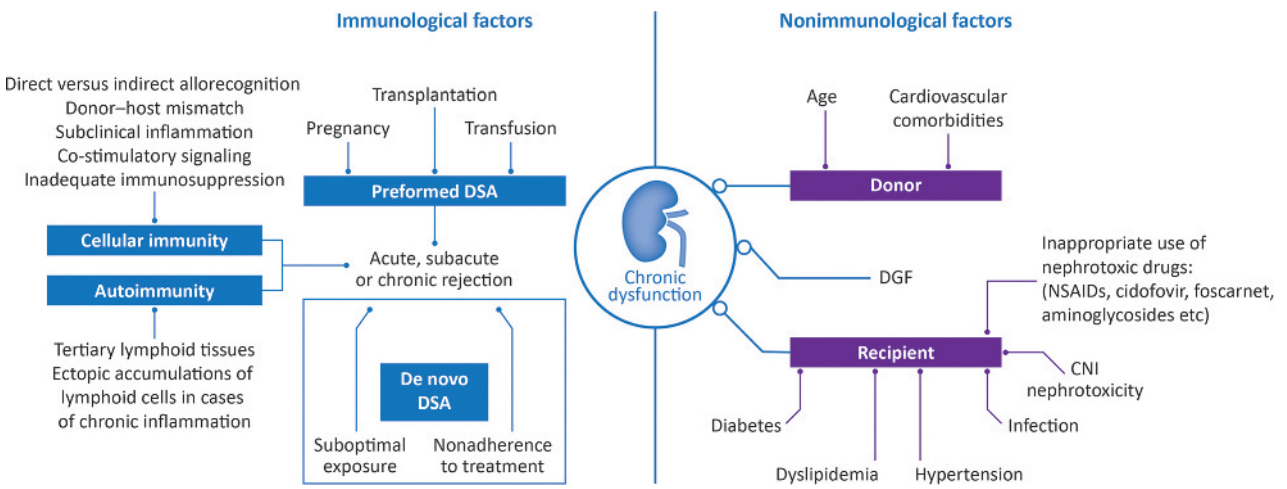


FIGURE 3. Causes of late graft loss in kidney transplant recipients. Figure based on data from Jevnikar 2008, Pazhayattil 2014, Sellarés 2012, Lefaucheur 2010, Koenig 2016, Valenzuela 2013, Siedlecki 2011 and Puttarajappa 2012.[18-25]

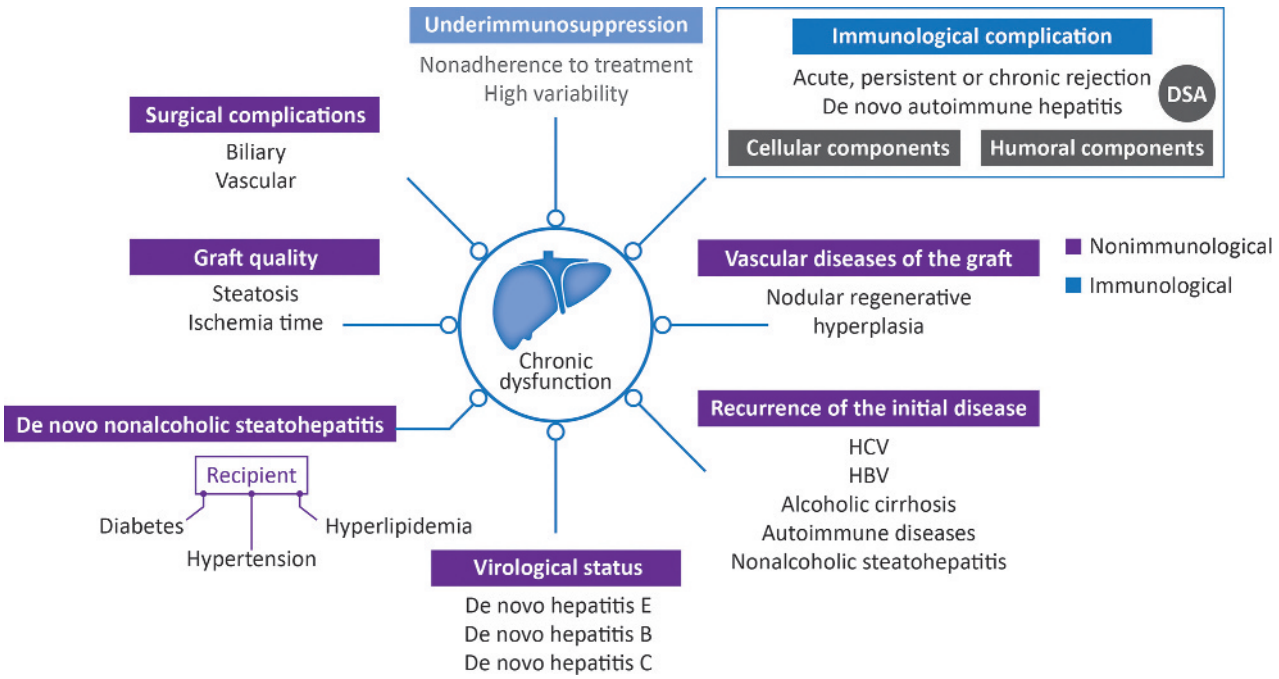


FIGURE 4. Causes of late allograft loss in liver transplant recipients. Diabetes, hypertension, hyperlipidemia, high variability and nonadherence to immunosuppressive agents are modifiable risk factors. Figure based on data from Hübscher 2011, Bekker 2009, O'Leary 2014, Supelana 2014, Charlton 2013 and Kamar 2008.[26-31]

Existing Clinical Guidance for Long-Term Management in Transplantation

There are several national and international guidelines outlining approaches to improve both kidney and liver graft outcomes. Implementation of some of the recommendations has been shown to improve outcomes; for example, implementation of the predefined donor management goals defined by the United Network for Organ Sharing (UNOS) has resulted in a significant decrease in the incidence of DGF in those cases where the donor management goals were met.[43] In addition, cardiovascular prediction models and risk calculators to predict the risk of developing cardiovascular complications posttransplant are being introduced in the clinic and their use may allow introduction of targeted interventions that will reduce morbidity and mortality.[44] However, comprehensive, standardized methods to identify, screen and manage potentially reversible risk factors for graft failure and patient death are lacking in many of the current guidelines, as discussed below. Furthermore, with the increasing number of surviving allograft recipients, many are being followed in nontransplant centers and by HCPs who may not be as familiar with current best practice as those working in transplant units.

Objectives and Aims of COMMIT

COMMIT was formed in 2015 to provide expert practical guidance for the long-term management of kidney and liver transplant patients, with the aim of improving outcomes by minimizing modifiable risks of poor graft and patient survival posttransplant. The COMMIT expert group comprises 20 leading kidney and liver transplant specialists from 9 countries across Europe.

Objectives

The group's objectives are to develop specific, practical recommendations that focus on the management of modifiable risk in those kidney and liver transplant patients who have survived the first postoperative year, including some pretransplantation and peritransplantation considerations.

Target Audience

The prime target audience are HCPs, including medical staff, nurses and pharmacists caring for allograft recipients outside transplant units, and junior professionals working in transplant units, although the recommendations will be relevant to all those involved in the care of transplant recipients.

Recommendations

The recommendations are intended to complement, rather than replace, local guidelines. Therefore, specific recommendations have not been provided on immunosuppression regimens or the investigation and management of abnormal graft function.

In this guidance document, we discuss each of the identified modifiable risk factors (Table 1) for both kidney and liver transplantation. Each section begins with a discussion of the evidence and current best practice related to the management of the risk factor, followed by a separate set of specific recommendations for each organ. To increase the clinical utility and accessibility of the recommendations, we have created a checklist (Appendices 2 and 3) that could be used as an aide-memoire for the professionals looking after these patients. Importantly, the checklist provides a systematic and efficient way to implement screening and monitoring of risk in the clinical setting.

It is important to stress that the recommendations are sometimes broad, because all treatment and interventions must be tailored to the individual transplant recipient. As mentioned, patient and graft outcomes will depend on many factors, including recipient age, sex, lifestyle,

TABLE 1.

Major modifiable risk factors for graft loss

Nonadherence
Intrapatient variability in immunosuppressive exposure
Underimmunosuppression/overminimization of immunosuppression
Adverse effects related to immunosuppression
DSAs
Early ischemic injury and DGF (kidney)/EAD and nonanastomotic biliary strictures (liver)
Cardiovascular and metabolic complications

comorbid diseases, and indication for transplant. Donor and surgical factors may also have a significant impact on outcomes. Nevertheless, we believe that formalized screening and management of modifiable risk factors in all patients after the first year of transplantation will lead to marked improvement in long-term outcomes. Specific recommendations have not been provided on immunosuppression regimens or the investigation and management of abnormal graft function.

General health recommendations, such as smoking cessation and avoidance of excessive alcohol consumption, have not been discussed in detail, because these should form part of every clinical appointment.

These guidelines focus on major modifiable risk factors that improve long-term outcomes after liver and kidney transplantation in adults. However, 2 aspects of general care merit mention: immunization, which plays an important role in reducing the risk of some infections; the response to immunization may be blunted and live and attenuated vaccines avoided.[45] Sexual health is also important, and patients should be advised about the teratogenicity of some immunosuppressive agents and the need to consider the impact of pregnancy both on the risk of rejection and the pharmacokinetic changes of drug metabolism.[46-48]

We have also not made recommendations on the frequency of follow-up after the first year because this will depend on many factors, including the clinical status of the patient, comorbidities, and graft function. If the patient is stable and with good graft function and over 1 year posttransplant, then most centers recommend assessing the patient every 3 months. If the patient becomes unwell, graft function deteriorates, changes medication, then the review should be more frequent. If the immunosuppression regimen is modified, then therapeutic drug monitoring and patient assessment should be done more frequently. If the immunosuppression is discontinued, drastically reduced or other drugs that affect metabolism of the immunosuppressive agents are prescribed, then the drugs and graft should be monitored more frequently, and daily monitoring may be indicated. Hospitalized allograft recipients will usually have drug levels of calcineurin inhibitors (CNIs) or mammalian target of rapamycin inhibitors (mTORi) checked daily.

METHODS

The COMMIT program featured 2 organ-specific working groups (kidney and liver). Each working group was further divided into workstreams to develop the recommendations for each of the modifiable risk factors in parallel.

A workstream lead was appointed to oversee the development of the practical recommendations and to facilitate consensus within the respective workstreams. All members of the COMMIT program reviewed and provided feedback on all sections of the guidance report as part of a Delphi study, as described below.

Literature Review

A literature review was conducted to gain an understanding of current posttransplant clinical practices and to identify the key gaps in the available guidance related to the practical management of modifiable risk factors in posttransplantation care. MEDLINE and Google Scholar databases, and resources from international transplant societies were searched for kidney and liver transplantation guidelines using varying search terms including kidney transplant guidelines, liver transplant guidelines, kidney transplant recommendations, liver transplant recommendations.

The original search was conducted between August 7, 2015, and September 10, 2015, and was restricted to English language articles; the guidelines included were published between 1999 and 2015. The search results were filtered according to relevance for kidney or liver transplantation and for guidance posttransplantation. A summary document, or "concept paper," was created based on the results of the literature review to focus and inform initial discussions on the concept and content of the recommendations. Subsequent literature reviews were conducted in early 2016 within the respective workstreams to develop and support the practical recommendations.

Development of Practical Recommendations Using a Modified Delphi Approach

A modified Delphi approach (Figure 5) was used to reach agreement and validate the practical clinical recommendations. The qualitative and interactive Delphi approach has been described previously.[49] A total of 18 members of the COMMIT group participated in the first online Delphi-like survey (November 2015). The first survey was used to explore the modifiable risk factors that lead to graft loss in clinical practice, and prioritize them for discussion in the guidance document. Furthermore, the survey gave the opportunity for the group to comment on those risk factors or topics that had not been addressed. This informed the development of the concept paper. A preliminary meeting of all authors was held on December 9, 2015, to discuss the results of the literature review and the Delphi-like online survey. Feedback and discussions from this meeting were collated into an initial discussion document, which formed the basis of the second Delphi-like survey (May 2016). In the second survey, COMMIT group members were asked to review the first draft of the guidance report, and to state their level of alignment with the content included. If not aligned, members were invited to provide reasons and supporting evidence for consideration for inclusion in the guidance report. The results of the second Delphi-like survey included responses from 18 COMMIT members. A second COMMIT meeting was held on June 22, 2016, to discuss the practical recommendations. A third Delphi-like survey included all 20 members of the group and was conducted in October 2016. The survey focused on the group's satisfaction with the recommendations that had been made, the checklist that had been developed, and final agreement on the guidance report.

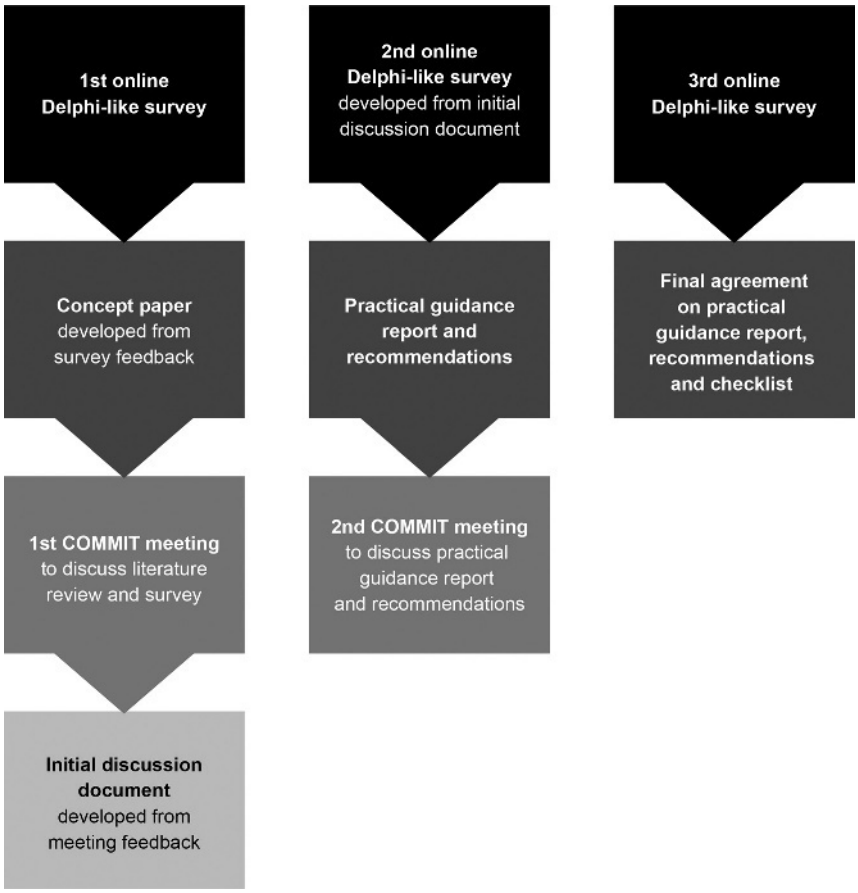


FIGURE 5. Modified Delphi approach.

Practical recommendation statements achieving 100% agreement were included in the final guidance document. The evidence supporting each recommendation was evaluated and graded according to the Oxford Centre for Evidence-Based Medicine (OCEBM) system (see Appendix 1).[50] The evidence is ranked on a hierarchy with the strongest best evidence (such as a systematic review of randomised trials) assigned level 1 and evidence based solely on understanding of known mechanisms assigned level 5 (lowest grade). This enables clinicians to understand the strength of the evidence.[50] The recommendations were proposed by the section authors and approved by all authors.

Limitations of Methodology

The use of any evidence ranking system, such as the OCEBM, for patient management recommendations should be carried out with clinical judgment as forethought.[50] Although these recommendations did achieve an acceptable level of agreement (100%) using the Delphi-like approach, this method identifies current medical opinion, and is not an alternative to rigorous clinical trials, where evidence is lacking.[49]

NONADHERENCE TO IMMUNOSUPPRESSIVE AGENTS AS A MODIFIABLE RISK FACTOR FOR POOR OUTCOMES IN LIVER AND KIDNEY TRANSPLANTATION

Problem to be Addressed

Transplantation offers patients with end-stage liver or kidney disease improved quality of life and longer survival.[51,52] However, transplant recipients need to adhere to complex therapeutic regimens often including 1 or more immunosuppressive agents and other medications to prevent or treat comorbidities.[10-12]

Historically, research relating to adherence has been focused on adherence to medication. However, it is now recognized that adherence includes a broad range of health-related behaviors that need to be considered in addition to taking prescribed medication, such as the relationship between the patient and healthcare provider.[53,54] In addressing some of these complexities, The World Health Organization defines nonadherence to a long-term therapy as "the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider."[53]

Nonadherence to a treatment regimen can entail not taking a dose, irregularity of drug taking, drug holidays, dose reduction, or discontinuation of drug taking.[55,56] Patients have to manage complex and sometimes changing medication schedules, deal with emotions and indebtedness towards clinicians and their organ donor, and cope with side effects of drugs.[57] Nonadherence can also be intentional or nonintentional.[58] Nonadherent transplant recipients tend to have less control over their lives, can be more forgetful, miss more doses when diverted from a daily routine, and skip doses, especially when short of money.[59] These nonadherent patients can also feel that immunosuppressive regimens are a disruption to their lives, or are not necessary at all.[59] In a study by Greenstein et al,[60] 3 distinct groups of noncompliers were identified

among adult renal transplant patients: accidental noncompliers, patients who felt invulnerable, and decisive noncompliers. Each of these groups required different interventions.[55,60]

There are several studies on the recipients' perspectives of medicine-taking. A study of 113 adult kidney transplant recipients found that there were 3 patient attitudes towards medication and adherence: "confident and accurate," "concerned and vigilant," and "appearance orientated and assertive."[54] However, the group discovered no significant association between attitudes and self-reported nonadherence.[54] Massey et al[61] found that in kidney transplant recipients, despite reporting a high degree of perceived necessity and had relatively few concerns about their immunosuppressive regimen, nonadherence increased significantly over a period of 18 months. The group concluded that beliefs about immunosuppressive medication and adherence in kidney transplantation were not related in this study.[61]

Variability in measurement modalities, operational definitions, and sampling methods makes comparisons between nonadherence studies challenging; however, the evidence points to a high level of nonadherence to immunosuppression posttransplant (approximately 22-68%) across the transplant continuum.[35,62-64] It has been established that posttransplant nonadherence to immunosuppressive regimens is an independent risk factor for poor clinical outcomes.[10-12]

In liver transplantation, a retrospective study of 359 transplant recipients showed that low adherence to treatment during the first 6 to 18 months posttransplant led to a higher risk of graft loss.[35] Nonadherence predicted acute rejection (odds ratio [OR], 4.95; 95% confidence interval [CI], 1.6-14.7) during a 5-year follow-up period.[65] Most importantly, nonadherence negatively impacted on graft and patient survival after liver transplantation.[66] A 2006 retrospective audit of the Scottish Liver Transplant Unit's database estimated nonadherence to be responsible for 1 in 10 deaths in liver transplant recipients.[67]

A meta-analysis by Dew et al[62] demonstrated the rate of nonadherence to have been more common in kidney transplant patients compared to recipients of other solid organs, including liver, heart and lung, with a rate of 36 cases per 100 patients per year in the kidney group. Furthermore, it has been reported that nonadherence may be a contributing factor to graft loss in 36% of kidney transplant recipients.[53] Nonadherence is also an independent risk factor for the development of de novo DSAs and higher rates of graft failure in kidney transplantation.[20] Sellarés et al[20] demonstrated a direct link between the development of DSAs, nonadherence to treatment and graft failure. Of the 315 patients in this prospective study, concerns about nonadherence were recorded in 26 patients. Grafts failed in 19 of these nonadherent patients, with a total of 17 reported as rejection-related failures.

Nonadherence pretransplant is a predictor of nonadherence posttransplant.[66] A prospective study of 141 lung, heart, and liver transplant patients showed that pretransplant nonadherence was a predictor of poor adherence posttransplant (OR, 7.9; 95% CI, 2.35-26.8).[68] This finding was supported by a larger prospective nationwide cohort study of 1505 renal, liver, lung and heart transplant patients (OR, 3.10; 95% CI, 2.29-4.21).[66] Pretransplant self-reported nonadherence has also been found to be a predictor of acute rejection (OR, 4.4; 95% CI, 1.18-16.16).[68]

The large impact that nonadherence has on treatment effectiveness is reflected in poor patient health outcomes, and increased healthcare costs.[53] Data demonstrate that the economic burden of nonadherence to immunosuppressive regimens is substantial, although specific data for liver transplantation are lacking.[10] Using an economic model of renal transplantation over a lifetime, Cleemput et al[69] showed that quality-adjusted life years, a measure of disease burden, was greater for adherent patients, than nonadherent patients. The considerable financial impact of nonadherence to immunosuppressive regimens is evidenced by the high costs of kidney transplantation.[70] Pinsky et al[71] reported that, 3 years after renal transplantation, a nonadherent patient, on average, generates US$ 12 840 higher medical costs compared with a highly adherent patient.

This evidence indicates that reducing nonadherence has the potential to significantly improve medium- and long-term outcomes in organ transplantation. Understanding the factors associated with nonadherence contributes to risk assessment, and could aid the development of preventative and remediating interventions.[72]

Multilevel Risk Factors for Nonadherence: Call for Multilevel Adherence Interventions

Nonadherence is the result of many interacting factors, and can be tackled at different levels of the healthcare system.[73] Established multilevel risk factors for nonadherence include sociodemographic factors, treatment- and condition-related factors, healthcare teams, and system-related factors.[12] More information on these multilevel risk factors can be found in Table 2. The relation between these factors is complex: a meta-analysis of 147 studies in kidney, heart,

TABLE 2.

Multilevel risk factors for nonadherence to immunosuppressive regimens[55,58,62,73-76]

Risk factor	Examples
Sociodemographic factors	• Adolescence, senior patient age (eg, when cognitively impaired) • Lack of social support • Non-white race
Patient-related factors	• Previous nonadherence • Disturbing side-effects • Barriers: busy lifestyle, interruption of daily routine • Forgetfulness • Inadequate health beliefs • History of substance abuse
Treatment-related factors	• Higher complexity and longer duration of the drug regimen, number of prescribed pills • Taste and size of the pill
Condition-related factors	• Depressive symptomatology
Healthcare teams and systems factors	• Lack of adherence assessment as part of regular transplant follow-up • Lack of adherence support as part of transplant follow-up • Lack of coverage of immunosuppressive drugs • HCPs not trained in behavioral assessment and interventions, or adequate communication style

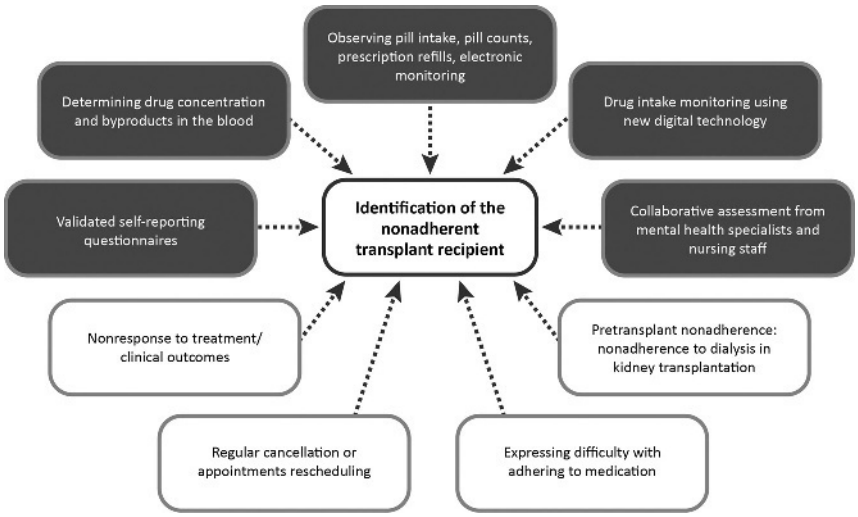


FIGURE 6. Identification of risk factors in nonadherent transplant recipients. Grey boxes represent methods of measurement/assessment of nonadherence, and white boxes are warning signs for the nonadherent patient. Figure based on data from Prendergast 2010, Pabst 2015, Denhaerynck 2005 and Dobbels 2010.[55,77-79]

liver, pancreas/kidney-pancreas, and lung/heart-lung transplant recipients, found little correlation between nonadherence and most patient psychosocial characteristics. Based on this, the authors suggested a shift in focus towards provider-related and system-related factors.[62,73]

Identification of Nonadherent Transplant Recipients

Accurate recognition of patients who are nonadherent is often difficult, so effective tools for identifying at-risk patients are very important.[77] Some of the available tools/methods for identifying nonadherent patients are shown in Figure 6.

Strategies for Managing Nonadherence

Identification of patients at risk for nonadherence could be initiated by routinely and systematically assessing medication adherence as the "fifth vital sign" (integrated into the electronic medical record) along the transplant continuum. In the absence of sophisticated methods for assessing nonadherence in daily clinical practice, such as electronic monitoring, it is advisable to combine all the information from available sources, such as self-reports, collateral reports, pharmacy refill data and/or assays,[80,81] to determine at each clinical encounter whether patients are experiencing issues with nonadherence.[12]

Once patients at risk of medication nonadherence are identified, they can be targeted for more intensive, tailored interventions. Implementation of these interventions should be tailored to the barriers to drug adherence that have been identified, or other targetable risk factors for nonadherence.[82,83] Transplant follow-up care based on principles of chronic illness management, in which support for patient self-management for adherence to an immunosuppressive regimen is integrated, resulted in higher levels of adherence and/or improved clinical and healthcare utilization parameters in 2 renal transplant studies.[84,85]

Current practice focuses strongly on patient education.[86] However, this approach has limited efficacy for improving adherence, and is therefore best combined with counseling/behavioral interventions and psychological/affective interventions.[86,87] A randomized controlled trial (RCT) of 150 adult renal transplant patients found that 1-year behavioral contract intervention significantly improved adherence to immunosuppressant therapy.[88] Table 3 highlights some patient-level interventions for managing nonadherence to immunosuppressive regimens.[82,86] A recently presented RCT that tested the efficacy of a multidimensional, 6-month adherence-enhancing intervention in heart, lung, and liver transplant recipients showed a 16% increase in adherence at the end of the intervention period, an effect that persisted during the 6-month wean-off phase. Moreover, the intervention group had a 10% decrease in mortality over the 5-year follow-up period ($P = 0.18$). The theory-based core and tailored intervention consisted of electronic monitoring of adherence;

TABLE 3.

Patient-level interventions for nonadherence to immunosuppressive regimens[55,82,83,86,93,95]

Patient-level interventions	Examples
Counseling/behavioral interventions	• Training patients during inpatient recovery on how to take medications • Providing adherence reminders during clinic visits • Medication schedules
Psychological/affective interventions	• Involving family • Providing support with educational and behavioral interventions • Establishing support groups directed at adherence
Educational/cognitive interventions	• Providing printed medication instructions/clear prescription instructions • Individual patient/family teaching
Medical interventions	• Simplified regimens, eg, monotherapy, once-daily dosing or long-acting parenteral administration • Medication reminder cues, prefilled/easy-to-use pill boxes, contingency plans for missed doses • Clinicians need to be aware of concomitant medications and focus on prescribing the most essential medication

feedback was provided to the patients by electronic monitoring printouts, goal setting, action planning and motivational interviewing. Patients found to be nonadherent received a high level of tailored adherence interventions.[89]

Motivational techniques are important in shaping medicine-taking behaviors, and 1 approach is the use of electronic devices. In a recent RCT, the effectiveness of wireless-enabled pill bottles to promote immunosuppression adherence in 120 kidney transplant recipients was investigated. Patient adherence was found to be significantly higher in groups using notifications and customized reminders, compared with the control group.[90] Another study demonstrated an association between electronic medication dispensers and higher adherence in a group of renal transplantation patients.[91]

Adherence interventions can be delivered in one-to-one sessions, group sessions or using (interactive) e-health technology. One recent communication also reported the development of an 18-minute consumer-driven video to deliver information about the importance of medication adherence to patients.[92] Future work should assess which intervention delivery mode is most appropriate for diverse clinical contexts, from an effectiveness, as well as from a health economic perspective.

Simplified drug regimens (eg, monotherapy, once-daily dosing, long-acting parenteral administration), medication reminder cues, the support of family and friends, contingency plans for missed doses, and easy-to-use pill boxes are all strategies for further limiting the unintentional form of nonadherence.[58,59,93] However, there is convincing evidence that a simplified immunosuppressive regimen might benefit all patients, regardless of their susceptibility to nonadherence.[83,93,94] The Adherence Measurement in Stable Renal Transplant Patients Following Conversion From Prograf to Advagraf (ADMIRAD) study demonstrated superior implementation of the once-daily prolonged-release tacrolimus regimen over the twice-daily regimen in adult renal patients treated with tacrolimus twice daily for at least 3 months before inclusion. The study highlighted that simplification of the regimen reduced the patient's pill burden and also eliminated the evening dose, which is more likely to be missed.[95] The authors suggested that further research should include investigation into the pharmacologic effect of a patient skipping a single twice-daily dose, versus skipping a single once-daily dose, to understand the impact of dosing error with each regimen.[95]

Nonadherence increases among adolescents, young adults, and with senior patient age, signifying that these patient subgroups may require specific attention.[55,96-98] A study of 108 adult liver transplant patients examined the risk factors for compliance with prednisolone treatment (as part of a double or triple drug immunosuppressive regimen) and found that age below 40 years was a significant risk factor for nonadherence.[99] Furthermore, Pinsky et al[71] reported that adolescent kidney transplant recipients aged 19 to 24 years were more likely to demonstrate persistent nonadherence, than patients aged 24 to 44 years. A particular concern is the risk of young adults not recognizing their own nonadherence.[100] These nonadherent groups may profit from targeted education, medication schedules, clear prescription instructions, and simplified drug regimens. Reminder cues and prefilled pill boxes might also be useful in these patient groups.[55] Community-based young adult clinics can have a positive impact on both medication and clinic adherence, and the social accountability in transition program has also shown promise for improving adherence in younger transplant patients.[97]

In view of the existing data, it seems reasonable to suggest that clinicians should routinely repeat key messages to patients at appropriate opportunities during posttransplantation consultations (eg, highlighting the risks associated with nonadherence to therapy). However, education alone may not be sufficient and further interventions may be required to modify a patient's habits and behavior.[86] In summary, a combination of different interventions may be the most effective strategy in enhancing patient self-management and adherence to medication, and ultimately improving outcomes posttransplant.[80]

Recommendations for Managing Nonadherence in Kidney Transplantation

1. Establish a "baseline" evaluation of medication adherence at the time of listing for transplantation. (*Level 3)*
   - ○ Assess the patient's previous ability to adhere to therapeutic regimens
     - ▪ Tools include the Immunosuppressant Therapy Adherence Scale (ITAS), simplified medication adherence questionnaire (SMAQ), Identification of Medication Adherence Barriers Questionnaire (IMAB-Q) (https://www.uea.ac.uk/pharmacy/research/imab-q/quest), Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS) questionnaire (available on request from the developers), or other validated self-report questionnaires
   - ○ Monitor the patient's adherence to dialysis regimens
2. Nonadherence to an immunosuppressive regimen should be assessed as the "fifth vital sign" at each clinical encounter posttransplantation, based on evidence that it is a common and independent risk factor for poor clinical outcomes. (*Level 1)*
3. Trough levels of relevant immunosuppressive drugs should be regularly monitored (at least every 3 months when the patient is stable) to assess for medication nonadherence; in particular, unexplained high IPV and unexpected fluctuations in immunosuppressant trough levels, despite a fixed dose, should prompt a discussion with the patient about the importance of drug adherence. *(Level 1)*
4. Maintain clinical awareness of direct risk indicators (eg, drug concentrations, fluctuations (IPV) in drug levels, development of de novo DSAs, prescription frequency, medication recall) and indirect risk factors (eg, patient's mental status, emotional/social status, adverse effects) of nonadherence. (*Level 3*)
   - ○ Assess the patient's social support network and emotional and mental status (eg, using available questionnaires)
   - ○ Evaluate the prescription frequency of the proposed immunosuppressive agent
   - ○ Use specific assays (eg, single-antibody bead assay) to monitor the development of de novo DSAs (also refer to recommendations in DSA section of this document)
     - ▪ In the case of de novo DSAs, consider nonadherence
     - ▪ If nonadherence is suspected, screen for de novo DSAs
5. Use different combined methods to objectively identify adherence (eg, questionnaires, drug concentrations) during the clinical visit. (*Level 2*)
   - ○ Discuss nonadherence with patients, and on indication, ask patients to complete a questionnaire

6. Simplified medication regimens, such as fixed-dose, once-daily medications should be administered to improve adherence. *(Level 1)*
7. In cases of adverse events, simplify/modify the immunosuppressive drug regimen as well as concomitant drugs. *(Level 1)*
8. Discuss any suspicion of nonadherence openly and nonjudgmentally with the patient. *(Level 5)*
9. Together with the patient, identify his/her current barriers to adherence and develop a personalized action plan with specific solutions, for example, pill boxes, (electronic) reminder systems, education and psychological behavioral support. *(Level 5)*
10. Together with the patient (and team), reassess the results of the intervention(s) and adjust the strategy when indicated (eg, residual nonadherence). *(Level 5)*
11. Patient-level interventions need to focus primarily on behavioral change techniques, including training patients during inpatient recovery on how to take medications, providing adherence reminders during clinic visits, etc. Although important, patient education is only a small component of an adherence intervention. Information must be given in a manner appropriate for the patient. *(Level 1)*

Recommendations for Managing Nonadherence in Liver Transplantation

1. Establish a "baseline" evaluation of medication adherence at the time of listing for transplantation. (*Level 3*)
   - Assess the patient's previous ability to adhere to therapeutic regimens
     - Tools include the Immunosuppressant Therapy Adherence Scale (ITAS), simplified medication adherence questionnaire (SMAQ), Identification of Medication Adherence Barriers Questionnaire (IMAB-Q) (https://www.uea.ac.uk/pharmacy/research/imab-q/quest), Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS) questionnaire (available on request from the developers), or other validated self-report questionnaires
2. Nonadherence to an immunosuppressive regimen should be assessed as the "fifth vital sign" at each clinical encounter posttransplantation, based on evidence that it is a common and independent risk factor for poor clinical outcomes. (*Level 1)*
3. Trough levels of relevant immunosuppressive drugs should be regularly monitored (at least every 3 months when the patient is stable) to assess for medication nonadherence; in particular, unexplained high IPV and unexpected fluctuations in immunosuppressant trough levels, despite a fixed dose, should prompt a discussion with the patient about the importance of drug adherence. *(Level 1)*
4. Maintain clinical awareness of direct risk indicators (eg, drug concentrations, fluctuations (IPV) in drug levels, prescription frequency, medication recall) and indirect risk factors (eg, patient's mental status, emotional/social status, adverse effects) of nonadherence. (*Level 3*)
   - Assess the patient's social support network and emotional and mental status (eg, using available questionnaires)
   - Evaluate the prescription frequency of the proposed immunosuppressive agent
5. Use different combined methods to objectively identify adherence (eg, questionnaires, drug concentrations) during the clinical visit. (*Level 2*)
   - Discuss nonadherence with patients, and on indication, ask patients to complete a questionnaire

6. Simplified medication regimens, such as fixed-dose, once-daily medications should be administered to improve adherence. *(Level 1)*
7. In cases of adverse events, simplify/modify the immunosuppressive drug regimen as well as concomitant drugs. *(Level 1)*
8. Discuss any suspicion of nonadherence openly and nonjudgmentally with the patient. *(Level 5)*
9. Together with the patient, identify his/her current barriers to adherence and develop a personalized action plan with specific solutions, for example, pill boxes, (electronic) reminder systems, education and psychological behavioral support. *(Level 5)*
10. Together with the patient (and team), reassess the results of the intervention(s) and adjust the strategy when indicated (eg, residual nonadherence). *(Level 5)*
11. Patient-level interventions need to focus primarily on behavioral change techniques, including training patients during inpatient recovery on how to take medications, providing adherence reminders during clinic visits, etc. Although important, patient education is only a small component of an adherence intervention. Information must be given in a manner appropriate for the patient. *(Level 1)*

IMPACT OF VARIABILITY OF IMMUNOSUPPRESSIVE REGIMEN IN LIVER AND KIDNEY TRANSPLANTATION

Problem to be Addressed

In solid organ transplantation, constant and controlled exposure to immunosuppression provides protection against the development of cellular and antibody-mediated rejection (AMR) and graft loss, while minimizing drug-related toxicity. Nowadays, the cornerstones of immunosuppression protocols, both in kidney and liver transplantation, are CNIs, particularly tacrolimus, which is superior to cyclosporine in the prevention of T cell–mediated rejection (TCMR) and graft loss. Oral bioavailability of tacrolimus is poor (25% mean), and is highly variable among individuals (range, 5-90%).[101-103] Tacrolimus is able to be absorbed throughout the gastrointestinal tract.[104] The immediate-release formulation is mainly absorbed in the small bowel. There is extensive presystemic metabolism by the CYP3A enzymes in the gut wall and first-pass metabolism in liver, which limits its oral bioavailability.[105] Expressers of the CYP3A5 enzyme (as is more often the case in black and Asian patients) do require higher dosages to reach therapeutic tacrolimus exposure.[105-107] The recently developed prolonged-release formulation in tablet form (also known as LCP-tacrolimus) is released and absorbed more distally in the gut.[105,106] This newer formulation of prolonged-release tacrolimus in tablets has shown some differences in terms of pharmacokinetics but long-term clinical outcome data is yet to be established.[106] After absorption, tacrolimus diffuses extensively in blood cells and tissues. In the plasma, 90% of tacrolimus is bound to proteins.[103] After being metabolized by the liver, the inactive metabolites are bile-excreted. Thus, the intrinsic pharmacokinetic and pharmacodynamic properties of tacrolimus, including erratic absorption, a variable first-pass effect, and unpredictable metabolism, may be responsible for its large intrapatient and inter-subject exposure variability.[105]

Moreover, tacrolimus has a narrow therapeutic margin and even slight exposure variability can translate into clinically harmful events.

Clinically significant variability within individual patients can be defined as an alternation between episodes of overexposure and underexposure to immunosuppression within a timeframe in which the dosage itself remains constant.[103] Figure 7 illustrates low IPV and high IPV with similar mean trough concentrations of CNIs.

In practice, IPV of tacrolimus is usually assessed by the coefficient of variance or by standard deviations of trough concentrations. Persistent significant variability may be responsible for alloimmune activation during low exposure and toxicity or low immunity during overexposure. This conflicting situation is often seen early after transplantation and leads to inferior outcomes.[103]

During pregnancy, the pharmacokinetics properties of CNIs may vary from the nonpregnant state, so drug levels should be closely monitored during pregnancy, with dose adjustment when necessary.[46] Similar considerations may apply during intercurrent illness.[108,109]

In renal transplantation, IPV in immunosuppressive drug exposure is now recognized as a predictor of poor clinical outcome. In a study of 297 patients, IPV of tacrolimus was correlated with a composite endpoint comprising graft loss, biopsy-proven chronic allograft nephropathy and doubling of plasma creatinine concentration.[38] Of 34 patients who reached the composite endpoint, 24 had increased IPV (70.6%).[38] A larger study (n = 356) confirmed the impact of IPV on long-term outcome.[110] In the largest series to date, a follow-up of a study performed by Borra et al,[38] the impact of IPV was studied in 808 renal transplant recipients transplanted between 2000 and 2010.[111] Almost a quarter of the patients (23.3%; n = 188) reached the composite endpoint consisting of graft loss, late biopsy-proven rejection, transplant glomerulopathy, or doubling of serum creatinine concentration between month 12 and the last follow-up. The cumulative incidence of the composite endpoint was significantly higher in patients with high IPV than in patients with low IPV (hazard ratio, 1.41; 95% CI, 1.06-1.89; $P = 0.019$).[111] In addition, increased IPV of tacrolimus has been associated with the development of de novo DSAs,[112] and faster progression of interstitial fibrosis.[113]

In the context of liver transplantation, the clinical impact of tacrolimus variability has seldom been studied. Patients with biopsy-proven TCMR showed increased standard deviations of tacrolimus trough concentrations according to 1 report.[29] In another study, the conversion from twice-daily tacrolimus to prolonged-release tacrolimus capsules within the first month after liver transplant resulted in reduced exposure variability, which was accompanied by halved TCMR rates.[114] These studies were hampered by the absence of multivariate analysis to control for possible confounders. In addition, the actual hard endpoints in liver transplant, namely graft loss and death, were not investigated. The most important study reporting a relationship between tacrolimus variability and increased likelihood of late rejection and graft loss was performed in a pediatric population, and it considered heart, lung, kidney, and liver transplantations together, making it difficult to draw firm conclusions.[115]

It may well be that liver transplant recipients are more tolerant of tacrolimus variability as compared with renal transplant patients, as they are to TCMR episodes.[116] Further studies with larger sample sizes and longer surveillance periods are needed to determine to what extent variability increases the risk of graft loss and/or death. In the meantime, large fluctuations in tacrolimus levels, with high levels of exposure early after liver transplant, should be avoided because they increase mortality due to overimmunosuppression-related events, such as infections, cardiovascular events (CVEs), and malignancies.[117]

Slightly Modifiable Contributors to Tacrolimus Variability

Determinants of tacrolimus variability are shown in Table 4. They are classified according to their detectability and the ease with which they can be modified by clinicians and/or patients. Nonmodifiable factors will not be discussed here because they are hard to detect and/or impossible to control in daily practice. Slightly modifiable determinants of variability are easily detected in clinical practice and cannot be modified per se, but benefit from more frequent assessment of tacrolimus trough concentrations and dose adjustments. Nonadherence is the paradigm within this category (see dedicated section). Gastrointestinal events such as diarrhea and vomiting may impact on tacrolimus concentrations, and may motivate intensive monitoring until gut function is restored.[118,119]

The impact of graft dysfunction on tacrolimus IPV varies depending on the transplanted organ. In kidney transplantation, the impact is likely to be limited given the intrinsic pharmacokinetics of tacrolimus (ie, liver metabolism and bile excretion), although supporting literature is lacking. In patients needing hemodialysis, it is reasonable to give the

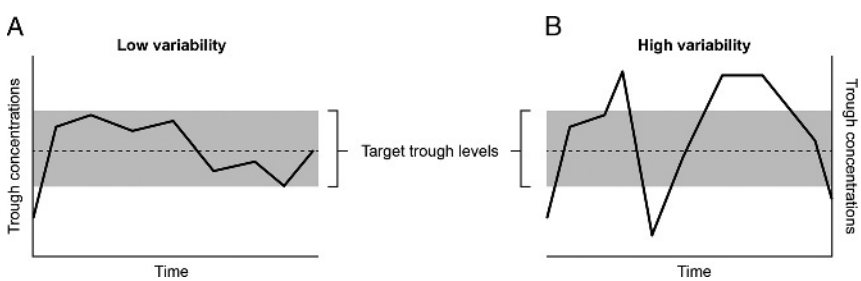


FIGURE 7. Concept figure depicting tacrolimus exposure variability. On the left, patient A keeps all tacrolimus trough concentrations within a narrow range and no significant variability is observed. On the right, patient B shows a wide fluctuation of trough concentrations, alternating periods of overimmunosuppression and underimmunosuppression, thus indicating significant exposure variability.

next dose immediately after the dialysis session, although no robust studies are available to support this recommendation. In liver transplantation, graft dysfunction and/or biliary complications may interfere with metabolism and elimination of tacrolimus. With mildly impaired liver function, the effect on tacrolimus pharmacokinetics is negligible.[120] However, as liver function deteriorates, tacrolimus trough concentrations are expected to rise in an unpredictable and individual manner. Again, close monitoring of tacrolimus levels is required, and a dosage reduction may be anticipated.

Hypoalbuminemia and anemia may alter the distribution of tacrolimus by increasing its circulating free fraction, leading to significant variability and increased exposure.[121,122] Therefore, special attention is warranted in patients with malnourishment and iron deficiency, which are frequent conditions among the transplant population.[123]

Highly Modifiable Contributors to Variability

Diet content and interactions with other drugs (or some herbal products) may be the focus of patient education.[125,126] Tacrolimus should be taken in a fasting state to increase bioavailability.[127] Foods that interfere with hepatic CYP3A and/or intestinal CYP3A4 enzymes, such as grapefruit,[128,129] pomelo,[130] star fruit,[131] turmeric, and ginger,[132] should be avoided because they can increase tacrolimus exposure. Drugs that interfere with CYP metabolism are able to modify tacrolimus exposure when used simultaneously, and sometimes have a clinically significant impact.[133] The calcium channel blocker diltiazem has been used as a tacrolimus-sparing agent due to its effect as an inhibitor of tacrolimus metabolism.[134,135] Evidence in kidney transplant patients suggests that CYP3A5 expressers are more susceptible to diltiazem-induced tacrolimus metabolism than nonexpressers.[135] The drugs that are most frequently responsible for interactions with tacrolimus in the liver transplant population are other immunosuppressants, antifungals, macrolide antimicrobials and the protease inhibitors commonly used in chronic hepatitis C virus (HCV) and human immunodeficiency virus (HIV).[133]

Regarding immunosuppressive drugs, anti-IL2 receptor agents and corticosteroids are able to decrease and increase the tacrolimus dose requirement, respectively, but the interaction is usually mild and without clinical consequences.[136,137] No significant interaction is expected when tacrolimus and mycophenolate are combined.[138] This is in contrast to the reduction in mycophenolic acid (MPA) exposure in patients on co-treatment with cyclosporine. As a result of cyclosporine-induced inhibition of enterohepatic recirculation, the MPA area under the curve (MPA-AUC) is significantly lower in case of cyclosporine as compared with tacrolimus co-treatment.[139] The evidence regarding mTORi is contradictory.[140,141] Azole antifungals are potent inhibitors of CYP3A4 and P-glycoproteins, and lead to increased serum concentrations of tacrolimus. A significant reduction in the tacrolimus dosage should be anticipated, with recommendations for dose reduction in the ranges of 40% (fluconazole), itraconazole (50-60% reduction), 66% (voriconazole), and 75% (posaconazole).[142] Furthermore, we recommend reducing the dose at the time of triazole treatment initiation, and not wait for the first tacrolimus concentration after starting a triazole regimen. Other significant interactions may be experienced when using other medications sharing CYP3A metabolism (eg, HIV drugs).[143,144]

A dedicated comment about hepatitis C antivirals is warranted. With the introduction of new, more potent antivirals, many transplant patients with HCV may receive therapy after transplantation. In general, it is mandatory to check for potential interactions with immunosuppressive drugs in all transplant patients before starting antiviral therapy. Sofosbuvir, the cornerstone of most antiviral protocols, and its combinations with ledipasvir or daclatasvir, is usually well tolerated with tacrolimus.[145,146] However, the first-generation protease inhibitors, telaprevir and boceprevir, and the combination ombitasvir/paritaprevir/ritonavir+/–dasabuvir, have a major impact on tacrolimus metabolism, increasing tacrolimus trough concentrations exponentially; therefore, these drugs should be avoided whenever possible.[147,148] The

TABLE 4.

Determinants of IPV of tacrolimus[103,120,121,123,124]

	Factors	Interventions
Nonmodifiable	• Pharmacogenetics: polymorphisms in CYP3A genes • Circadian rhythm of tacrolimus exposure	Not applicable
Slightly modifiable	• Nonadherence • Gastrointestinal events (diarrhea, vomiting) • Any clinical situation motivating liver graft dysfunction • Low serum proteins (hypoalbuminemia) • Anemia	(a) More frequent assessment of tacrolimus trough concentrations and refined dose adjustments (b) Correction of the underlying factors whenever possible (c) Additional precaution needed when the patient experiences liver allograft rejection, infections, liver impairment, vascular/biliary complications or recurrence of primary liver disease (d) Specific measures to improve adherence (see dedicated section)
Highly modifiable	• Food (dietary fat content, grapefruit juice, pomelo) • Drug–drug interactions: antifungals, antivirals, other immunosuppressants, and other drugs • Herbal products • Uncontrolled generic substitution	(a) Patient education (b) Healthy diet. Avoid food contents and herbal products interfering with hepatic CYP3A and/or intestinal CYP3A4 enzymes (c) Anticipate and avoid drug interactions (d) If significant variability occurs, consider switching to prolonged-release tacrolimus capsules

Factors are classified according to their detectability and the ease with which they can be modified in routine clinical practice.
CYP3A, cytochrome P450 family 3 subfamily A.

interaction with simeprevir is less strong and tacrolimus dosage modifications should be carried out according to trough concentrations.[149] Additional and updated information may be found at www.hep-druginteractions.org.[146] HCV infection also affects tacrolimus and cyclosporine levels, so when the HCV is cleared, the dose of tacrolimus needs to be reviewed and usually increased, to maintain trough levels.[150]

Another potential source of tacrolimus variability is conversion to generic formulations; however, the evidence is scarce and of low quality.[151] Bioequivalence between generic tacrolimus and its innovator has been demonstrated in healthy volunteers and kidney transplant recipients. In the subgroup of kidney transplant patients older than 60 years caution is needed as 1 randomized study showed bioequivalence standards were not met by generic tacrolimus.[152] The evidence for the use of generics in liver transplant population comes from short and uncontrolled clinical experiences.[153] There appears to be insufficient evidence to provide reassurance that, in transplanted patients, generics are therapeutically equivalent to innovator immunosuppressants. As outlined in the European Society for Organ Transplantation (ESOT) recommendations, there are many cases where prescribing generics is fully appropriate, for example, in cost-conservative markets.[154] Indeed, there are no data to firmly suggest that generics are not equivalent and therefore unsafe. However, for narrow therapeutic index drugs, concerns exist regarding the safety of generic substitution given the clinical consequences linked to both overexposure and underexposure. Conversion from branded tacrolimus to a generic formulation should only be undertaken by a transplant specialist and with close monitoring of trough levels. Uncontrolled switching, particularly between generic formulations, should be avoided.[151,154]

The conversion from twice-daily to prolonged-release tacrolimus (capsules), both in kidney and liver transplant recipients, leads to lower blood trough concentrations and a reduced IPV of tacrolimus.[155,156] In a single study performed in liver transplant recipients, the early conversion to prolonged-release tacrolimus capsules was accompanied by a significant reduction of TCMR rates.[114] It remains unclear, however, whether a reduction in IPV motivated by conversion to prolonged-release tacrolimus capsules would also lead to improved clinical outcomes; prospective trials are needed.[157]

Finally, in some liver transplant patients experiencing TCMR or chronic rejection, the transplant physician increases tacrolimus dosage abruptly. This strategy has little therapeutic impact if the baseline trough concentrations are within the recommended therapeutic range, but it may lead to large "intended variability," particularly when liver function is impaired.[158] If tacrolimus levels are elevated and graft dysfunction progresses, the risk of high levels of exposure becomes too great, thus increasing mortality due to overimmunosuppression-related events.[117] As a general recommendation, tacrolimus dosage modifications should be carried out progressively and with special caution in patients with liver dysfunction.

Recommendations for Managing IPV in Kidney Transplantation

1. Regular assessment of the serum trough concentrations of the immunosuppressive medication is mandatory (every 3 months or when there is an unexplained change in graft function), even in patients who are stable in the long term and are taking a constant dosage. *(Level 1)*
2. Potential problems with drug adherence should be discussed with patients in whom tacrolimus trough concentrations fluctuate more than expected, despite a stable dose. *(Level 2)*
3. Drug–drug interactions should be anticipated and/or avoided. *(Level 4)*
4. In patients with documented variability receiving tacrolimus twice daily, conversion to once-daily prolonged-release tacrolimus capsules may be helpful. *(Level 4)*
5. Substitution to generic tacrolimus formulations, if considered, should be attempted only in stable patients and under close monitoring of trough concentrations. Generic substitution should only be carried out if subsequent substitutions from one generic to another generic will not be attempted. *(Level 5)*
6. Low tacrolimus trough levels will increase the risk of TCMR, even in the presence of CNI-associated renal impairment. Therefore, low levels of tacrolimus/underexposure should be avoided. *(Level 5)*

Recommendations for Managing IPV in Liver Transplantation

1. Frequent assessment of CNI serum trough concentrations is mandatory (every 3 months or when there is an unexplained change in graft function), even in patients who are stable in the long term and on a constant dosage. *(Level 1)*
2. CNI trough levels should be assessed once every 2 or 3 days within the first 15 days after liver transplant, weekly from week 2 to week 4, monthly until the sixth month after liver transplant, and every 3 months thereafter. In long-term stable patients, longer intervals may be acceptable. *(Level 5)*
3. Avoiding significant variability, particularly large fluctuations in tacrolimus trough concentration early after liver transplant, is strongly recommended, as these are associated with inferior outcomes. *(Level 2)*
4. Significant variability can be avoided if patients comply with their pharmacist's recommendations: this can be optimized by patient education, healthy diet, and avoidance of use of drugs and other medicines that affect tacrolimus metabolism. *(Level 4)*
5. The occurrence of determinants of variability, such as liver graft dysfunction, gastrointestinal events, renal impairment and anemia/hypoalbuminemia should lead to more (eg, at least weekly) intensive monitoring of tacrolimus trough concentrations and dose adjustment if required. Regular surveillance should be resumed as soon as the risk factor for variability has been corrected. *(Level 4)*
6. Drug–drug interactions should be anticipated and/or avoided. Any treatment modification should motivate checking for potential interactions and more frequent assessment of trough levels. *(Level 4)*
7. In patients receiving tacrolimus twice daily with documented significant variability, conversion to once-daily prolonged-release tacrolimus capsules might be helpful, particularly early after liver transplant. *(Level 2)*
8. Substitution to generic tacrolimus formulations should only be undertaken by a transplant specialist and with close monitoring of trough levels. Uncontrolled switching, particularly between generic formulations, should be avoided. *(Level 5)*
9. In patients with histologically confirmed TCMR and baseline trough concentrations of tacrolimus within the recommended range, an abrupt increase of tacrolimus dosage should be avoided. *(Level 5)*

UNDERIMMUNOSUPPRESSION AFTER KIDNEY AND LIVER TRANSPLANTATION

Problem to be Addressed

One of the clinical challenges in managing transplant recipients is to identify and manage those patients who may require less immunosuppression.[159] Strategies for optimal immunosuppression will vary and transplant units will develop their own regimens, usually based on a CNI—usually tacrolimus, often with an antimetabolite (such as azathioprine) or mycophenolate. Tolerance levels vary not only between patients, but also over time.[159] Some liver transplant recipients may not require high levels of immunosuppression, or indeed any immunosuppression in the long term.[116] However, complete withdrawal of immunosuppression is normally reserved for clinical trials under intense surveillance.[159]

The clinician needs to strike a balance between overimmunosuppression, which unnecessarily increases the probability of developing complications of immunosuppression such as metabolic, cardiovascular, neoplastic and nephrotoxic complications, and underimmunosuppression, which is linked to reduced graft survival and poor patient outcomes for both kidney and liver transplant recipients.[160]

The aim of immunosuppression minimization is to develop an immunosuppression protocol for the individual recipient, which provides maximum protection for both patient and graft from immune-mediated damage with the minimum immunosuppressive burden. Although the term "immunosuppressive burden" is a useful concept, it cannot readily be measured.

Ten years ago, nephrotoxicity was considered to be a major risk factor for kidney graft loss.[160] CNI-minimization strategies for tacrolimus and cyclosporine were proposed in an attempt to prevent kidney damage and improve patient outcomes.[161] This approach has been challenged,[162] and it is now believed that the histological lesions classically attributed to CNI nephrotoxicity are nonspecific and some of the allograft damage is a consequence of alloimmunity.[162,163] Thus, it is often difficult to establish whether renal allograft damage is a consequence of CNI toxicity, requiring reduction in CNI dose, or alloimmunity, requiring increased immunosuppression.[163]

In contrast to kidney transplantation, alloimmunity associated with low CNI levels after liver transplantation does not contribute to damage of the native kidney.[163,164] CNI minimization could, therefore, preserve kidney function in this instance,[165] and reduce other consequences of long-term immunosuppression. Furthermore, the characteristic operational tolerance of the liver represents the reduced incidence of rejection episodes and a normal liver function/histology despite minimal immunosuppression. In fact, the liver is more forgiving to temporary underimmunosuppression after liver transplantation compared with other solid organs, including the kidney, heart and lung.[166] This immune unresponsiveness has led to some liver transplant recipients being managed on minimal immunosuppressive regimens with CNIs.[116] Although tolerance can evolve after organ transplantation, in most patients, underexposure of immunosuppression is linked to reduced graft survival and poor patient outcomes in both kidney and liver transplantation,[117,167] so clinicians must be aware of the factors that can lead to suboptimal immunosuppression.

Patient nonadherence and variability of drug exposure to immunosuppressive regimens have been discussed elsewhere within this report; this section focuses on the importance of physicians managing the risk of underimmunosuppression in their kidney and liver transplant patients. Because CNI-based immunosuppression is the most commonly used regimen for management of both liver and kidney transplant recipients, we have focused on CNI minimization in reducing the immunosuppressive burden. Nevertheless, for some patients, alternative strategies such as moving to regimens based on mTORi, corticosteroids with mycophenolate or azathioprine, and regimens based on belatacept (for renal recipients), may be more appropriate. Some authors have advocated the use of protocol biopsies to help manage immunosuppression. Absence of evidence of immunological activity may allow for reduction of the immunosuppressive load; conversely, immune activity, even in the absence of serological abnormalities suggesting graft dysfunction may indicate the need for increased immunosuppression.[168] However, protocol biopsies are used relatively infrequently largely because of concerns of safety, cost, and patient acceptance.[169]

The Basis for CNI-Sparing Regimens

Over the last 10 years, there has been a strong move in the renal transplant community to minimize CNI-based immunosuppressive regimens, largely based on reports of long-term nephrotoxicity.[161] For liver transplantation, historically, it was considered that there might be advantages to having a lower immunosuppressive burden. However, these views were based on evidence from small patients series, animal experiments and the immunological role of the liver in supporting operational tolerance, rather than on data from RCTs in liver transplantation.[170] In 1996, Calne proposed the window of opportunity for immunological engagement (WOFIE) hypothesis that some degree of immunological engagement promotes tolerance.[171]

In 2003, Ojo et al[172] reported results of a 5-year study of 69 321 nonrenal transplant patients showing that the cumulative incidence of chronic renal failure was 6.9 to 21.3% (depending on the organ transplanted). In this study, the risk of chronic renal failure associated with the use of a CNI increased with a cyclosporine regimen compared with tacrolimus therapy (overall relative risk 1.24 [1.17-1.30]). In the same year, Nankivell and colleagues[173] reported a 10-year follow-up study of yearly biopsies in 120 simultaneous kidney and pancreas recipients receiving cyclosporine-based immunosuppression and attributed the progressive high-grade arteriolar hyalinosis with luminal narrowing, increasing glomerulosclerosis, and additional tubulointerstitial damage to CNI exposure. Despite the assumed CNI nephrotoxicity in this study, 10-year death-censored graft survival was 95.2%, with excellent 10-year renal function (mean serum creatinine, 0.14 ± 0.04 mmol/L [1.62 ± 0.48 mg/dL]).[173] These, and other observations, led to the principles that whereas CNIs reduced acute rejection episodes in the immediate posttransplant period, in the long term, CNIs were nephrotoxic, causing fibrotic kidney lesions and leading to poor long-term graft survival.[163]

The introduction of mTORi, such as sirolimus, that combine both immunosuppressive and antiproliferative actions with potentially non-nephrotoxic properties,[174] coincided with the move toward CNI minimization strategies in kidney

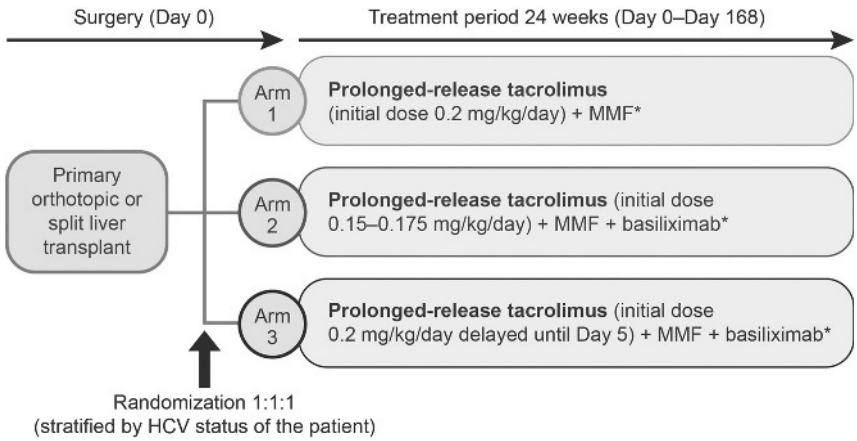


FIGURE 8. DIAMOND study design. *0 to 1000 mg IV bolus corticosteroid (preoperatively, intraoperatively, or postoperatively) on day 0. Arm 2 only: if the patient had not received treatment for an acute rejection episode and the last recorded trough level recorded was ≥5 ng/mL at day 43, then the dose was reduced by 20% to 25%. IV, intravenous. Reprinted with permission from Trunecka P, Klempnauer J, Bechstein WO, et al. Renal function in de novo liver transplant recipients receiving different prolonged-release tacrolimus regimens—the DIAMOND study. *Am J Transplant.* 2015;15:1843–1854.[178]

transplantation and in liver transplantation. As a result, CNI avoidance or conversion to mTORi regimens have been investigated in a number of large, prospective, multicenter, randomized clinical trials in kidney transplantation, with less study data available for liver transplantation.

Evidence for CNI-Minimization Strategies

In kidney transplantation, studies have failed to show long-term benefits for transplant recipients on CNI-free regimens.[175] These findings are corroborated by the Efficacy Limiting Toxicity Elimination (ELITE)-Symphony study, a large, 1-year, multicenter, randomized, controlled study in 1645 kidney transplant recipients.[176] Patients were treated with standard-dose cyclosporine, mycophenolate mofetil (MMF) and corticosteroids (prednisone or equivalent) versus daclizumab induction, MMF, and corticosteroids in combination with low-dose tacrolimus, low-dose cyclosporine, or low-dose sirolimus.[176] The most favorable outcome for controlling acute rejection and providing good renal function was obtained in the low-dose tacrolimus arm, with the worst outcomes in the CNI-free arm.[176] At the 3-year follow-up, these differences had reduced over time and were often not significant.[177] An overview is provided in Table 5. Additionally, a large meta-analysis of 56 randomized clinical trials in 11 337 renal transplant recipients provides an overview of 3 different early CNI-sparing strategies[161] (Table 5).

Similar to kidney transplantation, CNI minimization strategies using low-dose tacrolimus in liver transplantation have shown favorable outcomes. Results from a 24-week study of 857 liver transplant recipients (Figure 8) indicated that lower-dose prolonged-release tacrolimus capsules (0.15-0.175 mg/kg per day subsequently reduced by 20-25%, target trough level, 4-12 ng/mL)[a], administered with MMF and basiliximab immediately posttransplant, was associated with a significant renal function benefit and a significantly lower incidence of biopsy-confirmed acute rejection, compared with a higher-dose (5-15 ng/mL until day 42 then 5-12 ng/mL) prolonged-release tacrolimus-based regimen.[178]

The Impact of Underimmunosuppression

In kidney transplantation, excessive minimization of immunosuppression can lead to the development of DSAs and possible TCMR, with a negative impact on kidney graft survival.[179] Using Luminex assays, Liefeldt et al[179] prospectively assessed the presence of DSAs in 126 patients who had either received cyclosporine-based immunosuppression or had been randomized to everolimus and MMF conversion at 3 to 4.5 months, with progressive withdrawal of steroids in 60% of patients. DSAs developed in 10.8% of patients on cyclosporine and 23.0% of patients on everolimus; significantly more patients developed TCMR with everolimus (n = 8) versus cyclosporine (n = 2; P = 0.036).[179] The appearance of DSAs could be considered a biomarker of underimmunosuppression after kidney transplantation, although these antibodies may become detectable only after the initiation of organ damage.[179,180]

There is increasing evidence that the formation of de novo DSAs in liver transplantation is an independent risk factor for graft loss.[39,181] Underimmunosuppression immediately after liver transplantation carries a higher risk of rejection.[158] Tacrolimus trough concentrations less than 7 ng/mL in the first week after liver transplantation is associated with higher rates of moderate/severe rejection compared with levels greater than 7 ng/mL.[117] In the first year after liver transplant, underimmunosuppression (tacrolimus levels <3 ng/mL[a] or cyclosporine levels <75 ng/mL) is associated with an increase in de novo DSA formation.[39] However, in liver allografts (and in contrast to kidney transplants), early acute cellular rejection does not appear to be associated with worse graft outcomes.

Optimizing Immunosuppression Levels

The Collaborative Transplant Study (CTS) report in 2014 found that kidney transplant recipients are at a significantly higher risk of graft failure due to alloimmunity if maintained on tacrolimus trough levels less than 5 ng/mL at year 1 posttransplant compared with patients maintained at

[a]*As per the Advagraf (tacrolimus prolonged-release hard capsules) license recommendations, it is necessary to consider the clinical condition of the patient when interpreting whole blood levels. In clinical practice, whole blood trough levels have generally been in the range of 5-20 ng/mL in liver transplant recipients and 10-20 ng/mL in kidney transplant patients in the early posttransplant period. During subsequent maintenance therapy, blood concentrations have generally been in the range of 5-15 ng/mL in liver and kidney transplant recipients.*

TABLE 5.

Results of studies investigating CNI-free/minimization regimens[161,176-178]

Study type	No. of participants	Intervention	Results
ELITE-Symphony study (large, 1-year, multicenter, randomized, controlled study). The study was then extended to 3 years	1645 renal transplant recipients	Patients were treated with either: – MMF and corticosteroids (prednisone or equivalent), standard-dose cyclosporine Or – MMF, corticosteroids (prednisone or equivalent), and daclizumab induction, with low-dose cyclosporine, low-dose tacrolimus, or low-dose sirolimus	– The most favorable outcome for controlling acute rejection and providing good renal function was obtained in the low-dose tacrolimus arm, with the worst outcomes in the CNI-free arm[a] – At the 3-year follow-up, these differences had reduced over time and were often not significant, but many patients were switched from sirolimus and cyclosporine to tacrolimus
Large meta-analysis of 56 randomized clinical trials	11 337 renal transplant recipients	– Patients were treated with three different early CNI-sparing strategies: CNI avoidance, CNI minimization and the delayed introduction of CNIs	– The use of mTORi, in combination with MMF and no CNIs, increased the odds of graft failure (OR, 1.43; 95% CI, 1.08-1.90; $P = 0.01$) – CNI-sparing strategies were associated with fewer cases of DGF (OR, 0.89; 95% CI, 0.80-0.98; $P = 0.02$), improved graft function, and fewer cases of new-onset diabetes
DIAMOND study (multicenter, 24-week, randomized study)	857 liver transplant recipients	Patients were treated with: – Prolonged-release tacrolimus (initial dose 0.2 mg/kg/day) + MMF Or – Prolonged-release tacrolimus (0.15-0.175 mg/kg/day) + basiliximab + MMF Or Prolonged-release tacrolimus (0.2 mg/kg/day delayed until Day 5) + basiliximab + MMF	Lower-dose prolonged-release tacrolimus capsules (initially 5-15 ng/mL, then 4-12 ng/mL after 3 months)[b], administered with MMF and basiliximab immediately posttransplant, was associated with a significant renal function benefit and a significantly lower incidence of BCAR, compared with a higher-dose (5-15 ng/mL until day 42 then 5-12 ng/mL) prolonged-release tacrolimus-based regimen

[a] The actual levels in the low-dose arm were at the top of the target range (approximately 7 ng/mL, rather than 3-7 ng/mL).
[b] As per the Advagraf (tacrolimus prolonged-release hard capsules) license recommendations, it is necessary to consider the clinical condition of the patient when interpreting whole blood levels. In clinical practice, whole blood trough levels have generally been in the range of 5-20 ng/mL in liver transplant recipients and 10-20 ng/mL in kidney transplant patients in the early posttransplant period. During subsequent maintenance therapy, blood concentrations have generally been in the range of 5-15 ng/mL in liver and kidney transplant recipients.
BCAR, biopsy-confirmed acute rejection; ELITE, Efficacy Limiting Toxicity Elimination.

trough levels greater than 5 ng/mL (categories, 5-6.9 ng/mL, 7-9.9 ng/mL, ≥10 ng/mL; $P < 0.001$). Long-term data from the CTS also showed that maintaining tacrolimus trough levels at ≥5 ng/mL versus <5 ng/mL[b] had a beneficial effect on renal function over 5 years of treatment.[36] The Symphony study confirmed that patients with a mean tacrolimus trough level of 6.4 ng/mL at year 1 and 6.5 ng/mL at year 3 had better allograft survival compared with patients in the standard-dose cyclosporine, or low-dose sirolimus treatment groups.[177]

In liver transplantation, current clinical opinion suggests optimal target trough levels are 6 to 10 ng/mL in the first month posttransplant, decreasing to 4 to 8 ng/mL[b] (except in combination with mTORi) after the first month. This consensus is backed up by a systematic review and meta-analysis of 64 studies (32 randomized controlled, 32 observational), published in 2013, which found that tacrolimus trough concentrations of 6 to 10 ng/mL in the first month posttransplant led to a twofold reduction in renal impairment, with no increase in TCMR.[158] A further study investigating tacrolimus exposure within the first 15 days after liver transplantation found that patients with trough levels greater than 7 ng/mL experienced less moderate/severe rejection compared with patients with trough levels less than 7 ng/mL over an approximate 7-year follow-up.[117] Although lower tacrolimus trough levels are still sometimes used as a target within real-world clinical practice,[158] this is in contrast to some clinical guidelines, regulatory authority and pharmaceutical industry recommendations which only support target tacrolimus trough concentrations of greater than 10 ng/mL in the first 6 weeks after liver transplantation.[117]

Factors suggesting an increased need for immunosuppression include original indication for transplant (autoimmune liver diseases such as autoimmune hepatitis, primary sclerosing cholangitis (PSC), or primary biliary cholangitis) and retransplant for rejection.[182,183]

The level of immunosuppression required is usually greater than for those grafted for hepatocellular carcinoma (HCC), alcohol or hepatitis B virus (HBV)-related liver disease.[184] For those grafted for HCV, where there is ongoing viral replication, higher levels of immunosuppression are related to increased viral replication, so the clinician must balance the need to prevent rejection (as high-dose antirejection immunosuppression will greatly enhance viral replication and graft damage) and the need to maintain a low burden of immunosuppression.[184,185] Other factors that are associated with a greater need for immunosuppression include those with greater variation in drug levels. Optimal

[b] *As per the Advagraf (tacrolimus prolonged-release hard capsules) license recommendations, it is necessary to consider the clinical condition of the patient when interpreting whole blood levels. In clinical practice, whole blood trough levels have generally been in the range of 5-20 ng/mL in liver transplant recipients and 10-20 ng/mL in kidney transplant patients in the early posttransplant period. During subsequent maintenance therapy, blood concentrations have generally been in the range of 5-15 ng/mL in liver and kidney transplant recipients*

target trough levels for those liver allograft recipients on combination therapy remain unclear.

Despite the lack of data on immunosuppression-minimization strategies in liver transplantation, complete immunosuppression withdrawal has shown to be feasible in approximately 20% of carefully selected liver transplant recipients.[159] These patients are generally older, with a longer time posttransplant,[159] not transplanted for autoimmune diseases and with no evidence of rejection at the time of immunosuppression withdrawal.

In a retrospective study of 78 patients (mean age, 53 years), with a median time from liver transplant to drug conversion of 12 months, switching from a CNI-based immunosuppression regimen to a CNI-free mTORi regimen (everolimus or sirolimus) improved renal function. The rejection rate (5.1%) was similar compared to patients maintained on the CNI-based regimens.[186] However, to fully elucidate long-term outcomes of these strategies, large clinical trials on CNI minimization and withdrawal are needed.[159,187]

In a prospective multicenter study, of 500 screened liver transplant recipients, 102 were enrolled into a withdrawal trial. Of these, 41 were found tolerant, 57 developed acute rejection 6.44 months after the start of drug minimization (standard deviation, 4.37; range, 1.28-21.35). On liver biopsy 1 year after weaning of immunosuppression, portal inflammation, interface hepatitis and lymphocytic cholangitis were found more frequently. These changes, however, were mild and could no longer be observed 3 years after drug discontinuation. Macrovesicular steatosis was also found with further progression (up to 20%; $P < 0.001$) over time. Despite many limitations, this very interesting study has showed that weaning of immunosuppression could be feasible in a minority of carefully selected patients long term after transplantation.[164]

Strategies for Prevention of Underimmunosuppression

In kidney transplantation, it is important to stratify patients according to their immunological risk.

Higher risk patients include those who[188]:

- Are sensitized from previous blood transfusions or previous transplant
- Had successive pregnancies
- Present with HLA-DR mismatch
- Panel reactive antibody (PRA) above 0%, and preformed DSAs
- Younger age at time of transplant
- Recipients of black ethnicity

A standard CNI protocol is generally advisable in these patients,[188] with target trough levels of tacrolimus between 5 and 10 ng/mL and concomitant use of azathioprine, mycophenolate or corticosteroids.

In liver transplantation, although it is easier to reverse the effect of underimmunosuppression compared with the adverse effects of overimmunosuppression, defining and adhering to the appropriate target levels for immunosuppressive regimens should remain a priority.

There is also a strong unmet need for pharmacodynamic biomarkers that reflect the biological effect of the immunosuppressive regimen to guide dosing in individual patients. An immune function assay, investigated in a liver transplant RCT, has shown additional benefits for optimizing immunosuppression and improving patient outcomes.[189]

It is important to take into account that the "how low can you go" immunosuppression considerations of the past 10 years,[160] have now shifted toward the need to maintain immunosuppression at a certain minimum level.

Recommendations for Managing Underimmunosuppression in Kidney Transplantation

1. Determine pretransplant risk factors and immunological risk status for each patient before transplantation. *(Level 1)*

> **Pretransplant risk factors, including patients with a "higher risk" immunological risk status[188]**
>
> - Sensitized from previous blood transfusion(s), previous transplant, or pregnancies
> - HLA mismatch (particularly HLA-DR mismatch)
> - PRA >0% (HLA antibodies)
> - Preformed HLA-DSA
> - Younger age at time of transplant
> - Adolescents are at higher risk of nonadherence
> - Black recipient ethnicity
> - Previous graft loss as a result of immunological reasons

2. Take into account both the risks and the benefits to each individual patient when determining their immunosuppressive regimen and optimal trough levels. Consider the following: *(Level 2 or Level 3)*
   - ○ Aim for tacrolimus target trough levels of 5 to 10 ng/mL in the first year after transplantation *(Level 1)*
3. Identify patients potentially at higher risk of underimmunosuppression, including young patients, adolescents and patients who have previously lost a graft due to immunological causes. *(Level 1)*
   - ○ For higher risk patients, consider induction therapy *(Level 1)*
   - ○ The standard CNI protocol is generally advisable in higher risk patients with trough target levels of tacrolimus between 5 and 10 ng/mL and concomitant use of azathioprine, mycophenolate or corticosteroids *(Level 5)*
   - ○ Monitor nonadherence and the development of adverse events (for recommendations on nonadherence, please see the relevant chapter)
4. Discourage minimization of immunosuppression unless there is a convincing reason (eg, polyomavirus-associated nephropathy), due to the increased risk of TCMR and AMR. Any minimization strategies involving CNI reduction, avoidance or late conversion should be carefully evaluated in each patient and the risks and benefits weighed. *(Level 1)*

Recommendations for Managing Underimmunosuppression in Liver Transplantation

1. Take into account both the risks and the benefits to each individual patient when determining their immunosuppressive regimen and optimal trough levels. Consider the following: original liver disease, overall status (age, nutritional status, tumor history, infection status, etc.) and transplant history (other organ transplantation, causes of graft loss). *(Level 3)*

2. After transplantation, avoid underimmunosuppression (tacrolimus trough levels <6 ng/mL in the absence of induction agents, other immunosuppressive agents or mTORi). *(Level 1)*
3. a) Aim for tacrolimus target trough levels of 6 to 10 ng/mL in the first month after transplantation, reduced to 4 to 8 ng/mL[c] in the maintenance phase after the first month *(Level 1)*
   b) For combination therapy, lower tacrolimus trough levels (4-12 ng/mL)[c] are acceptable with MMF, mTORi, and basiliximab induction therapy *(Level 2)*
   c) For combination therapy where tolerability/toxicity is an issue, lower tacrolimus trough levels are acceptable. *(Level 4)*
4. Maintenance steroids are generally unnecessary for the avoidance of TCMR in liver transplantation. In most scenarios, steroids can be safely withdrawn within the first 6 months after liver transplant. *(Level 1)*
5. Withdrawal of immunosuppression after liver transplantation should be confined to a research environment under strict clinical and histopathological surveillance protocols. *(Level 3)*

ADVERSE EFFECTS RELATED TO IMMUNOSUPPRESSION IN KIDNEY AND LIVER TRANSPLANTATION

Problem to be Addressed

Kidney transplant recipients and the vast majority of liver transplant recipients require lifelong immunosuppression to maintain graft integrity. However, immunosuppressive agents inhibit the immune system beyond the alloimmune response, particularly when immunosuppression levels are high. This results in adverse effects, including generic effects (eg, increased risk of infections and certain cancers), class effects (eg, renal impairment with CNIs), and drug-specific side effects.[190,191] The clinical impact of toxicities associated with immunosuppression has led to the concept of minimization of immunosuppression and combination of drugs in low concentration.[192] This is discussed further in the underimmunosuppression section.

In the absence of early biomarkers of overimmunosuppression, HCPs are therefore faced with maintaining the delicate balance of suppressing the immune response to prevent graft rejection, and avoiding unnecessarily high levels of immunosuppression.[193,194] Therapeutic drug monitoring of trough levels is performed; however, trough levels only provide an indirect measure of immunosuppression. Overimmunosuppression is often late to be identified, generally after the diagnosis of related adverse effects.[192] Although the reduction of immunosuppression is common practice in patients with infection or neoplasm, there are no clear guidelines on how modification of the immunosuppressive regimen should be managed for the different types of adverse events. Risk stratification, preventative measures and early detection of adverse events in liver and kidney transplant recipients are therefore paramount for graft and patient survival.

Immunosuppression can lead to poorer patient and graft survival by increasing the risk of fungal, bacterial, or viral infections (eg, Epstein–Barr virus [EBV], cytomegalovirus [CMV], polyomavirus, human herpes virus), development of certain malignancies, renal insufficiency, cardiovascular risk and metabolic complication.[193-195] Infections occur more commonly during the first year of transplant, when immunosuppression levels are highest (Figure 9).[193,195]

On the other hand, malignancies (other than post-transplant lymphoproliferative disease [PTLD]) tend to occur after the first year of transplantation, presumably due to cumulative immunosuppression.[193] The 2010 study by Collett et al[196] compared the incidence of malignancy in solid organ transplant recipients with the general population in the United Kingdom, using standardized incidence ratios matched for age, sex, and time period. The study showed the 10-year incidence of de novo cancer in transplant recipients is twice that of the general population, with the incidence of non-melanoma skin cancer being 13 times greater.[196] Risk factors for malignancies vary for different tumor types, with the development of some cancers being linked to viral infections.[193] In liver transplant recipients, de novo neoplasms are one of the most common causes of late mortality.[197]

Certain biomarkers associated with risk of infection, such as low levels of IgG,[198] complement C3 fraction,[199] mannose-binding lectin levels,[200] or low CD4- and CD8-positive T-cell counts,[201] may eventually provide a role in helping to predict infection in liver and kidney transplant recipients.[198,202] Two assays have been developed in this field. The Cylex ImmuKnow Cell Function Assay measures T-cell function by the release of adenosine triphosphate from CD4-positive lymphocytes in culture after a mitogenic stimulus.[203] The T-cell IFN-γ enzyme-linked immunospot (ELISPOT) assay quantifies memory T-cells in peripheral blood that respond to donor HLAs or CMV antigens.[204] The clinical utility of both these biomarker assays in clinical practice is yet to be determined.

Kidney Transplantation

Overimmunosuppression and Infection

Increased risk and severity of infection are explained by many factors, including the recipient's condition, such as surgical complications, or the use of indwelling catheters; the possibility of transmission of infection from donor to recipient; overimmunosuppression; active smoking; and obesity, etc.[205] Viral infections, which occur more frequently during the first few months after transplantation, are most likely in the context of greater immunosuppression.[195,204,206-208] Furthermore, recipient age is often a significant risk factor for bacterial infections, but not viral/fungal infections.[209] Type of immunosuppressive agent such as use of induction therapy with antithymocyte globulin is also associated with viral infections.[195]

Common viral infections in kidney transplantation

- Cytomegalovirus
- Polyomavirus
- Epstein–Barr virus
- Human herpes virus (HHV-6, HHV-8)
- Varicella-zoster virus

Polyomavirus-associated nephropathy (PVAN) is probably the most specific infectious complication after kidney transplantation, indicating clinical overimmunosuppression.[204,210]

[c]*As per the Advagraf (tacrolimus prolonged-release hard capsules) license recommendations, it is necessary to consider the clinical condition of the patient when interpreting whole blood levels. In clinical practice, whole blood trough levels have generally been in the range of 5-20 ng/mL in liver transplant recipients and 10-20 ng/mL in kidney transplant patients in the early posttransplant period. During subsequent maintenance therapy, blood concentrations have generally been in the range of 5-15 ng/mL in liver and kidney transplant recipients.*

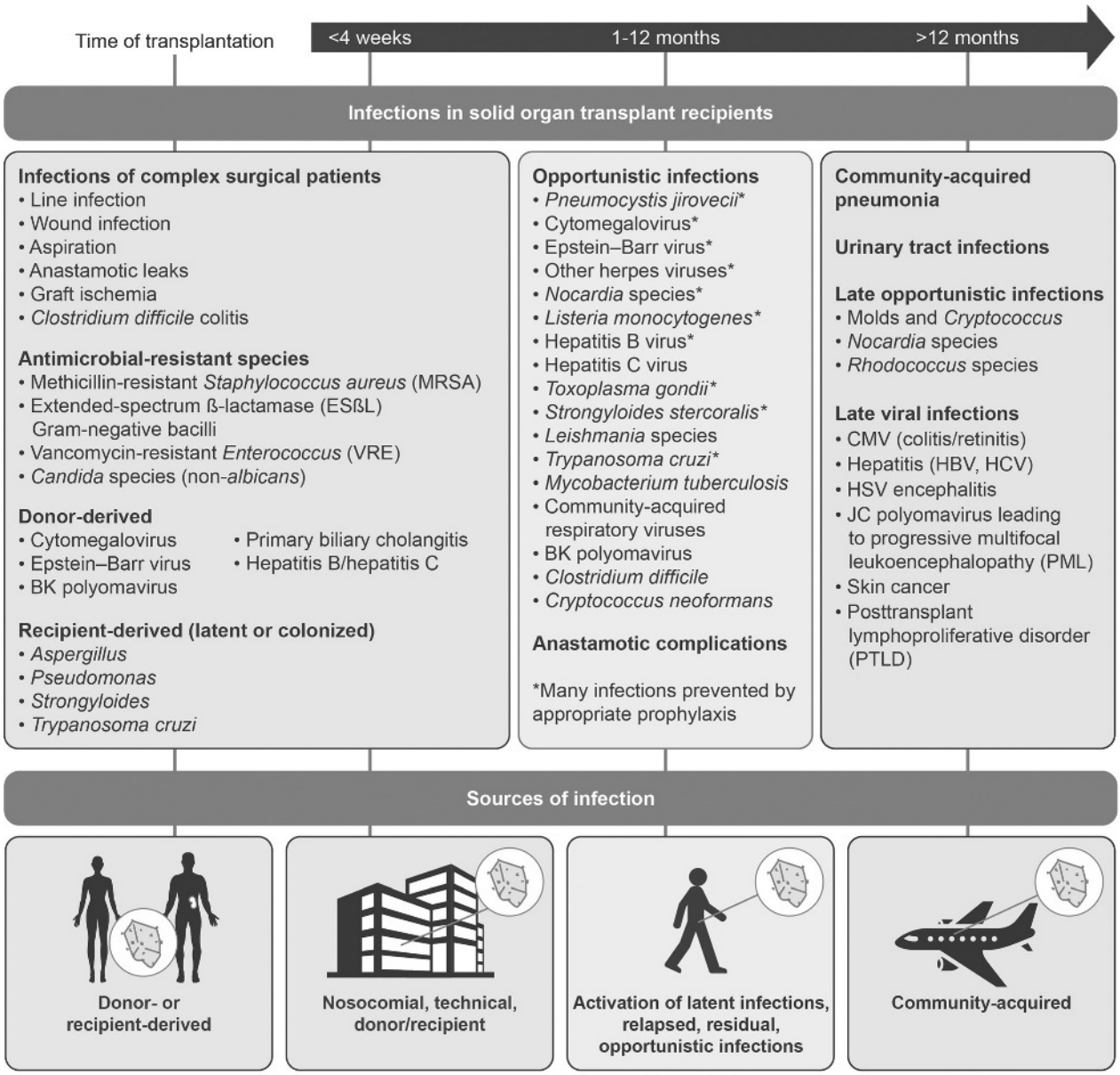


FIGURE 9. Infections in solid organ transplant recipients. The timeline of infections after organ transplantation. The risk for infection after organ transplantation follows a standard pattern with routine immunosuppression and infectious exposures. The potential pathogens for which the risk is modified by prophylaxis, including vaccinations and antimicrobial agents, are indicated (*). Individual risk is modified by events such as surgery, treatment of graft rejection, or malignancy. Note that graft rejection and drug reactions may be among noninfectious causes of fever in transplant recipients. JC virus, John Cunningham virus; HSV, herpes simplex virus. Modified with permission from the author; reprinted with permission from Fishman JA. Opportunistic infections – coming to the limits of immunosuppression? *Cold Spring Harb Perspect Med*. 2013;3:1–14; original source of data: Fishman J. Infection in solid-organ transplant recipients. *N Engl J Med*. 2007;357:2601–2614. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.[195,205]

Figure 10 shows the screening and management of kidney transplant recipients for human BK polyomavirus, the major cause of PVAN, which puts 1% to 15% of kidney transplant patients at risk of premature allograft failure.[211]

The relationship between bacterial infection and overimmunosuppression is well established. However, in many cases there are additional identifiable risk factors for bacterial infection, including surgical complications, intravenous or urinary catheters, urinary retention or vesicoureteral reflux.[195,205,212] Patients with a tuberculin purified protein derivative-positive skin test or a positive IFN-γ release assay for tuberculosis (TB) before transplantation are also at increased risk of *Mycobacterium tuberculosis* infection after transplantation.[213,214]

Prophylaxis is an efficient strategy to prevent some common posttransplant infections, such as TB, CMV and the fungal infection *Pneumocystis jirovecii*, more closely associated with high steroid exposure.[195] Ganciclovir or valganciclovir prophylaxis can prevent CMV infections. Prophylaxis of CMV infection also prevents secondary events such as acute allograft rejection or other opportunistic

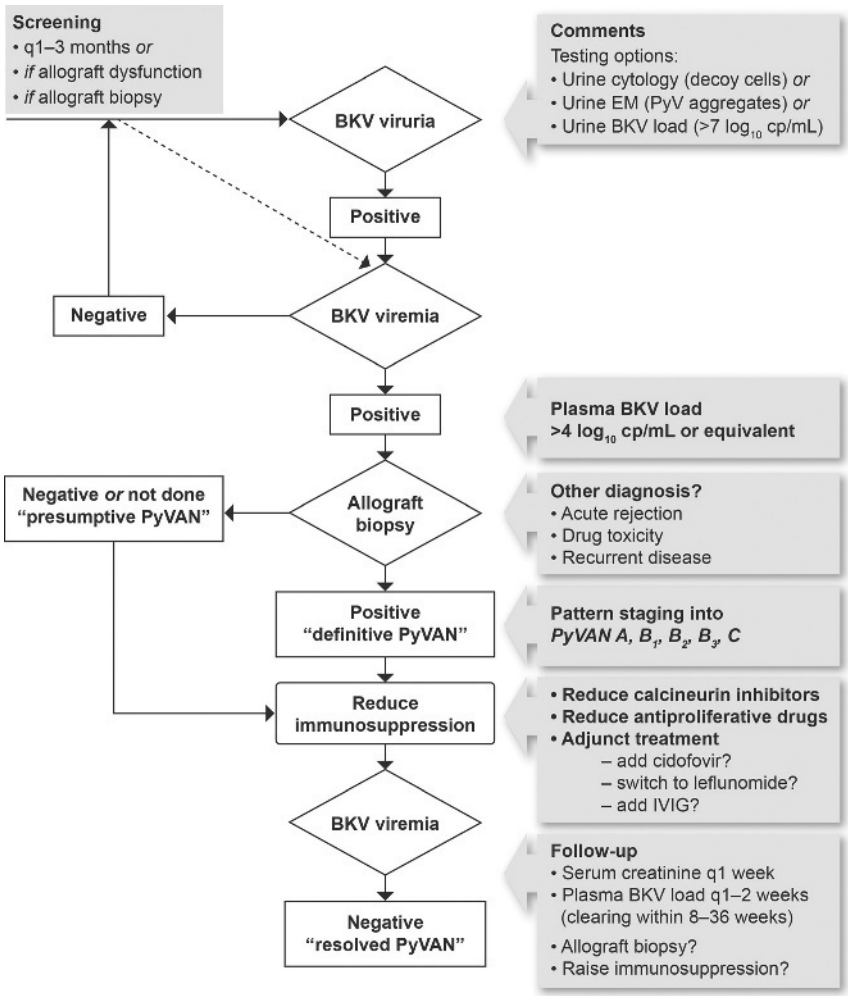


FIGURE 10. Screening and management of kidney transplant recipients for BKV replication and PVAN. BKV, BK virus; EM, electron microscopy; IVIG, intravenous immunoglobulin. Reprinted with permission from Hirsch HH, Randhawa P. BK polyomavirus in solid organ transplantation. *Am J Transplant*. 2013;13(Supp. 4):179–188.[211]

infections. Trimethoprim-sulfamethoxazole, administered to prevent *Pneumocystis jirovecii*, also decreases the rate of urinary infections after transplantation.[195,205]

In patients with subclinical or clinical infections, especially viral infections, reduction of immunosuppression favors an immune response against microorganisms.[205] Treatment with mTORi is associated with a reduced incidence of posttransplant CMV infection.[215] Although, this effect has led to suggestions that CMV prophylaxis may not be necessary, this needs to be explored further.[216-218] Similarly, some reports suggest that mTORi regimens have a lower incidence of PVAN.[219]

Overimmunosuppression and Cancer

The risk of cancer is increased after kidney transplantation; the relationship between cancer incidence and immunosuppression depends on the type of cancer, the immunosuppressive burden, and time posttransplant. The Standardized Incidence Ratios (SIR) for the most common malignancies in kidney transplant recipients include: Kaposi's carcinoma (17.1), nonmelanoma skin cancer (16.6), and cancer of the lip (65.6).[196]

Certain immune characteristics in the recipient, such as an increased number and proportion of regulatory T-cells, may prove to be useful in stratifying cancer development after transplantation.[220] Prevention and screening for cancer, such as gynecological and breast cancer, and prostate cancer, should follow the same recommendations as for the general population.[221] Studies have shown that the clinical benefit of colorectal cancer screening in patients with functioning kidney transplants may well be equivalent to the benefit found in the general population.[222]

Decreasing immunosuppression is common practice in kidney transplant patients with cancer; however, this is associated with an increased risk of graft rejection.[223] An mTORi with antineoplastic properties can be used for reducing the occurrence of new cancers and preventing cancer recurrence in allograft recipients who received allografts for renal cell carcinoma,[174] and is effective in Kaposi's sarcoma[224] and nonmelanoma skin cancer.[225] In kidney transplant recipients, further trials of mTORi are ongoing in secondary prevention of nonmelanoma skin cancer[226,227]; there is evidence in these patients for mTORi in the reduction of de novo cancer incidence.[228]

Liver Transplantation

Overimmunosuppression and Infection

Invasive fungal infection is associated with high morbidity and mortality in liver transplant recipients,[229,230] with candidiasis, aspergillosis and cryptococcosis respectively being the most common fungal infections.[229] It is important to

screen liver transplant candidates, if admitted to the intensive care unit (ICU) pretransplant, for fungal colonization, to determine whether targeted pretransplant or posttransplant antifungal prophylaxis is required.[230] The improvement of perioperative and postoperative care, modification of immunosuppression, use of prophylactic measures such as trimethoprim-sulfamethoxazole against pneumocystic pneumonia, and fluconazole in high-risk patients waiting for a liver graft in the ICU, have led to a reduction in invasive fungal infections postliver transplant.[205,230]

CMV infection is also common postliver transplant.[231] Prophylaxis with valganciclovir in high-risk patients (CMV-seropositive donors in CMV-seronegative recipients) improves outcomes.[232] It has also been suggested that mTORi may decrease the incidence of CMV infections; however, more studies are required.[233]

Recurrence of HBV infection is almost universal after liver transplantation without hepatitis B immunoglobulin (HBIg) prophylaxis. All HBV-positive patients undergoing transplantation for HBV-related end-stage liver disease and active viral replication should be treated before transplantation with a potent nucleos(t)ide analog that has a high barrier to resistance.[234] Nucleos(t)ide analogs in combination with HBIg have shown a reduction in the risk of graft infection to less than 10%.[234,235] Also, entecavir prophylaxis without HBIg is proven to be clinically well tolerated and an effective option for the prevention of HBV recurrence.[236] Monitoring of renal function should be regularly performed if nucleos(t)ide analogs are used.

Liver disease attributed to chronic HCV infection is a common indication for liver transplantation in Europe.[237] Recurrence of chronic HCV infection postliver transplantation is universal in recipients with detectable HCV RNA and it is a risk for graft loss and poor patient survival due to rapid progression to cirrhosis or fibrosing cholestatic hepatitis.[237,238] Prophylaxis with direct-acting antiviral agents has revolutionized HCV recurrence therapy in liver transplant recipients, showing high sustained virological response rates, shorter treatment duration and reduced adverse events compared with interferon- and ribavirin-based therapies.[237] In general, it is mandatory to check for potential interactions with immunosuppressive drugs in all transplant patients before starting antiviral therapy.

Overimmunosuppression and Cancer

De novo neoplasms are one of the most common causes of late mortality in liver transplant patients (cumulative incidence of 34.7% at over 15 years postliver transplant versus 8.9% in the nontransplanted population), and typically associated with male sex and patients aged >34 years.[197] The most common malignancies directly related to immunosuppression are nonmelanoma skin cancers and PTLD (Table 6).[239]

Patients with a history of alcohol abuse and smoking have a high risk of upper gastrointestinal, oropharyngeal-laryngeal and lung cancers.[239] Patients transplanted for PSC and inflammatory bowel disease (IBD) are at an increased risk for colorectal carcinoma.[239]

HCC is a leading indication for liver transplantation.[240] With the improved selection criteria and preoperative bridging therapies available, the HCC recurrence rate at 5 years postliver transplant, which is fatal in the majority of patients within 1 year after diagnosis, is now at an acceptable level (<20%).[240] Challenges still remain, however, in determining the type and dose of immunosuppressive therapy posttransplant to further reduce HCC recurrence and improve its prognosis. CNIs in general are reported as having direct prooncogenic activity[241]; high levels of cyclosporine (>300 ng/mL) and tacrolimus (>10 ng/mL) have been associated with an increased risk of HCC recurrence.[242]

mTORi have antiangiogenic and antiproliferative properties.[243] One recent randomized, phase 3 open-label study has shown that sirolimus in liver transplant recipients with HCC does not improve long-term (5-year) recurrence-free survival, but there may be some benefit in the first 3 to 5 years, especially in low-risk patients.[244] Although some studies suggest that T-cell antibody induction may have a negative effect in terms of neoplasm development, a systematic review found no differences in the development of malignancies or HCC recurrence versus placebo.[245] As such, chronic maintenance immunosuppression might play a more important role than short intense periods of immunosuppression.

Managing cancer risk posttransplant remains challenging. Despite the increased risk of malignancies, tumor screening programs are not validated in the liver transplant setting.[221] Findings from the National Lung Screening Trial Research Team highlight that screening high-risk individuals with low-dose computed tomography reduces mortality from lung cancer in the general population[246]; this may prove to be beneficial in high-risk liver transplant recipients (with a history of, or still smoking).

In liver transplantation, accepted tumor surveillance options include yearly colonoscopies in patients with PSC and IBD, as well as annual skin examinations in all patients.[239,247]

Renal Impairment

There is some evidence that a link exists between the use of CNIs and renal impairment postliver transplant.[248,249] However, CNIs remain necessary to prevent rejection ≤1 year postliver transplant.[37] A long-term beneficial effect on renal function can be achieved by combining reduced-dose CNIs with non-nephrotoxic immunosuppressive agents early after liver transplantation.[248,250] Interventions later on are less successful,[114] therefore, a preferable approach is early

TABLE 6.

Risk factors associated with common malignancies postliver transplantation

Cancer type	Risk factors
Nonmelanoma skin cancers	Age >40 years, male sex, skin type, sun exposure, smoking and previous alcohol abuse
PTLD	Age >50 years and EBV infection
Head and neck or lung cancers	History of alcohol abuse and smoking
Colorectal carcinomas	PSC and IBD

Table based on data from Chak and Saab, 2010.[239]

postoperative reduction of tacrolimus (≥50%) in association with MPA or everolimus.[248,250,251] In the case of everolimus, this results in a significantly better renal function at 2 years after transplantation.[250] Started after 1 year postliver transplant, MMF combined with CNI reduction still can improve renal function.[251] The randomized controlled DIAMOND study (Figure 8) showed that an initial lower dose prolonged-release tacrolimus capsules regimen, or the delayed initiation (Day 5) of the higher dose prolonged-release tacrolimus capsules regimen (together with MMF and basiliximab), was associated with significant improvement in renal function at 6 months, compared to the prolonged-release tacrolimus-based regimen administered at a higher initial dose immediately after transplantation.[178] A recent nonrandomized study showed that conversion from immediate-release to prolonged-release tacrolimus >1 month postliver transplantation limits the increase in serum creatinine concentrations.[114]

It is generally accepted that methods based on serum creatinine for the detection of kidney dysfunction underestimate the extent of renal impairment in transplant recipients. As such, limited effective interventions are available by the time an elevation in serum creatinine levels is detected. There is, therefore, a need for timely intervention and early and sensitive indicators to detect CNI-related nephrotoxicity. Cystatin C-based calculations have been shown to be superior in estimating glomerular filtration rate (GFR) compared with creatinine-based estimations; however, GFR is still underestimated using this method in patients with low GFR.[252]

Strategies to reduce the risk of renal impairment postliver transplantation

1. Induction therapy with reduced or delayed initiation of prolonged-release tacrolimus capsules combined with MMF and basiliximab
2. Early after liver transplantation combination of low-dose CNI with MMF or everolimus

Metabolic Syndrome

Metabolic syndrome is highly prevalent after liver transplantation, with an incidence of 50% to 60% in liver transplant recipients. Therefore, liver transplant recipients are at a high risk of cardiovascular complications—ranging from approximately 10% at 5 years to up to 25% at 10 years.[238] As a priority, all elements of metabolic syndrome should be treated, including arterial hypertension, hyperlipidemia, diabetes mellitus and obesity.

Conversion from CNIs to mTORi increases the incidence of diabetes mellitus and arterial hypertension postliver transplant.[253,254] Moreover, compared with CNIs, mTORi are associated with a higher incidence of dyslipidemia.[174] On the other hand, the results from several studies suggest a reduced weight gain with mTORi versus CNIs.[255]

Recommendations for the Management and Prevention of Adverse Effects Related to Immunosuppression in Kidney Transplantation

1. Patients with a positive purified protein derivative skin test or a positive IFN-γ release assay for TB should receive prophylaxis (isoniazid for 9 months). *(Level 3)*
   - Advocate TB prophylaxis in patients of Indian subcontinent origin *(Level 5)*
2. Prophylaxis (trimethoprim-sulfamethoxazole) should be given to all patients during the first 6 months after kidney transplantation to prevent *Pneumocystis jirovecii* infection, and in patients treated with mTORi, the duration of prophylaxis could be extended. *(Level 1)*
3. Prophylaxis for CMV infection with valganciclovir should be given for 6 months in recipient-negative/donor-positive (R-/D+) renal transplant patients, for 3 months in D+ patients, or as a preemptive strategy based on nucleic acid amplification testing. *(Level 1)*
4. BK viremia should be regularly monitored (at least every 3 months) during the first 24 months. *(Level 2)*
5. In patients with consistent BK viremia (presenting 2 consecutive positive determinations), consider step-wise reduction of immunosuppression and renal biopsy. *(Level 3)*
6. In patients with persistent BK viremia and increasing proteinuria and/or deterioration of renal function, a renal biopsy is indicated to confirm pathology. *(Level 3)*
7. Prevention and screening for cancer should follow the same recommendations as for the general population (eg, gynecological, breast, prostate or colon cancer screening). *(Level 5)*
8. Self-examination by patient and annual dermatological examination (by the primary care physician or dermatologist) are recommended for the early detection of skin cancer. *(Level 3)*
9. Yearly abdominal ultrasound examination is recommended for the detection of intra-abdominal tumors, especially cancer of the native kidneys. *(Level 5)*
10. Patients:
    - With Kaposi's sarcoma should be switched to an mTORi when possible *(Level 1)*
    - With nonmelanoma skin cancer, the use of mTORi should be considered in the individual patient by weighing up the risks and benefits *(Level 2)*
11. Immunosuppression reduction in patients with cancer should be balanced, taking into consideration the prognosis of cancer, the type of antineoplastic therapy and the risk of rejection. *(Level 4)*

Recommendations for the Management and Prevention of Adverse Effects Related to Immunosuppression in Liver Transplantation

1. Liver transplant recipients surviving post-1 year after transplantation should be monitored every 3 months for the first 5 years then at least every 6 months, or when complications develop for evidence of unwanted side effects of immunosuppression, such as:
   - Renal impairment *(Level 1)*
   - Development of skin cancer and PTLD *(Level 1)*
   - New onset of diabetes, obesity, arterial hypertension and hyperlipidemia *(Level 1)*
2. Liver transplant recipients should be screened annually for malignancies:
   - Annual dermatological screening (by the patient and the primary care physician or dermatologist) regardless of age *(Level 3)*
   - Annual colonoscopies should be performed in patients receiving liver transplants for PSC who also have IBD *(Level 3)*
   - Liver transplant patients should be encouraged to adhere to established population screening programs for common malignancies in the general population *(Level 3)*

3. The type of immunosuppressive regimen to be used is dependent on the patient's situation:

   - mTORi-based immunosuppression can be used for secondary prevention of squamous cell carcinoma of the skin or treatment of Kaposi's sarcoma based on the kidney transplant experience *(Level 4)*
   - CNI-based immunosuppression is preferred over mTORi in patients at risk of developing dyslipidemia *(Level 2)*
   - Decline of renal function postliver transplant can be reduced by:
     - Using a combination of reduced-dose CNIs with mTORi or mycophenolate *(Level 1)*
     - Conversion from immediate-release to prolonged-release tacrolimus capsules *(Level 3)*

4. Routine screening and vaccination should be conducted for pneumococcal and influenza viruses. *(Level 4)*

IMPACT OF ANTIHUMAN LEUKOCYTE ANTIGEN DSAs IN KIDNEY AND LIVER TRANSPLANTATION

Problem to be Addressed

The presence of de novo donor-specific anti-HLA antibodies after kidney transplantation is well documented.[256,257] Improvements in immunological tools to detect anti-HLA antibodies using single-antigen bead technology have highlighted that up to 20% of kidney transplant recipients develop DSAs after kidney transplantation.[180,256,257] DSAs can cause acute AMR, chronic AMR, vascular AMR and decreased kidney allograft survival.[256] Kidney allograft survival is also affected by the complement-binding ability of DSAs, with complement-binding DSAs (C1q or C3d) being associated with lower kidney allograft survival compared with noncomplement-binding DSAs.[258,259] IgG3 DSAs are also associated with a significantly increased risk of graft loss compared with nonIgG3 DSAs.[260] Although several strategies use apheresis and/or B-cell-blocking drugs and/or complement-blocking drugs to treat acute and chronic AMR, unfortunately there is still no established effective therapy in this setting.[180,261]

Whereas both acute and chronic AMR have also been described extensively after heart, lung and pancreas transplantation,[262] the incidence and consequences of DSAs after liver transplantation are less well established.[40] Liver transplant recipients were considered to be resistant to DSAs, so neither the presence of preformed DSAs or de novo DSAs was considered in the routine management of these patients.[263] Difficulties in characterizing acute AMR, a lack of a clear definition for chronic AMR,[181,264] and the lack of specificity of markers of complement activation (eg, C4d immunostaining) are some of the challenges in evaluating the role of DSAs in liver transplantation.[263] A large retrospective study has suggested an incidence of de novo DSAs at 1 year postliver transplant of 8%.[39] While DSAs are now identified as a risk factor for graft rejection and are detrimental to patient survival, the full impact of DSAs postliver transplant remains to be fully elucidated.[41]

For clarity, this section describes evidence for the impact of DSAs in kidney transplantation and current knowledge on the impact of DSAs in liver transplantation.

Impact of Anti-HLA DSAs in Kidney Transplantation

Risk Factors for the Development of DSAs

Risk factors for the development of DSAs after kidney transplant are classified according to their detectability and clinical factors.

Slightly Modifiable or Nonmodifiable Contributors to DSA Occurrence

The age of the recipient (younger, usually <50 years) has been identified as a risk factor for de novo DSAs—potentially attributable to nonadherence.[180] In addition, there is evidence that the risk of development of de novo DSAs is greater for deceased-donor recipients, and increased by the presence of non-DSA antibodies before transplantation.[265] An increased number of HLA mismatches are also associated with the occurrence of DSAs.[257] Although kidney allocation algorithms aim to reduce HLA mismatches, complete matching is not often feasible and the benefits of donor/recipient HLA matching have to be balanced against other issues, such as waiting time. Early TCMR has been linked with the risk of development of de novo DSAs.[266] In a study of 315 consecutive renal transplants without pretransplant DSAs, there was a strong trend towards clinical rejection before de novo DSA onset.[257] Further risk factors for the development of de novo DSAs include

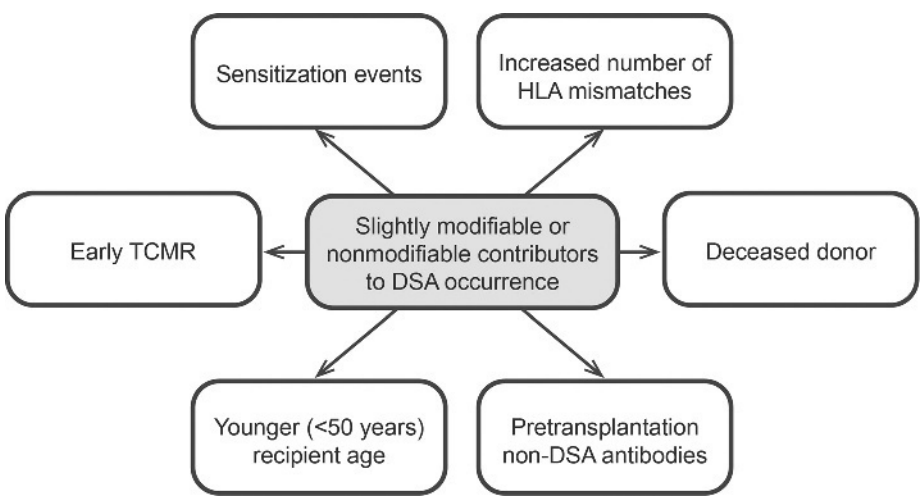


FIGURE 11. Slightly modifiable or nonmodifiable contributors to DSA occurrence.[180,257,265-267]

TABLE 7.

Highly modifiable risk factors for de novo DSAs[20,270,273]

Cause of de novo DSA	Study
Reduction or discontinuation of CNI therapy	Registry studies published by Opelz et al report that dose reduction or discontinuation of cyclosporine, tacrolimus, or MPA were associated with reduced graft survival compared with full-dose regimens
CNI-free mTORi-based immunosuppression	In a prospective multicenter study, the incidence of de novo DSAs was 27.2% in everolimus-based immunosuppression without CNIs compared with 4.9% in a CNI-based immunosuppression regimen ($P = 0.001$)
Nonadherence to treatment	A prospective cohort study demonstrated that nonadherence to immunosuppression is a major factor for DSA occurrence and kidney transplant failure

retransplantation, and other sensitization events, such as previous pregnancy.[180,267-269] Figure 11 highlights the slightly/nonmodifiable contributors to DSA formation.

Highly Modifiable Contributors to DSA Occurrence

Reduction or discontinuation of CNI therapy, CNI-free mTORi-based immunosuppression, and nonadherence to treatment are well-established risk factors for the occurrence of de novo DSAs (Table 7).[20,270]

Nonadherence to immunosuppression is a major risk factor for the formation of DSAs.[20] There are many reasons for nonadherence, including side effects and the complexity of treatment (pill numbers, frequency of dosing).[11] More effective educational programs, better engagement of younger recipients, and use of long-acting parenteral immunosuppressive therapies and once-daily drugs can be used to reduce the complexity of immunosuppressive regimens and improve adherence.[74,86,95,271]

The long-term use of belatacept significantly reduces the risk of de novo DSAs compared with cyclosporine A–based immunosuppression.[271] However, it is still not fully clear whether the decreased incidence of de novo DSAs arises from better adherence, the drug's ability to block the second signal and T-cell follicular helper cells, or both factors. Conversion from twice-daily tacrolimus to once-daily prolonged-release tacrolimus capsules intake has significantly improved adherence to therapy, as assessed by electronic monitoring of drug intake.[95] However, it is unknown whether the use of once-daily prolonged-release tacrolimus capsules is associated with a lower incidence of DSAs compared with twice-daily tacrolimus. We are not aware of any prospective comparison of belatacept and tacrolimus regimens on the development of DSAs.[272]

Hence, to improve kidney allograft survival, nonadherence must be reduced. To achieve these goals, minimization strategies and complex immunosuppressive regimens should be avoided.

Detection of DSAs

DSA assessment should be done using solid-phase immunoassay technology.[274] The reactivity of DSA should be determined, and strength of reactivity expressed as mean fluorescence intensity (MFI). Quantification of antibody level is best achieved by titration.[274] Assessment of IgG subclasses is still not recommended. In 2013, the Transplantation Society proposed the following guidelines (Table 8)[274]:

In low-risk patients with stable kidney function, although there are no robust data to support systematic screening for DSAs, it is done in some centers at least once in the first 3 to 12 months after transplantation. After the first year posttransplant it is recommended that at least 1 serum sample is stored each year for patients in all risk categories, with evaluation of current serum in the case of significant change to an immunosuppressive regimen, suspected nonadherence, graft dysfunction, and before transfer to a remote center.[274] Currently, there is insufficient evidence to guide the management of de novo DSAs; however, kidney biopsies can be performed in patients that develop DSAs to optimize immunosuppression,[274] such as targeting higher CNI trough levels, introducing CNIs in patients on a CNI-free mTORi-based regimen, or using B-cell blocking agents.[180,270,273]

TABLE 8.

DSA assessment postkidney transplantation

Risk level	Risk factor	Frequency of monitoring
High-risk patients	Recipients with preexisting DSAs	DSAs should be monitored at least once during the first 3 months posttransplantation and a kidney biopsy should be performed, usually at Month 3
Intermediate-risk patients	Patients who have history of DSAs but are negative for DSAs at transplantation	DSAs should be monitored within the first month posttransplantation
Low-risk patients	Nonsensitized patients receiving a first kidney transplant	Screening for DSAs should be carried out: At least once 3 to 12 months posttransplantation When significant change in maintenance immunosuppression is considered (minimization/withdrawal/conversion) When nonadherence is suspected In cases of graft dysfunction Before transfer to a remote center

Table based on data from Tait 2013.[274]

TABLE 9.

Criteria for the diagnosis of active chronic AMR in liver allografts

Probable chronic active AMR: (all four criteria must be met)	1. Histopathological pattern of injury, both required: a. Otherwise unexplained and at least mild mononuclear portal and/or perivenular inflammation with interface and/or perivenular necroinflammatory activity b. At least moderate portal/periportal, sinusoidal and/or perivenular fibrosis 2. Recent (for example, measured within 3 months of biopsy) circulating HLA DSA in serum samples 3. At least focal C4d-positive (>10% portal tract microvascular endothelia) 4. Reasonable exclusion of other insults (such as low serum complement levels, thrombocytopenia, etc) that might cause a similar pattern of injury
Possible chronic active AMR:	1. As above, but C4d staining is minimal or absent

Table based on data from Demetris 2016.[276]

Liver Transplantation

AMR Postliver Transplant: Histopathological Definitions

The diagnosis of acute AMR should be based on the combination of the following[275]:

1. DSAs in serum
2. Histopathological evidence of diffuse microvascular endothelial cell injury and microvasculitis
3. Strong and diffuse C4d positivity in allograft tissue (if available)
4. Reasonable exclusion of other causes of injury that might result in similar histological findings

A recent report from the Banff group also proposes the following criteria (Table 9) for diagnosis of active chronic AMR in the liver allografts.[276]

Prevalence and Impact of Preformed DSAs on Graft Function and Patient Survival

Pretransplant DSA positivity with potential clinical significance has been tentatively defined as MFI ≥5000, but standardization is still needed.[276]

The prevalence of preformed DSAs according to MFI criteria was investigated in 113 consecutive ABO-compatible liver transplants in a prospectively maintained transplant database. Preformed DSAs were found in 67%, 32%, 25%, 19%, 16% and 9% of liver transplant recipients at MFI cutoffs of 300, greater than 1000, greater than 2000, greater than 3000, greater than 5000 and greater than 10 000, respectively.[277] The MFI cutoff beyond which DSAs may be consistently deleterious to the liver graft is debatable. Recent data suggest that activation of complement is observed more frequently with DSA MFIs greater than 10 000.[278]

Data from 3 studies have shown an increased risk of early acute rejection in patients with pretransplant DSAs,[277,279,280] including in patients with a very low MFI. In addition, a high mortality rate after living-donor liver transplantation (64%; n = 11) was reported in patients with preformed DSAs with MFI greater than 10 000; however, no comparison with a control group, nor adjustment for confounding factors was performed.[278] The presence of anti-class I HLA, but not class II DSAs was associated with a significantly lower adult patient survival at 1, 3, and 5 years post-retransplantation.[281]

A postliver transplant follow-up of preformed DSAs has been investigated in 3 studies.[279,280,282] These studies showed that preformed DSAs, notably anti-class I HLAs, frequently disappeared after liver transplantation; high preliver transplant MFI was associated with high risk of persistence.[279,280] Persistence of preformed anti-class II DSAs with MFI greater than 5000 was associated with an increased incidence of acute cellular rejection, and persistence of preformed anti-class I and/or class II DSAs with MFI greater than 5000 was associated with reduced patient survival.[279,280] Results from other studies suggest that persistence of DSAs with high MFI or a positive cross-match 1 week postliver transplant is associated with an increased risk of severe graft lesions and reduced patient and graft survival.[283,284] Induction immunosuppression may limit the consequences of sensitization in high-risk patients.[284]

Prevalence and Impact of De Novo DSAs on Graft Function and Patient Survival

The incidence of de novo DSAs was reported in a retrospective study of 749 patients.[39] The incidence of de novo DSAs (MFI >5000) at 1 year was 8% and 0.4% for anti-class II and anti-class I, respectively.[39] De novo DSAs had a negative impact on both graft and patient survival, reducing 5-year survival rates by 6% to 7%. Predictors of de novo DSA development included cyclosporine-based immunosuppression (versus tacrolimus) and low CNI trough levels.[39] In an update, presence of IgG3 antibodies, antibody-fixing complement (C1q) and de novo DSAs with MFI greater than 5000 were found to be associated with an increased risk of mortality.[285]

Long-term data on the prevalence of de novo DSAs postliver transplant are scarce. In a cross-sectional study of patients with and without histologically proven chronic rejection (n = 39 each), de novo DSAs were observed in 62% of patients with chronic rejection versus 38% without rejection ($P = 0.047$).[286] The prevalence of de novo DSAs less than 1 year postliver transplant was significantly higher in patients with chronic rejection compared to those without rejection (44% vs 13%; $P = 0.004$).[286] These data indicate that DSA monitoring postliver transplant may be beneficial, especially in patients in whom immunosuppression minimization is a consideration. DSAs should also be monitored in patients presenting with long-term graft dysfunction.

Another area in which DSAs can impact on graft function is liver fibrosis posttransplant. Studies have suggested that, in liver transplant recipients with no obvious cause of fibrosis, or in patients with stable liver graft function, DSAs can promote graft fibrosis posttransplant and can accelerate fibrosis progression in patients with HCV recurrence.[280]

Recommendations for Managing DSAs in Kidney Transplantation

Routine screening for DSAs is neither universally available nor implemented in all centers. Firm conclusions with regard

to the effect on outcomes cannot be drawn in the absence of any proven therapy. The following recommendations may be considered where routine posttransplant DSA screening is undertaken.

1. Low immunosuppression and protocols aimed at minimizing CNI-based immunosuppression (eg, low-dose CNI or CNI-free therapies) are high-risk factors for the development of de novo DSAs; the risk of these regimens should be balanced with the potential benefit to the patient. *(Level 1)*
2. Simplified immunosuppressive therapies that have been shown to enhance adherence should be used in selected high-risk recipients. Refer to nonadherence section of this document. *(Level 2)*
3. Patients should be screened for DSAs in the scenarios below *(Level 1)*:
   - In cases of underimmunosuppression, for example, development of acute cellular rejection or subclinical rejection
   - Suspicion of nonadherence associated with graft dysfunction
4. Solid-phase immunoassay technologies, such as the single-antigen bead assay, are able to identify DSAs not readily detected using other methods, and are, therefore, favored over other DSA detection methods. This should be supplemented with cell-based assays to establish the potential for a positive cross-match. *(Level 2)*
5. Risk stratification should be performed and the frequency of DSA monitoring should be adjusted according to the risk level of DSA occurrence:
   - In high-risk patients (such as recipients with preexisting DSAs), DSAs should be monitored in the first 3 months posttransplantation and a surveillance kidney biopsy should be performed at 3 months
   - In intermediate-risk patients (such as those who have a history of DSAs but are negative for DSAs at transplantation), DSAs should be monitored within the first month
   - In low-risk patients (such as nonsensitized patients receiving a first kidney transplant) with stable kidney function, although there are no robust data to support systematic screening for DSAs, it is done in some centers at least once in the first 3 to 12 months after transplantation *(Level 2)*

Recommendations for Managing DSAs in Liver Transplantation

Routine screening for DSAs is neither universally available nor implemented in all centers. There is a small, but growing evidence base for the possible benefits of measuring DSAs in liver transplantation, but their role remains uncertain. Firm conclusions with regard to the effect on outcomes cannot be drawn in the absence of any proven therapy. The following recommendations may be considered in those centers where DSAs are measured.

These recommendations are based on low-level evidence from literature and expert opinion.

1. Screening for DSAs is encouraged before any attempt to strongly minimize immunosuppression. *(Level 4)*
   - If DSAs are detected (strong positive), caution is required before further immunosuppression minimization; a liver biopsy should be considered to ensure no silent AMR process develops in the graft and the risk–benefit ratio of minimization must be discussed
2. Screening for DSAs should also be performed in case of unexplained graft dysfunction. *(Level 5)*
   - If DSAs are detected strongly positive (MFI >5000) and the histological pattern is consistent with chronic AMR, reinforcement of baseline immunosuppression must be considered, irrespective of the class of anti-HLA antibodies:
     - Increase in CNI trough level if consistent with tolerability
     - Introduction of mycophenolate or other agents in patients receiving CNI monotherapy
     - Corticosteroids in cases where the histological pattern is suggestive of de novo autoimmune hepatitis with positive DSAs
     - Further follow-up and evaluation of therapeutic changes will be based on repetition of liver biopsy and DSA/MFI monitoring
3. In patients whose liver function tests are normal over the long term, screening for DSAs at 1, 5 and 10 years postliver transplant is proposed. *(Level 5)*
   - In cases of persistent or de novo DSAs with MFI >5000:
     - Noninvasive evaluation of fibrosis or protocol biopsy is recommended for early detection of silent fibrosis progression
     - If minimization of immunosuppression is required due to side effects, this should be exercised with caution
   - In the case of moderately positive DSAs (MFI, 1000-5000), yearly screening for DSAs is suggested in addition to noninvasive evaluation of fibrosis

CARDIOVASCULAR COMPLICATIONS AFTER KIDNEY AND LIVER TRANSPLANTATION

Problem to be Addressed

CVD is a leading cause of morbidity and nongraft-related mortality in liver and kidney transplant recipients,[287,288] with heart failure (HF), coronary artery disease (CAD), and sudden cardiac death being the most common CVEs impacting on transplant recipients.[289,290] Prevalence of CVEs is likely to increase in liver transplantation with the increasing number of older and higher-risk patients undergoing transplantation.[291] Compared with the nondialysis general population, age-, race-, and sex-matched kidney transplant recipients (25-55 years) have a significantly higher CVD mortality.[292]

Metabolic disorders, such as diabetes, hyperlipidemia, arterial hypertension and proteinuria are widely observed in liver and kidney transplant recipients,[293-295] and are risk factors for CVEs. Marked increases in these disorders are evident after both liver and kidney transplantation.[296,297]

With CVEs as a leading cause of death after transplantation, intervention strategies that target modifiable risk factors for CVE (eg, obesity, diabetes, hypertension, dyslipidemia, smoking, and renal dysfunction (such as reduced renal function or albuminuria) will be key for improving long-term outcomes in kidney and liver transplant recipients.[298-300]

This section describes CVD and metabolic disorders in kidney and liver transplant recipients, and the risk factors for CVEs in these transplant populations. This is followed by the management of cardiovascular risk after kidney and liver transplantation.

CVD in Kidney and Liver Transplant Recipients

Registry data show that CVD accounts for 18% to 30% of premature deaths among kidney transplant recipients,[292] and almost 40% of kidney transplant recipients experience a

CVE in the first 3 years posttransplant.[301] In a UK registry study, cardiovascular and cerebrovascular events, combined, were the leading cause of death (22.9%) in the first year postkidney transplantation, accounting for more deaths than infection (21.6%).[302] Data from observational studies suggest particularly high frequencies of CVEs during the first few months after kidney transplantation.[303] The annual risk of death from CVD in kidney transplant recipients may be as high as 3.5% to 5%, which is fifty times higher than that of the general population.[294]

In a study of 54,697 liver transplant recipients, conducted between 2002 and 2012, 2.9% died within 30 days; CVE was the leading cause of 30-day mortality, accounting for 42.1% of fatalities—more than infection (27.9%) or graft failure (12.2%).[304] When a wider composite cardiovascular end point was assessed (including atrial fibrillation [AF], HF, and pulmonary embolism) the event rate was 8% and 11% at 30 and 90 days after liver transplantation, respectively.[305] AF was the major event, and was associated with longer hospital stays, a higher incidence of acute kidney injury, and lower rates of recipient and graft survival.[305,306]

A retrospective review of 455 consecutive liver transplant patients has shown that despite the exclusion of high CV risk candidates for liver transplantation, CVD occurs in 10.6% of liver transplant recipients at 1 year, 20.7% at 5 years, and 30.3% at 8 years posttransplant.[307] Fatal and nonfatal CVEs can also persist into the second decade postliver transplant.[308]

Metabolic Disorders in Kidney and Liver Transplant Recipients

Marked increases in the prevalence of metabolic disorders (diabetes, hyperlipidemia, and arterial hypertension) are observed after liver transplantation,[296,297] and as many as 58% of liver transplant recipients may meet the criteria for metabolic syndrome posttransplant (Table 10).[293,309]

Estimates of NODAT range up to 25% in renal transplant recipients and 25% in liver transplant recipients, with prevalence increasing to 40% to 60% in HCV-infected liver transplant recipients.[310,311] A study of Italian kidney transplant recipients showed that 41% had metabolic syndrome at 6 months posttransplant, demonstrating the significance of this risk factor for the occurrence of severe CVD.[312] Other metabolic disorders, such as hypertension, affects up to 90% of kidney transplant recipients, and dyslipidemia is also highly prevalent (Table 10).[292-294]

Risk Factors for CVEs in Kidney and Liver Transplant Recipients

In general, risk factors for CVEs, for both kidney and liver transplant recipients, can be present before transplantation and posttransplantation. Pretransplant risk factors for CVEs include conventional demographic (and nonmodifiable) factors, such as age (young age in kidney transplantation and older age in liver transplantation), sex, race, preexisting conditions, such as diabetes, ischemic heart disease, duration of dialysis for kidney transplant recipients, smoking and general patient health (Figure 12).[289,292,313,314] Posttransplant risk factors for CVEs include NODAT, hypertension, impaired glucose tolerance,[288,289,292,315] impaired kidney function[295,316] and posttransplant hyperglycemia (Table 11 and Figure 12).[317,318]

In clinical trials and registry studies in kidney transplantation, hypertension shows a strong association with major adverse cardiovascular event (MACE), as well as graft failure and mortality[289]; increased systolic and pulse pressure—markers of vascular stiffness—are specifically associated with cardiac death and stroke.[289]

Other nonclassic CVE risk factors (anemia, proteinuria, number of episodes of graft rejection, reduction in allograft function) have also been identified in kidney transplant recipients.[295,319-321] Anemia has been shown to be an independent risk factor for de novo congestive heart failure, and for all-cause and cardiovascular mortality.[319] The number of episodes of graft rejection has been linked to an increased risk of CVE,[320] while graft loss resulted in increased incidence of noncardiovascular death, all-cause mortality, MACE and nonfatal myocardial infarction.[321] Furthermore, proteinuria is associated with CVD, graft failure and poor patient survival among kidney transplant recipients.[295]

For liver transplant recipients, diabetes and hypertension are each associated with an approximate twofold higher risk of experiencing a CVE posttransplant (multivariate analysis).[288] In liver transplantation, diabetes has also been linked with long-term CVD,[307] with duration of diabetes, but not hypertension or hyperlipidemia, shown to be an independent predictor of long-term mortality due to the combination of CVE, recurrent HCV, and infection.[330] The evaluation of inflammatory markers also suggests that patients are at high cardiovascular risk after liver transplantation.[328,329]

In the United States, where obesity is highly prevalent, nonalcoholic steatohepatitis (NASH) is now the second most common indication on the waiting list for adult liver transplantation, after hepatitis C.[333] This rise is significant because patients transplanted for NASH are at a high risk of CVEs. These patients have a fourfold higher risk of CVE compared to patients transplanted for alcohol-induced cirrhosis,[332,333] and a higher risk of both early and long-term cardiovascular mortality after liver transplantation compared to non-NASH patients.[331] Renal impairment is the strongest predictor of postliver transplant cardiovascular mortality among NASH recipients,[331] and preoperative renal

TABLE 10.

Incidence of metabolic disorders in liver and kidney transplant recipients[289,292,294,309-312]

Metabolic disorder	% of liver transplant recipients	% of kidney transplant recipients
Metabolic syndrome	44-58%	41% (at 6 months posttransplantation)
Diabetes (NODAT)	2.5-25%	2-53%
	40-60% (HCV-infected liver transplant recipients)	
Dyslipidemia	45-69%	60-80%
Hypertension	Up to 70%	50-90%

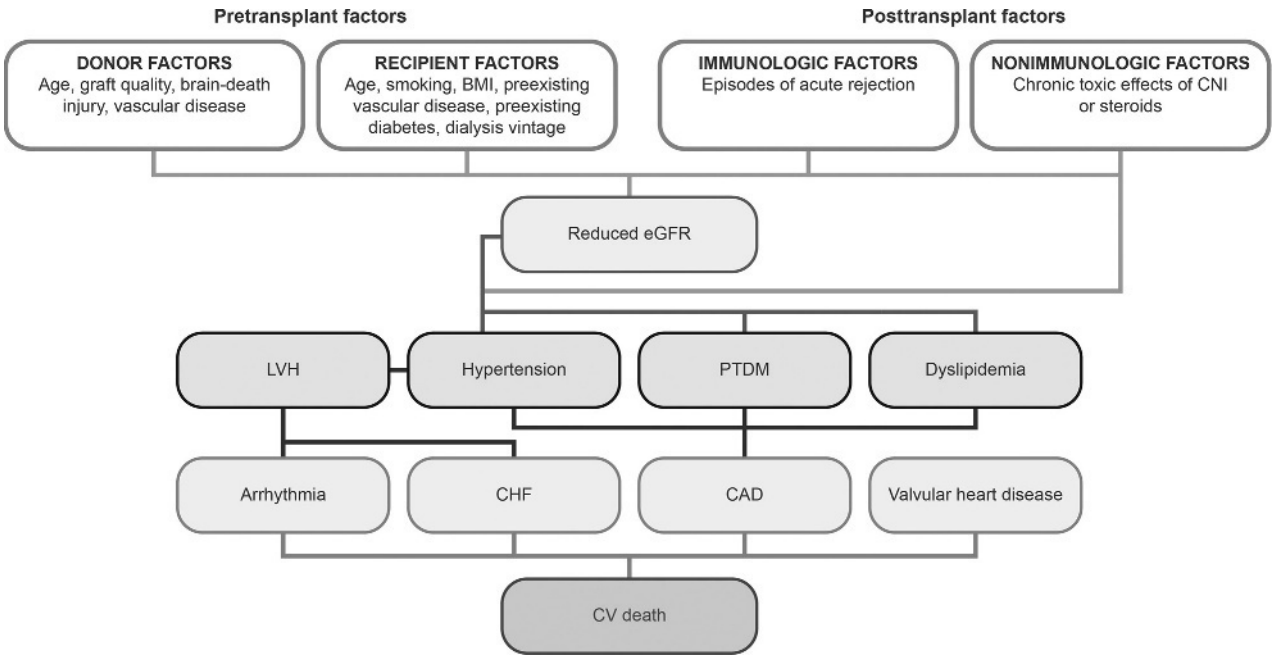


FIGURE 12. Risk factors for CVE after kidney transplantation. Pretransplant and posttransplant factors conferring increased cardiovascular risk after kidney transplantation. CHF, congestive heart failure; CV, cardiovascular; LVH, left ventricular hypertrophy; PTDM, posttransplantation diabetes mellitus. Reprinted with permission from Stoumpos S, Jardine AG, Mark PB. Cardiovascular morbidity and mortality after kidney transplantation. *Transpl Int*. 2015;28:10–21.[292]

impairment is also a predictor of posttransplant cardiac events among patients transplanted for liver cirrhosis.[324] Decreased kidney function (as assessed by estimated GFR [eGFR]) is an independent predictor of cardiovascular risk among patients after liver transplantation.[316]

Managing Cardiovascular Risk After Transplantation

In general, modifiable risk factors for CVE after transplantation should be targeted and proactively managed to improve patient outcomes. Routine monitoring for CVE risk factors in kidney and liver transplant recipients should be performed every 3 months in the first year of transplantation and then annually after the first year. Transplant recipients at risk of developing cardiovascular complications should be managed according to established guidelines.[299]

Educating patients in lifestyle changes, including the addition of exercise into their daily/weekly routine, reduction of high salt intake and cessation of smoking and alcohol consumption, is important to minimize the risk of cardiovascular complications after transplantation.[289,292,334-337]

TABLE 11.

Risk factors for CVE after liver transplantation[288,304,305,307,316,322-333]

Pretransplantation factors	• Pretransplant prolonged QTc interval, AF, and stroke
	• Pretransplant diastolic dysfunction
	• Severe preoperative CAD
	• Previous history of CVD (independent risk factor)
	• Cardiovascular risk score indicating moderate/severe CVD
	• Preoperative renal impairment and decreased kidney function assessed by eGFR (independent predictor of CV risk)
Metabolic disorders	• Concomitant obesity and diabetes
	• Diabetes and hypertension (twofold higher risk of CVE each)
	• Duration of diabetes, but not hypertension or hyperlipidemia (independent risk factor for mortality due to the combination of CVE, recurrent HCV and infection)
	• Inflammatory markers
Nonalcoholic fatty liver disease	• NASH which is now the second most common indication for liver transplant among adults on the waiting list after hepatitis C (fourfold higher risk of NASH from 2002 to 2012). NASH recipients have increased risk of CVD mortality after liver transplantation
	• Renal impairment among NASH recipients
Some immunosuppressive regimens	• Non–CNI-based treatment
Other risk factors	• Recipient factors: age; preoperative hospitalization; ICU status; ventilator status; calculated MELD score; portal vein thrombosis
	• Donor factors: BMI
	• Surgical factor: cold ischemic time (results from a large database analysis)

MELD, Model for End-Stage Liver Disease.

Kidney Transplantation

Diabetes

Frequent monitoring of plasma glucose levels is recommended, particularly soon after transplantation and in patients receiving high-dose steroid treatment for acute rejection.[301] This should be done at least every day during the first postoperative week, during treatment with high-dose steroids and at least 3-monthly during the first year. A study by Choi and Kwon[338] demonstrated the incidence of NODAT is higher in patients receiving tacrolimus (25%) compared to patients receiving cyclosporine (9.5%) ($P < 0.001$). The risk of developing NODAT is increased by 5% for every 0.01 mg/kg increase in prednisolone dose.[289] A hemoglobin A1c (HbA1c) assay should be used for the monitoring of NODAT in kidney transplant patients with a target of less than 7%.[339] Both the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trials have raised concerns regarding intensive hypoglycemic therapy in nontransplant type 2 diabetic individuals, and an HbA1c target of 6.5% to 7.5% would be recommended in renal transplant recipients.[340,341] Table 12 summarizes the oral hypoglycemic agents for patients with NODAT.[339] A recent study suggests that the early introduction of insulin in patients developing NODAT may actually reduce persistent diabetes in the longer term, although this effect remains to be proven,[342] and the use of the newer agents such as the DPP-4 inhibitor, vildagliptin, has been shown to be safe and effective in NODAT, without the risk of hypoglycemia.[343] Management of diabetes in kidney transplant recipients should mirror that of the general population, and follow these guidelines.[289] The management of NODAT should also include modification of immunosuppression in kidney transplant patients; specifically, the minimization and possible withdrawal of corticosteroids, with the option to switch from tacrolimus to cyclosporine.[338]

Dyslipidemia

Evidence from the Assessment of Lescol in Renal Transplant (ALERT) trial supports the benefits of statin therapy in kidney transplant recipients.[344,345] Reductions in low-density lipoprotein (LDL) cholesterol with fluvastatin were associated with a reduced risk of cardiovascular endpoints, although improvements in the primary composite outcome (cardiac death, nonfatal myocardial infarction, or coronary intervention) were not statistically significant.[344] However, a 2-year study extension showed significant long-term benefits in the primary outcome.[345] Kidney Disease Improving Global Outcomes (KDIGO) 2013 guidelines for lipid management suggest prescription of statins to all kidney transplant recipients.[336] It should be noted that although all statins have broadly similar modes of action, the potential for drug–drug interactions and toxicity varies between statins.[346] Simvastatin (and to a lesser extent atorvastatin) may have greater interaction with CNI metabolism, resulting in increased statin exposure and side effects, so other statins may be preferred. Statins may cause liver dysfunction but this is rare, and mild abnormalities of liver tests should not preclude statin use. Myopathy may be more common with high doses of simvastatin compared with atorvastatin or rosuvastatin.[346]

TABLE 12.

Glucose-lowering agents used in kidney transplant patients with NODAT

Class	Drug	Avoid/dose adjustment	Drug–drug interaction
First-generation sulfonylureas	All	Avoid	Increase cyclosporine levels
Second-generation sulfonylureas	Glipizide, Gliclazide	—	Increase cyclosporine levels
	Gliquidone	—	—
	Glibenclamide (Glyburide)	Avoid if GFR <50 mL/min per 1.73 m^2	Increase cyclosporine levels
	Glimepiride	Start with 1 mg/d	Increase cyclosporine levels
	Glisentide	Avoid if advanced CKD	—
Biguanides	Metformin	Avoid if GFR <60 mL/min per 1.73 m^2	—
	Phenformin	Avoid	—
Alpha-glucosidase inhibitors	Acarbose, Miglitol	Avoid if GFR <30 mL/min per 1.73 m^2	—
Meglitinides	Repaglinide	Cautious titration (start 0.5 mg if GFR <40 mL/min per 1.73 m^2)	Increased levels of repaglinide with cyclosporine
	Nateglinide	Cautious use if GFR <60 mL/min per 1.73 m^2	Increased levels of nateglinide with cyclosporine
Thiazolidinediones	Pioglitazone	Avoid if heart failure	—
	Rosiglitazone	Avoid if heart failure	—
Incretin mimetic	Exenatide	Avoid if GFR <30 mL/min per 1.73 m^2	—
Analog of amylin	Pramlintide	Avoid if GFR <20 mL/min per 1.73 m^2	—
DDP-4 inhibitor	Sitagliptin	Reduce dose to 50mg/d (GFR 50-30 mL/min per 1.73 m^2), 25 mg (GFR <30 mL/min per 1.73 m^2)	Metabolized by CYP3A4/5*
	Vildagliptin	Avoid if dialyzed, caution if GFR <60 mL/min per 1.73 m^2 (need more data)	No interaction with CYP3A4/5 substrates
	Saxagliptin	2.5 mg daily if GFR <50 mL/min per 1.73m^2	Metabolized by CYP3A4/5*

Table reprinted with permission from Ghisdal L, Van Laecke S, Abramowicz MJ, et al. New-onset diabetes after renal transplantation: risk assessment and management. *Diabetes Care.* 2012;35:181–188.[339]
*Potential increase in the levels of cyclosporine, tacrolimus and mTORi.
CYP, cytochrome P450; DDP-4, dipeptidyl peptidase-4.

Hypertension

Analyses of patients from the CTS database suggest that control of systolic blood pressure (BP) may be associated with improved graft, patient, and CVD-free survival.[347] However, evidence from large-scale studies evaluating the effects of antihypertensive agents in kidney transplant recipients is limited. The Study on Evaluation of Candesartan Cilexetil after Renal Transplantation (SECRET), a randomized, double-blind, multicenter trial evaluating the effects of candesartan therapy on BP control and cardiovascular outcomes, was halted prematurely owing to low event rates.[348] However, it did show that candesartan provided improved BP control and decreased proteinuria in kidney transplant recipients compared with placebo. A recent randomized, double-blind, placebo-controlled trial in kidney transplant recipients with proteinuria showed no significant reduction in the doubling of serum creatinine, end-stage renal disease, or death, with ramipril therapy compared with placebo.[349]

Recent meta-analyses suggest that calcium channel blockers should be preferred over renin-angiotensin system (RAS) blockers for BP control, because RAS blockers are associated with progressive worsening of renal graft function without additional benefits in cardiovascular risk.[350,351] The KDIGO guidelines recommend a target of 130/80 mm Hg[301]; however, the evidence for specific BP targets is still lacking.[289]

Furthermore, CNIs and steroids play a major role in the development of hypertension in kidney transplant patients; therefore, modifications of immunosuppressive regimen may be considered for lowering BP in these patients.[292,352] The changes in immunosuppressive drugs include CNI minimization, conversion from cyclosporine to tacrolimus, the use of CNI-free immunosuppressive regimens and avoiding steroids.[289] Although, BP control is particularly challenging in kidney transplant patients[292]; in practice modification of immunosuppression is rarely done because of the potential risks of acute rejection and development of DSA.[39,179,289,292]

Lifestyle Changes

Lifestyle changes (eg, diet, exercise, smoking cessation) should be promoted because they can be helpful in reducing the risk of CVE. However, there is limited evidence to support this, with the benefits of exercise shown in a small cohort study of kidney transplant recipients.[289,292]

Liver Transplantation

In 2013, the American Association for the Study of Liver Diseases (AASLD) published a practice guideline for the long-term management of recipients after a liver transplant; key points from this guidance are included in the recommendation section.[353] These recommendations were based on relevant published information with the aim of improving the long-term outcomes in adult liver transplant recipients.

Lifestyle Changes

Educating patients in lifestyle changes, such as including exercise into their daily/weekly routine, cessation of smoking and (excessive) alcohol consumption, is important to minimize the risk of cardiovascular complications posttransplant. The benefit of exercise should be emphasized as this can lead to improvements in activity levels, overall health and the ability to perform daily tasks.[334] Physically active liver transplant recipients report a better quality of life compared with inactive patients.[335]

Bariatric surgery in liver transplantation may be performed more frequently in the future in patients with early-stage liver disease, to reduce weight-related CVE; however, the efficacy of this approach requires verification by well-designed clinical studies.[354] Noninvasive endoscopic techniques, such as use of the endobarrier,[355,356] may be effective and safer alternative approaches but their role in transplant recipients has to be assessed.

Managing Cardiovascular Risk After Transplantation: Immunosuppressive Regimen

In kidney transplantation, modifying the immunosuppressive regimen may reduce the risk of hypertension, dyslipidemia and diabetes,[289] but has yet to be endorsed by guidelines. For example, switching from cyclosporine to tacrolimus has been associated with a reduction in LDL cholesterol.[357] In the Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT) and BENEFIT-EXT (extended criteria) studies, belatacept-based regimens were associated with lower BP levels and an improved lipid profile over the cyclosporine regimen in kidney transplant recipients.[358] Modeling analysis of these 2 studies suggests that the use of belatacept could lead to a reduction in MACE of over 20%.[359]

In a retrospective study in liver transplant patients, tacrolimus use was associated with a reduced risk of CVD versus noncalcineurin-based treatment in, but not versus, cyclosporine.[307] A small randomized trial showed better preservation of kidney function and reduction of cardiovascular risk score at 1-year postliver transplantation when patients received a steroid-free regimen with tacrolimus and MMF compared to a regimen with tacrolimus and steroids.[360] A small retrospective study suggested that mTORi were not associated with an increased risk of CAD/cerebrovascular

TABLE 13.

Effect of maintenance immunosuppression on cardiovascular risk factors in kidney and liver transplant patients

	Corticosteroids	Cyclosporine	Tacrolimus	mTORi	Belatacept	Azathioprine	Mycophenolate
Lipids	↑↑	↑↑	↑	↑↑ ↑	↑↑	↔	↔
Hypertension	↑↑	↑↑	↑		↑	↔	↔
Diabetes	↑↑	↑	↑↑			↔	↔
eGFR	↔	↓	↓	↔	↔	↔	↔
Acute rejection	↓	↓↓	↓↓	↓	↓	↓	↓

Direction of arrows shows effect, with number of arrows demonstrating semi-quantitative effect. Data not available for effect of belatacept on cardiovascular risk factors in liver transplant recipients. Table based on data from Gillis 2014 and Jardine 2011.[289,362]

events after liver transplant compared with patients on CNIs.[361] Table 13 summarizes the various effects of immunosuppressive drugs on cardiovascular risk in transplant patients.[289]

Recommendations for Managing CVD Complications in Kidney Transplantation

1. Ensure that patients undergo regular monitoring for risk factors for CVE after transplantation (eg, BP, lipids [at 2-3 months after transplantation and at least annually thereafter], plasma glucose levels, HbA1c every 6 months after the first postoperative year). *(Level 5)*
2. Manage risk factors for CVE according to current established treatment guidelines. Because specific guidelines for kidney transplant recipients are lacking, guidelines for normal individuals (ie, nontransplant recipients) should be followed. *(Level 5)*
   - Obesity: patients should aim to achieve a target body mass index (BMI) of <25 kg/m^2 through lifestyle changes (diet/exercise), and the potential use of pharmacotherapy and surgery where appropriate *(Level 5)*
   - Diabetes: target HbA1C 7.0% to 7.5% using lifestyle modification, oral agents and insulin, as required *(Level 5)*
     - Modification of immunosuppressive regimens that cause hyperglycemia, for example, CNI reduction and withdrawal or avoidance of corticosteroids (when appropriate and safe)
     - Insulin therapy is the best choice during high-dose steroids administration (eg, antirejection therapy); however, recipients with new-onset diabetes mellitus should be preferably treated with oral hypoglycemic agents before insulin-based maintenance therapy is considered
     - Metformin or sulfonylureas may be used in kidney transplant recipients with normal renal function
     - Sulfonylureas such as glipizide and glimepiride are preferable in cases of impaired renal function
3. Hypertension: BP should be controlled using lifestyle modification and antihypertensive therapy, as required; KDIGO 2009 guidelines suggest a BP target of 130/80 mm Hg. *(Level 5)*
   - Modification of immunosuppressive regimens that cause hypertension, for example, cyclosporine minimization and withdrawal or avoidance of corticosteroids (where appropriate and safe)
   - Lifestyle modifications, including reduction of salt intake, should be implemented
   - If lifestyle modification and a safe reduction of immunosuppression do not achieve target BP, antihypertensive medications should be introduced
   - Calcium channel blockers (first-line) are preferred over RAS blockers
4. Dyslipidemia: KDIGO 2013 guidelines suggest all kidney transplant recipients are treated with a statin (fluvastatin, pravastatin). Target levels are: total cholesterol level (<5.2 mmol/L [200 mg/dL]), target LDL level <2.6 mmol/L (100 mg/dL), and target triglyceride level (<1.7 mmol/L [150 mg/dL]). Fibrates and ezetimibe may be needed. *(Level 2)*
5. Educate patients on the benefits of lifestyle modification and provide support in achieving these goals (such as dedicated nurse practitioners). *(Level 5)*
   - Provide advice on healthy diet and including exercise in their daily/weekly routine *(Level 5)*
   - Provide advice on cessation of smoking and alcohol consumption *(Level 5)*

Recommendations for Managing CVD Complications in Liver Transplantation

1. Screen high-risk patients (chronic smokers, older than 50 years, or a clinical or family history of CAD or diabetes) preoperatively to establish risk factors for CVE (dobutamine stress echocardiography, followed by cardiac catheterization in case of abnormal findings). *(Level 4)*
2. Consider preoperative interventions for CAD where clinically indicated. *(Level 4)*
3. Ensure that patients undergo regular surveillance every 3 months in the first year and annually thereafter for risk factors for CVE (eg, BP, lipids, HbA1c). *(Level 5)*
4. Manage risk factors for CVE according to current established treatment guidelines. Because specific guidelines for liver transplant recipients are lacking, guidelines for normal individuals (ie, nontransplant recipients) should be followed. *(Level 5)*
   - Obesity: patients should aim to achieve a target BMI of <25 kg/m^2 through lifestyle changes (diet/exercise), and the potential use of pharmacotherapy and surgery where appropriate
   - Diabetes: aim to normalize target values and reestablish metabolic control (fasting plasma glucose <6.7 mmol/L (120 mg/dL), peak <8.88 mmol/L (160 mg/dL) or HbA1C <7%)
     - Conversion of immunosuppression from tacrolimus to cyclosporine in liver transplant recipients with poor glycemic control (persistently elevated blood glucose [>11 mmol/L] and glycosylated hemoglobin [>9%] over a period of >6 months despite treatment with optimal antidiabetic treatment)
     - Insulin therapy is the best choice when high-dose steroids are administered; however, new-onset diabetes mellitus patients may require less insulin to control the blood glucose level with time, and oral hypoglycemic agents may be administered in cases of normal liver function
     - Metformin or sulfonylureas may be used in liver transplant recipients with normal renal function
     - Sulfonylureas such as glipizide and glimepiride are preferable in cases of impaired renal function
   - Hypertension: target BP should be 130/80 mm Hg
     - Immunosuppressants that cause hypertension, such as CNIs and corticosteroids, should be minimized
     - Lifestyle modifications, including reduction of salt intake, should be implemented
     - If lifestyle modification and a reduction of immunosuppression do not achieve target BP, antihypertensive medications should be introduced
     - Calcium channel blockers, as well as beta-blockers, may be effective in liver transplant recipients
     - Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and direct renin inhibitors should be considered first-line antihypertensive therapy in liver transplant recipients with diabetic nephropathy, chronic kidney disease and/or significant proteinuria
     - The combination of diuretics with other classes of antihypertensive medication may be effective in some liver transplant patients
   - Hyperlipidemia: the target LDL cholesterol level is dependent on the patient's cardiac risk level; the target of 3.4 mmol/L (130 mg/dL) should be reduced to 2.6 mmol/L (100 mg/dL) or 1.8 mmol/L (70 mg/dL) for those with increasing risk
     - Therapeutic lifestyle and dietary changes
     - Statins
     - Addition of ezetimibe (preference in cyclosporine-treated patients)

- In cases of hypertriglyceridemia with normal cholesterol
  - Fish oil at 1000 mg twice daily to 4 g daily if tolerated
  - Fibric acid derivatives
- In cases of refractory hyperlipidemia: consider changes in immunosuppression
  - Conversion from cyclosporine to tacrolimus
  - CNI reduction (eg, substitute with mycophenolate)
  - Replacing sirolimus with other agents

5. Educate patients on the benefits of exercise; provide advice on including exercise in their daily/weekly routine. *(Level 4)*
6. Educate patients on the benefits of other lifestyle changes, such as cessation of smoking and alcohol consumption. *(Level 5)*

EARLY ISCHEMIC INJURY AND DGF IN KIDNEY TRANSPLANTATION

Problem to be Addressed

Due to an increasing organ shortage, the proportion of grafts procured from donors with a high Kidney Donor Profile Index (KDPI) (>85%) has increased markedly with the inherent risk of increased rates of DGF. Ischemia-reperfusion injury (IRI) is considered an unavoidable, but potentially modifiable, risk factor for poor long-term graft survival in solid organ transplantation. The presence and severity of DGF is associated with inferior graft and patient survival after renal transplantation.[363,364] Specifically, DGF has been associated with a 41% increased risk of graft loss and a higher mean serum creatinine of 0.06 mmol/L (0.66 mg/dL) at 3.2 years of follow-up.[363] In patients with DGF >15 days, 1-year death-censored graft survival was 79.3% versus 95.7% in patients without DGF (P < 0.001), and 1-year patient survival was 88.86% versus 95.2%, respectively (P = 0.003).[364]

Prevention of Early Ischemic Injury and DGF in Kidney Transplantation

With the marked negative impact of DGF on graft and patient survival, UNOS has released recommendations to optimize the hemodynamic stability of a transplanted graft using a variety of predefined donor management goals (Table 14).[43,365] The implementation of these strategies in clinical practice reduces the risk of DGF by approximately 50%.[43] Such donor management goals may, in the future, also include pretreating donors with low-dose dopamine pretransplantation to improve graft function (Table 15).[366]

TABLE 14.

UNOS region 5, donor management goals in kidney transplantation

Parameter	Goal
Central venous pressure	4-10 mm Hg
Ejection fraction	>50%
Vasopressors	≤1 and low dose*
Arterial blood gas pH	7.3-7.45
PaO2:FiO2	>300
Serum sodium	135-155 mmol/L
Blood glucose	<150 mg/dL
Urine output	0.5-3 mL/kg per hour over 4 h
Mean arterial pressure	60-100 mm Hg

Recommended donor management goals to raise organ yield per donor. *dopamine ≤10 μg/kg/min, phenylephrine ≤60 μg/kg/min and noradrenaline ≤10 μg/kg/min. Table based on data from Malinosky 2013 and Mundt 2015.[43,365]

With the progress made in organ preservation, the use of mild hypothermia may lower the rate of DGF in kidney transplant recipients, especially with the use of high-risk donors, such as donors with a high KDPI.[367] Moreover, recent RCTs have demonstrated a beneficial effect of hypothermic machine perfusion on kidneys from all donor types (donation after brain death, DCD, and donors with a high KDPI), by reducing the incidence of DGF.[368-370] Graft survival rates varied among the studies, but Moers et al[369] reported improved 1-year graft survival in the machine-perfusion group.[368,369] A first single case report in humans performed by Hosgood et al in 2011 and a larger case series in 2013 demonstrated the feasibility of normothermic machine perfusion for the preservation of the kidney graft before transplantation. Indeed, normothermic machine perfusion may have the advantage of maintaining cellular metabolism compared with hypothermic machine perfusion and allow monitoring of viability, with the potential to increase the efficacy of drugs administered before transplantation. Further studies are needed to establish a clear comparison between hypothermic and normothermic machine perfusion and cold storage.[371,372]

Other areas of research include findings from a retrospective analysis that suggest combined hormonal resuscitation (methylprednisolone, vasopressin, and triiodothyronine/L-thyroxine) increases the yield of recovered organs.[365,373] However, data on the efficacy of the individual components of this combined technique have been negative or controversial: for example, methylprednisolone has no effect in renal transplantation, but may be beneficial in liver transplantation.[365]

Irish et al[33] developed a validated score index based on a multivariate analysis of data from 24 337 deceased donor renal transplant recipients. Risk factors for DGF and outcomes were studied to predict DGF and long-term outcomes at the time of transplant.[33] Based on their findings, the group created a web-based DGF risk calculator, in which individual or population information can be inputted to obtain a DGF risk prediction.[33] This score index has now been adopted in a number of phase 2 trials to predict which high-risk patients would benefit from selective interventions. These assessments of risk for DGF may be useful tools in clinical practice in order to select those patients who may benefit most from new techniques and pharmaceutical interventions.

A more systematic approach to donor management with the aim of reducing DGF is required in the future. That means that donor management goals must be generally applied in current organ procurement, their impact must be monitored continuously, and new additional approaches must be introduced.[365]

Recommendations for Managing Early Ischemic Injury and DGF in Kidney Transplantation

1. Donor management goals (see also Table 14) should routinely include:
   - Sufficient fluid resuscitation aiming at a central venous pressure of 4 to 10 mm Hg; if brain death-induced central diabetes insipidus (diuresis >5 mL/kg/h with specific gravity <1005 mg/mL) is present, desmopressin should be used to prevent polyuria *(Level 2)*
   - Keeping the left ventricular ejection fraction (EF) above 50% and the mean arterial pressure (MAP) between 60 and 100 mm Hg *(Level 2 for MAP and Level 3 for EF)*

TABLE 15.

Considerations for managing early ischemic injury and DGF in kidney transplantation[43,365,369,373]

Considerations	Potential interventions
Donor management	• UNOS goals (see Table 14)[a] • Pretreatment of donors with low-dose dopamine (4 μg/kg per minute) • Application of mild hypothermia • Hypothermic machine perfusion • Combined hormonal resuscitation • Future research: a number of compounds are currently in clinical development, including a small interfering RNA (siRNA) that blocks p53 and may have a positive effect on ischemia injury postkidney transplant
Recipient management	• Aim for good hydration and hemodynamic stability, taking into account central venous pressure, clinical presentation (eg, edema formation), actual body weight in comparison with dialysis "dry weight," heart–lung X-ray findings, and MAP/heart rate • In routine practice, avoid nephrotoxic insults where possible: NSAIDs, radio-contrast media, antibiotics (eg, vancomycin, aminoglycosides), toxic CNI levels

[a] As part of the consideration for sufficient fluid resuscitation, aim at a central venous pressure of 4 to 10 mm Hg; if brain death-induced central diabetes insipidus (diuresis >5 mL/kg per hour with specific gravity <1005 mg/mL) is present, desmopressin should be used to prevent polyuria.
siRNA, small interfering ribonucleic acid; NSAIDs, nonsteroidal anti-inflammatory drugs.

- ○ Avoiding use of multiple vasopressors and keeping vasopressors at a low dose *(Level 2)*
- ○ Keeping laboratory parameters in the target range: arterial pH 7.30 to 7.45, serum sodium 135 to 155 mmol/L, blood glucose concentration less than 8.3 to 10.0 mmol/L (<150-180 mg/dL) *(Level 2)*
- ○ Keeping PaO2:FiO2 at >300 and urine output between 1.0 and 3.0 mL/kg body weight (0.5 is considered to be too low) *(Level 2)*

2. In addition to such donor management goals, some or all of the following approaches will presumably be added in future recommendations *(Level 2)*:

- ○ Pretreatment of donors with low-dose dopamine (4 μg/kg/min) *(Level 2)*
- ○ Application of mild hypothermia *(Level 2)*
- ○ Hypothermic machine perfusion *(Level 2)*
- ○ Combined hormonal resuscitation *(Level 2)*

3. After renal transplantation in clinical practice, a good hydration level and hemodynamic stability is aimed at, taking into account central venous pressure, clinical presentation (eg, edema formation), actual body weight in comparison with dialysis 'dry weight', heart–lung X-ray findings, and MAP/heart rate. *(Level 4)*
4. Furthermore, nephrotoxic insults (nonsteroidal anti-inflammatory drugs, radiocontrast media, antibiotics such as vancomycin and aminoglycosides, toxic CNI levels) should be routinely avoided, if possible. *(Level 4)*

EAD AND NONANASTOMOTIC BILIARY STRICTURES IN LIVER TRANSPLANTATION

Problem to be Addressed

DGF is a common early complication associated with higher risk of EAD and biliary strictures (BS), increased hospital stay and/or hospital readmission, inferior graft and patient survival, and increased costs.[374] BS are classified according to the area of localization as anastomotic or nonanastomotic. Anastomotic BS can usually be managed endoscopically; this approach is more difficult and less successful in patients with nonanastomotic BS. Up to 50% of patients with nonanastomotic BS, and in particular diffuse intrahepatic BS, are not amenable to endoscopic or surgical treatments.[375]

EAD and BS are the end result of a cascade of tissue injuries that precede transplantation (preexisting disease in the donor, brain death-induced injury, surgical trauma, cold preservation and warm ischemia), and culminate in IRI in the recipient.[376] The incidence of EAD in liver transplant recipients ranges from 21% to 25%[377]; the incidence of nonanastomotic BS is 0.5% to 10% and these account for 10% to 25% of all strictures complicating liver transplant.[378]

Potential Risk Factors Associated With EAD and Nonanastomotic BS After Liver Transplantation

Liver transplantation studies have highlighted the risk factors for EAD and nonanastomotic BS (Table 16). Modifying these risk factors and preventing organ damage may improve results in liver transplantation and widen its application by increasing the pool of organs suitable for transplantation.[376]

Prevention of EAD and Nonanastomotic BS in Liver Transplantation

A variety of interventions can be considered for the prevention of EAD and nonanastomotic BS after liver transplantation

TABLE 16.

Potential risk factors associated with EAD and nonanastomotic BS in liver transplantation[374,376,379-382]

Potential risk factors for EAD	Potential risk factors for nonanastomotic BS
Use of imported livers	DCD
HTK as a preservation solution	Donor age
High MELD scores	Prolonged warm and cold ischemia time
Longer cold ischemia time	Extended use of vasopressors in the donor
Recipient preoperative ventilator status[a]	
DCD allografts[a]	
Donor age[a]	
Allograft size[a]	
Degree of steatosis[a]	
Duration of surgery[a]	
Intraoperative transfusion requirements[a]	

[a] Significant associations with development of EAD ($P < 0.01$); data from a large cohort study in 1950 consecutive primary liver transplants.
HTK, histidine-tryptophan-ketoglutarate; MELD, Model for End-Stage Liver Disease.

TABLE 17.

Considerations for managing EAD and nonanastomotic BS in liver transplantation[32,384,387,388,392,395,397-402]

Considerations	Potential interventions
Donor management	• Pretreatment of donors with steroids as standard practice • Cold ischemia time (the period between cold flush in the donor and graft implantation in the recipient) should be kept as short as possible, particularly for higher risk livers (DCD, steatosis) • All periods of warm ischemia should be kept as short as possible • Warm ischemia during procurement by: a rapid dual (aortic and portal) cold flush, an abundant use of topical cooling, and a rapid extraction time • Bile ducts abundantly and properly flushed during, and at the end of procurement • HTK should be avoided for liver preservation, and University of Wisconsin/Celsior preservation solutions preferentially used • Multi-interventional strategies (targeting simultaneously multiple pathways) still to be tested for the prevention of IRI • Future research: hypothermic and, particularly, normothermic machine perfusion have been proven to be clinically safe and have the potential to better preserve and assess (and resuscitate) livers, and decrease EAD and nonanastomotic BS
Recipient management	• Future research: mesenchymal stem cells have been shown to enhance recovery from acute renal failure, and protect against liver IRI in animal models

(Table 17). Modification of risk factors should begin during preretrieval of the organ for transplantation, and should continue throughout procurement, preservation of the organ, and peritransplantation and posttransplantation.

Transplant teams classically aim to procure organs rapidly to avoid sustained brain death-induced inflammation. Recent studies on kidney transplantation suggest that delaying retrieval after brain death is beneficial for organ recovery,[383] because it allows anti-inflammatory mechanisms to become activated. Whether this strategy ('relax and repair' instead of 'rush and retrieve')[383] is also valid in liver transplantation is still to be confirmed. A recent clinical trial has demonstrated that the use of steroid therapy in deceased donors reduces IRI and biliary injury, and improves graft function.[384] The administration of an infusion of *N*-acetylcysteine before and during procurement has also shown efficacy in improving graft survival in liver transplantation.[385]

Organ manipulation, which can induce liver injury during procurement,[386] should be minimized. Rapid extraction is necessary to prevent rewarming of the organ after perfusion, because prolonged extraction time has been linked to early graft failure in kidney transplantation.[387] The use of a double perfusion strategy (aortic and portal flush) is beneficial for suboptimal livers because it reduces primary graft dysfunction and increases patient and graft survival.[388] The incidence of nonanastomotic BS has been reduced through the use of low-viscosity preservation fluids, fluid pressurisation, and the addition of urokinase to the preservation solution in the hepatic artery.[389,390] However, a recent retrospective study has shown that flushing the liver with urokinase immediately before implantation did not lead to a lower incidence of nonanastomotic BS.[391]

Data from the European Liver Transplant Registry suggest that the University of Wisconsin, Celsior and Institut Georges Lopez-1 preservation solutions perform better than histidine-tryptophan-ketoglutarate (HTK) solution, the latter being associated with a 10% increase in the risk of graft loss.[32] A recent meta-analysis has also confirmed that the University of Wisconsin and Celsior preservation solutions result in similar outcomes, including rates of EAD.[392] The administration of a pan-caspase inhibitor to the preservation solution has also been shown to result in lower transaminase levels.[393] In animal models, the addition of trophic factors to preservation solutions may also improve organ function immediately posttransplant.[394] For low- and normal-risk organs, cold storage may be suitable, but the time taken to reach 4 °C and the low, yet persistent, level of metabolism at this temperature can cause tissue trauma in the absence of oxygen. Conversely, towards the end of cold storage, retrograde oxygen perfusion may actually reduce EAD.[395,396]

Recently, organ preservation has been revolutionized by the development of hypothermic machine perfusion and normothermic machine perfusion. In normothermic machine perfusion, the liver is kept viable ex situ by perfusion with warm oxygenated blood.[395,399] Mild hypothermia may lower the rate of DGF in kidney transplantation recipients, especially if high-risk donors, such as donors with a high KDPI, are used.[367]

In a study of hypothermic machine perfusion in 31 adults receiving livers from donors with a high KDPI, EAD was lower in this group (19%) compared to the static cold storage control group (30%), with significantly less biliary complications (4 vs 13; $P = 0.016$).[397] Reperfusion injury is also rare in these machine-perfused DCD livers.[398]

Liver studies in animal models are ongoing. In a porcine model, continuous hypothermic machine perfusion reduced hepatocyte injury but also led to an increase in Kupffer and sinusoidal endothelial cell activation, which can eventually result in poor long-term graft survival.[403] However, improved results may be achieved through the use of postcold storage hypothermic machine perfusion.[404] The big question is whether hypothermic machine perfusion techniques reduce the incidence of nonanastomotic BS. Studies in pigs and rats have shown a reduction in arteriolo-necrosis of the peribiliary plexus[405] and reduced intrahepatic biliary fibrosis,[406] but these results require verification in RCTs. A recent study in rats reported that normothermic machine perfusion provided better preservation of bile duct epithelial cell function and morphology in both DCD, and non-DCD livers (after 3 hours, followed by 2 hours ex vivo reperfusion), compared with static cold storage.[399] Another study using continuous normothermic machine perfusion from procurement to transplantation in pig liver transplants resulted in good posttransplantation survival, even after 20 hours of warm preservation.[400] The use of continuous perfusion is thought to be necessary because normothermic

machine perfusion is less effective after cold storage.[400] Ongoing trials will hopefully answer whether this strategy can reduce the incidence of EAD and nonanastomotic BS.[400] With advances in the understanding of the etiology of nonanastomotic BS, machine perfusion may be best placed to provide a better protective effect during donor liver preservation.[407]

Organ management in the recipient is especially important when attempting to mitigate IRI. Currently, there is uncertainty as to whether the use of erythropoietin derivatives is beneficial[408]; however, the use of antiselectins does appear to reduce IRI after liver transplantation,[409] and inhaled nitric oxide can be used to recover liver function posttransplantation.[410]

In conclusion, EAD and nonanastomotic BS remain major risk factors for poor graft survival in liver transplantation. However, certain known risk factors can be adjusted and interventions can be used to mitigate them in clinical practice. Some strategies are already available, and should be part of the standard of care for patients, and some are in development, but it is important that interventions be applied at each step of the transplantation process.

Recommendations for Managing EAD and Nonanastomotic BS in Liver Transplantation

1. EAD and nonanastomotic BS should be prevented by targeting all the factors related to all stages of liver transplantation, from preretrieval of the organ, through to procurement, preservation of the organ, and posttransplantation. *(Level 4)*
2. Donor pretreatment with corticosteroids should be standard. *(Level 2)*
3. Cold ischemia time (the period between cold flush in the donor and graft implantation in the recipient) should be kept as short as possible, particularly for higher-risk livers (DCD, steatosis, etc). *(Level 3)*
4. All periods of warm ischemia should be kept as short as possible. *(Level 4)*
   - Warm ischemia in DCD donors
   - Warm ischemia during procurement by:
     - a rapid dual (aortic and portal) cold flush
     - an abundant use of topical cooling, and
     - a rapid extraction time, and
   - Finally, a short implantation time in the recipient *(Level 5)*
5. Bile duct should be abundantly and properly flushed during and at the end of the procurement. *(Level 2)*
6. HTK should be avoided for liver preservation. *(Level 3)*
7. Multi-interventional strategies (simultaneously targeting multiple pathways) will have to be tested for the prevention of IRI. *(Level 4)*
8. Hypothermic and, particularly, normothermic machine perfusion have proven to be clinically safe and have the potential to better preserve and assess (and resuscitate) livers, and decrease EAD and nonanastomotic BS. *(Level 3)*

CONCLUSION AND CALL TO ACTION

Patient and graft outcomes continue to improve in the short-term postkidney or postliver transplant, with survival rates now at over 80% at the 1-year mark. Unfortunately, there are still challenges remaining that negatively affect longer-term prognosis of these individuals. Improving the maintenance of grafts and health of patients would not only improve quality of life, but would also reduce the need for retransplantation and thus increase the number of organs available for transplant. The clinical transplant community needs to identify and manage those patient factors which are within its control to modify, to decrease the risk of graft failure and improve longer-term outcomes.

There are many risk factors for graft loss. Modifiable risk factors influencing the longer-term maintenance of the graft and patient include nonadherence, IPV, underimmunosuppression, adverse effects due to immunosuppression, DSAs, and cardiovascular and metabolic complications. With this guidance document and checklist, the COMMIT group have provided practical recommendations for both the identification and management of these modifiable risk factors postkidney and postliver transplant. It is hoped that these recommendations will become a routine part of the posttransplantation management paradigm to maximize the life of the graft and patient.

Some strategies to manage risk are already available, and should be part of the standard of care for patients, and some are still in development. For others, such as DSAs, emerging evidence will help to fully establish the implications on long-term outcomes. Nevertheless, it is important that the interventions are applied at each step of the transplantation process in order to improve graft and patient outcomes for both kidney and liver transplants in the long as well as the short term.

The field of transplantation will undoubtedly benefit from research, which will result in better understanding the immunological mechanisms of graft rejection. It will also lead to improved use of immunosuppression, which will promote tolerance and reduce or even abolish the need for long-term treatment with immunosuppressive agents, and so reduce associated adverse effects. Improved management of the donor and improved preservation techniques, with the development of validated biomarkers to identify viable organs and to help guide immunosuppression, will increase the number and quality of organs for transplantation. Although the future looks promising for the field of transplantation, recipients and HCPs must not lose sight of those factors that can be modified today, so leading to the best possible future outcomes for the recipients, and giving consolation to the donor family.

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Appendix 1

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

Appendix 2

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POST-KIDNEY TRANSPLANT PATIENT CARE CHECKLIST

This checklist is intended to help the clinician in the management of modifiable risk factors for graft loss in kidney transplant patients over 1 year post-transplant and should be used in conjunction with local guidelines.

Patient name:

Patient ID: DOB:

Gender:

Indication for transplant:

Date of transplant:

☐ Left kidney ☐ Right kidney

☐ Presence of preformed antibodies

☐ Presence of *de novo* DSAs ☐ Re-transplant

Other relevant comorbidities (e.g. HIV infection, combined transplant, previous PTLD/cancer):

BEFORE YOU SEE THE PATIENT

☐ Review the patient's immunosuppressive regimen, concomitant medication and over-the-counter medications

☐ Review immunosuppression serum trough levels over the previous year and identify any significant variation

☐ Review BMI, BP, fasting plasma glucose and renal function

☐ Document any known risk factors for non-adherence:

☐ Each year, consider immunisation status, cardiovascular status and cancer surveillance

CLINICAL VARIABLES

(This checklist is intended to be used in addition to the biochemistry and serology lab report for the patient):

BP: / mmHg

HR: /min Weight: kg

Height: m BMI: kg/m²

Current smoker: Yes No Number per day:

Average alcohol intake: units/week

Medication:

Immunosuppressant doses and levels:

Tacrolimus | Cyclosporine | Sirolimus

Everolimus | Mycophenolate | Corticosteroids

Azathioprine

Drug	Level	Corresponding daily dose
	ng/mL	/day
	ng/mL	/day
	ng/mL	/day

Other:

Latest renal allograft biopsy report (when applicable):

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REVIEW IMMUNOSUPPRESSION

Is the serum trough level within the desired range?

- ☐ **Yes** – continue to adhere to target immunosuppression levels, or consider a carefully monitored minimisation regimen if deemed clinically appropriate
- ☐ **No** – below therapeutic range
  Consider the possible causes
- ☐ **No** – above therapeutic range
  - ☐ Is this a true trough level? (check correct dosing time and sampling time)
  - ☐ Be aware of potential immunosuppressive drug-related adverse effects *See section 1*
  - ☐ Be aware of patients overdosing to compensate for non-adherence

Non-adherence
See section 3

Intra-patient variability

Consider:

- ☐ Drug–drug interactions
- ☐ Food intake
- ☐ Generic substitution
- ☐ Gastrointestinal causes
- ☐ Non-adherence

See section 4

Review the immunosuppression regimen

1. IS THE PATIENT EXPERIENCING ANY IMMUNOSUPPRESSIVE DRUG-RELATED ADVERSE EFFECTS OR SYMPTOMS?

e.g. tremor, headache, hypertension, renal impairment, diabetes, infection, malignancy

- ☐ *No – continue with annual screening listed below.*
- ☐ *Yes – investigate appropriately. Consider underlying factors and treat accordingly. Investigate trough levels and immunosuppressive regimen. Consider whether beneficial changes can be made.*

Annually:

- ☐ If appropriate, request a yearly abdominal ultrasound examination to detect intra-abdominal tumours (especially renal cell carcinoma of the native kidney)
- ☐ Enquire if the patient has been attending routine surveillance programmes for prostrate, breast, cervical and colon cancer as appropriate

If no – educate the patient on the importance of this and refer appropriately.

- ☐ Conduct surveillance of skin cancers

If no – educate them on the importance of routine self-examination/inspection and refer to dermatologist if the patient has a suspicious lesion. Consider annual review based on local practice.

- ☐ Does the patient have unexplained gastrointestinal symptoms?

If yes – request an endoscopy.

- ☐ Consider sexual and reproductive health (especially teratogenic effect of some immunosuppressive drugs) and discuss family planning
- ☐ Consider bone health: if at risk of osteoporosis, consider a DEXA scan and provide supplements such as calcium and vitamin D or treatment such as bisphosphonates
- ☐ Has the eGFR persistently decreased and/or fallen below 45mL/min/m^2 (CKDT3B) and/or is proteinuria present?

If yes – consider performing a renal ultrasound and/or renal biopsy.

- ☐ Cardiovascular check-up (e.g. cardiac ultrasound, stress test, arterial Doppler, etc)
- ☐ Any other relevant comorbid condition should be assessed or referred appropriately at least once yearly (e.g. diabetes mellitus, respiratory diseases, ophthalmic disorders, neurological diseases, etc)

2. CARDIO- AND CEREBRO-VASCULAR AND METABOLIC COMPLICATIONS

- ☐ Encourage regular exercise (at least 150 minutes per week, 10,000 steps/day)
- ☐ Encourage cessation of smoking (if indicated, refer to respiratory specialist team for coaching)
- ☐ Review alcohol consumption and advise/refer if appropriate (e.g. psychologist, alcohol counsellor)*
- ☐ Check BP, blood sugar and cholesterol concentrations
- Consider statins (e.g. fluvastatin), anti-hypertensives (e.g. calcium channel blockers) and glucose-lowering agents
- ☐ Encourage maintaining an adequate weight (BMI <25kg/m^2)
- ☐ Provide dietary information and/or support
- ☐ Establish allied health professional team support for lifestyle adjustment
- ☐ Annual cardiovascular check-up (e.g. ECG)

Follow guidelines for general population. If BMI, BP, glucose, HbA1c or low-density lipoprotein cholesterol are outside of normal range, consider underlying factors and provide patient education as necessary. Consider referral to cardiovascular specialist.

3. STRATEGIES FOR MANAGING NON-ADHERENCE

The 'fifth' vital sign post-transplantation. Non-adherence to immunosuppressive regimen is a common and independent risk factor for poor clinical outcomes.

Drug-adherence monitoring:

- ☐ Monitor prescription refills, patient self-report, pill counts, assess intra-patient variability over time (use new digital technology/electronic monitoring where appropriate/available)

Collaborative assessment (if clinically indicated):

- ☐ Psychologists
- ☐ Nursing staff
- ☐ Pharmacists

Self-reporting:

- ☐ BAASIS© or IMAB questionnaire
- ☐ Other validated self-reporting questionnaires

Patient-level intervention:

- ☐ Consider a more simplified regimen (e.g. monotherapy, once-daily dosing)
- ☐ Provide clear, printed medication instructions and medication schedules at an appropriate level for the patient's health literacy
- ☐ Encourage counselling/behavioural intervention (e.g. use of a pill box, reminders, motivational interview)
- ☐ Engage with the pharmacy team for help and support around adherence
- ☐ Involve family and the use of specialised support groups

4. INTRA-PATIENT VARIABILITY

- ☐ Has the patient been experiencing gastrointestinal events?

If yes – increase trough-level monitoring frequency (weekly if high risk) and investigate underlying factors or refer to gastrointestinal specialist as required. Consider prolonged-release dosing of immunosuppressant(s).

- ☐ Does the patient follow dietary advice (no grapefruit juice, avoid herbal products, etc)?

If no – increase trough-level monitoring frequency and encourage a healthy diet. Provide patient education or refer to a dietician or specialist nurse as required.

- ☐ Is there a potential drug–drug interaction?

If yes – correct as necessary, avoiding any potential interactions.

- ☐ Has there been a recent switch to a generic substitute?

If yes – return to prescribing the original drug regimen and increase trough-level monitoring frequency (weekly if high risk) until the variability is not clinically relevant.

- ☐ Has there been an episode of kidney graft dysfunction?

If yes – increase trough-level monitoring frequency (weekly if high risk) and correct the underlying factors if possible.

5. *DE NOVO* DONOR-SPECIFIC ANTIBODIES (DSAs)

The role of DSAs is not fully understood but it is worth considering, especially:

- ☐ Before considering minimising immunosuppression
- ☐ With unexpected graft dysfunction (e.g. after immunosuppression minimisation)
- ☐ With any type of rejection (clinical, subclinical, chronic)
- ☐ In patients with preformed DSAs:
  - DSAs should be tested for in the first 3 months post-transplant (ideally with a protocol renal biopsy at 3 months)
- ☐ In patients without preformed antibodies:
  - DSAs should be tested for once between 3–12 months post-transplant
- ☐ In patients with *de novo* DSA formation:
  - DSAs should be checked for as indicated and after adjustment of immunosuppressive regimen
- ☐ Suspicion of non-adherence associated with graft dysfunction

DSAs can be monitored through specific assays (e.g. single-antibody bead assay).

GUIDELINES

This checklist is intended to help the clinician in the management of modifiable risk factors for graft loss in kidney transplant recipients. It has been developed specifically for use with adult kidney transplant recipients during routine monitoring at 1 or more years post-transplant.

How to use the checklist:

This checklist can be used by clinicians in more than one way, with the optional step of tick boxes. It is intended to be suitable for use:

- In booklet form, as part of a patient's medical notes, to act as a useful guide before and during a patient consultation
- As an A3 wall poster (centre pages), providing generalised information on modifiable risk factors to be aware of during routine care post transplantation

Useful links:

http://www.riskfactorcalculator.eu/ (BAASIS® questionnaire, renal function calculator, variability calculator)

https://www.uea.ac.uk/pharmacy/research/imab-q/quest (IMAB questionnaire)

http://www.rxlist.com/drug-interaction-checker.htm (Drug–drug interaction checker)

http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/metric_bmi_calculator/bmi_calculator.html (BMI calculator)

http://www.drinkingandyou.com/site/pdf/Sensibledrinking.pdf (Alcohol consumption guidelines)

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/545937/UK_CMOs__report.pdf (Alcohol consumption guidelines)

Abbreviations:

BAASIS® – Basel Assessment of Adherence to Immunosuppressive Medication Scale

CKDT3B – Stage 3B chronic kidney disease (moderately reduced kidney function) in renal transplant recipient

DSA – Donor-specific antibodies

IMAB – Identification of Medication Adherence Barriers

PTLD – Post-transplant lymphoproliferative disorder

Multi-level risk factors for non-adherence to immunosuppressive regimens

Risk factor	Examples
Sociodemographic factors	• Adolescence, senior patient age (e.g. when cognitively impaired) • Lack of social support • Non-white race
Patient-related factors	• Previous non-adherence • Disturbing side-effects • Barriers: busy lifestyle, interruption of daily routine • Forgetfulness • Inadequate health beliefs • History of substance abuse
Treatment-related factors	• Higher complexity and longer duration of the drug regimen, number of prescribed pills • Taste and size of the pill
Condition-related factors	• Depressive symptomatology
Healthcare teams and systems factors	• Lack of adherence assessment as part of regular transplant follow-up • Lack of adherence support as part of transplant follow-up • Lack of coverage of immunosuppressive drugs • Healthcare professionals not trained in behavioural assessment and interventions, or adequate communication style

Disclaimers and development process:

The checklist should be used in conjunction with local guidelines and should not replace clinical judgment. It is intended to be used as a clinical aid, rather than a comprehensive protocol.

*Alcohol consumption policies will vary between transplant units and some patients should not drink alcohol. The recommendation of safe drinking varies between countries in healthy non-transplant adults. For liver transplant patients, advice on alcohol consumption will vary by indication.

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Appendix 3

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POST-LIVER TRANSPLANT PATIENT CARE CHECKLIST

This checklist is intended to help the clinician in the management of modifiable risk factors for graft loss in liver transplant patients over 1 year post-transplant and should be used in conjunction with local guidelines.

Patient name:

Patient ID: DOB:

Gender:

Indication for transplant:

Date of transplant:

Type of transplant: (e.g. whole, split, donation after cardiac death, donation after brain death)

Other relevant comorbidities:

BEFORE YOU SEE THE PATIENT

- ☐ Review the patient's immunosuppressive regimen, concomitant medication and over-the-counter medications
- ☐ Review immunosuppression serum trough levels over the previous year and identify any significant variation
- ☐ Review BMI, BP, fasting plasma glucose and renal function
- ☐ Document any known risk factors for non-adherence:
- ☐ Each year, consider immunisation status, cardiovascular status, cancer surveillance

CLINICAL VARIABLES

(This checklist is intended to be used in addition to the biochemistry and serology lab report for the patient)

BP: / mmHg

HR: /min Weight: kg

Height: m BMI: kg/m²

Current smoker: Yes No Number per day:

Average alcohol intake: units/week

Medication:

Immunosuppressant doses and levels:

Tacrolimus | Cyclosporine | Sirolimus

Everolimus | Mycophenolate | Corticosteroids

Azathioprine

Drug	Level	Corresponding daily dose
	ng/mL	/day
	ng/mL	/day
	ng/mL	/day

Other:

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REVIEW IMMUNOSUPPRESSION

Is the serum trough level within the desired range?

- ☐ **Yes** – continue to adhere to target immunosuppression levels, or consider a carefully monitored minimisation regimen if deemed clinically appropriate
- ☐ **No** – below therapeutic range
  Consider the possible causes
- ☐ **No** – above therapeutic range
  - ☐ Is this a true trough level? (check correct dosing time and sampling time)
  - ☐ Be aware of potential immunosuppressive drug-related adverse effects
    See section 1
  - ☐ Be aware of patients overdosing to compensate for non-adherence

Non-adherence
See section 3

Intra-patient variability

Consider:

- ☐ Drug–drug interactions
- ☐ Food intake
- ☐ Generic substitution
- ☐ Gastrointestinal causes
- ☐ Non-adherence

See section 4

Review the immunosuppression regimen

1. IS THE PATIENT EXPERIENCING ANY IMMUNOSUPPRESSIVE DRUG-RELATED ADVERSE EFFECTS OR SYMPTOMS?

e.g. tremor, headache, hypertension, renal impairment, diabetes, infection, malignancy

- ☐ *No – continue with annual screening listed below.*
- ☐ *Yes – investigate appropriately. Consider underlying factors and treat accordingly. Investigate trough levels and immunosuppressive regimen. Consider whether beneficial changes can be made.*

Annually:

- ☐ Is the patient high risk for head and neck or lung cancers (alcohol/smoking)?

If yes – conduct a physical examination, including the oropharynx. If >50 years and symptomatic also consider a low-dose CT scan or chest X-ray.

If no – conduct a physical examination, including the oropharynx.

- ☐ Enquire whether the patient has been attending routine surveillance programmes for prostate, breast, cervical and colon cancer as appropriate

If no – educate the patient on the importance of this and refer appropriately.

- ☐ Conduct surveillance of skin cancers

If no – educate them on the importance of routine self-examination/inspection and refer to dermatologist if the patient has a suspicious lesion. Consider annual review based on local practice.

- ☐ Does the patient have unexplained gastrointestinal symptoms?

If yes – request an endoscopy.

- ☐ Consider sexual and reproductive health (especially teratogenic effect of some immunosuppressive drugs) and discuss family planning
- ☐ Consider bone health: if at risk of osteoporosis, consider a DEXA scan and provide supplements such as calcium and vitamin D or treatment such as bisphosphonates
- ☐ Has the eGFR persistently decreased and/or fallen below 45mL/min/m^2 (CKDT3B)?

If yes – consider performing a renal ultrasound, referral to renal specialist and/or renal biopsy.

- ☐ Cardiovascular check-up (e.g. cardiac ultrasound, stress test, arterial Doppler, etc)
- ☐ Any other relevant comorbid condition should be assessed or referred appropriately at least once yearly (e.g. diabetes mellitus, respiratory diseases, ophthalmic disorders, neurological diseases, etc)

2. CARDIO- AND CEREBRO-VASCULAR AND METABOLIC COMPLICATIONS

- ☐ Encourage regular exercise (at least 150 minutes per week, 10,000 steps/day)
- ☐ Encourage cessation of smoking (if indicated, refer to respiratory specialist team for coaching)
- ☐ Review alcohol consumption and advise/refer if appropriate (e.g. psychologist, alcohol counsellor)*
- ☐ Check BP, blood sugar and cholesterol concentrations
  - Consider statins (e.g. fluvastatin), anti-hypertensives (e.g. calcium channel blockers) and glucose-lowering agents
- ☐ Encourage maintaining an adequate weight (BMI <25kg/m^2)
- ☐ Provide dietary information and/or support
- ☐ Establish allied health professional team support for lifestyle adjustment
- ☐ Annual cardiovascular check-up (e.g. ECG)

Follow guidelines for general population. If BMI, BP, glucose, HbA1c or low-density lipoprotein cholesterol are outside of normal range, consider underlying factors and provide patient education as necessary. Consider referral to cardiovascular specialist.

3. STRATEGIES FOR MANAGING NON-ADHERENCE

The 'fifth' vital sign post-transplantation. Non-adherence to immunosuppressive regimen is a common and independent risk factor for poor clinical outcomes.

Drug-adherence monitoring:

- ☐ Monitor prescription refills, patient self-report, pill counts, assess intra-patient variability over time (use new digital technology/electronic monitoring where appropriate/available)

Collaborative assessment (if clinically indicated):

- ☐ Psychologists
- ☐ Nursing staff
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Self-reporting:

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- ☐ Other validated self-reporting questionnaires

Patient-level intervention:

- ☐ Consider a more simplified regimen (e.g. monotherapy, once-daily dosing)
- ☐ Provide clear, printed medication instructions and medication schedules at an appropriate level for the patient's health literacy
- ☐ Encourage counselling/behavioural intervention (e.g. use of a pill box, reminders, motivational interview)
- ☐ Engage with the pharmacy team for help and support around adherence
- ☐ Involve family and the use of specialised support groups

4. INTRA-PATIENT VARIABILITY

- ☐ Has the patient been experiencing gastrointestinal events?

If yes – increase trough-level monitoring frequency (weekly if high risk) and investigate underlying factors or refer to gastrointestinal specialist as required. Consider prolonged-release dosing of immunosuppressant(s).

- ☐ Does the patient follow dietary advice (no grapefruit juice, avoid herbal products, etc)?

If no – increase trough-level monitoring frequency and encourage a healthy diet. Provide patient education or refer to a dietician or specialist nurse as required.

- ☐ Is there a potential drug–drug interaction?

If yes – correct as necessary, avoiding any potential interactions.

- ☐ Has there been a recent switch to a generic substitute?

If yes – return to prescribing the original drug regimen and increase trough-level monitoring frequency (weekly if high risk) until the variability is not clinically relevant.

- ☐ Has the patient experienced a liver graft event?

If yes – increase trough-level monitoring frequency (weekly if high risk) and correct the underlying factors if possible.

5. *DE NOVO* DONOR-SPECIFIC ANTIBODIES (DSAs)

The role of DSAs is not fully understood but it is worth considering, especially:

- ☐ Before considering minimising immunosuppression
- ☐ With unexpected graft dysfunction
- ☐ With any type of rejection (clinical, subclinical, chronic)
- ☐ In all patients at 1, 5 and 10 years post-transplant

DSAs can be monitored through specific assays (e.g. single-antibody bead assay).

GUIDELINES

This checklist is intended to help the clinician in the management of modifiable risk factors for graft loss in liver transplant recipients. It has been developed specifically for use with adult liver transplant recipients during routine monitoring at 1 or more years post-transplant.

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Useful links:

http://www.riskfactorcalculator.eu/
(BAASIS® questionnaire, renal function calculator, variability calculator)

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(IMAB questionnaire)

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(Drug–drug interaction checker)

http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/metric_bmi_calculator/bmi_calculator.html
(BMI calculator)

http://www.drinkingandyou.com/site/pdf/Sensibledrinking.pdf (Alcohol consumption guidelines)

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/545937/UK_CMOs__report.pdf (Alcohol consumption guidelines)

Abbreviations:

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CKDT3B – Stage 3B chronic kidney disease (moderately reduced kidney function)

DSA – Donor-specific antibodies

IMAB – Identification of Medication Adherence Barriers

Multi-level risk factors for non-adherence to immunosuppressive regimens

Risk factor	Examples
Sociodemographic factors	• Adolescence, senior patient age (e.g. when cognitively impaired) • Lack of social support • Non-white race
Patient-related factors	• Previous non-adherence • Disturbing side-effects • Barriers: busy lifestyle, interruption of daily routine • Forgetfulness • Inadequate health beliefs • History of substance abuse
Treatment-related factors	• Higher complexity and longer duration of the drug regimen, number of prescribed pills • Taste and size of the pill
Condition-related factors	• Depressive symptomatology
Healthcare teams and systems factors	• Lack of adherence assessment as part of regular transplant follow-up • Lack of adherence support as part of transplant follow-up • Lack of coverage of immunosuppressive drugs • Healthcare professionals not trained in behavioural assessment and interventions, or adequate communication style

Disclaimers and development process:

The checklist should be used in conjunction with local guidelines and should not replace clinical judgment. It is intended to be used as a clinical aid, rather than a comprehensive protocol.

*Alcohol consumption policies will vary between transplant units and some patients should not drink alcohol. The recommendation of safe drinking varies between countries in healthy non-transplant adults. For liver transplant patients, advice on alcohol consumption will vary by indication.

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ADVAGRAF™ 0.5 mg, 1 mg, 3 mg and 5 mg Prolonged-release hard capsules (tacrolimus) PROGRAF™ 0.5 mg, 1 mg and 5 mg hard capsules (tacrolimus)

Presentations: ADVAGRAF Prolonged-release hard capsules containing tacrolimus 0.5 mg, 1 mg, 3 mg and 5 mg PROGRAF hard capsules containing tacrolimus 0.5 mg, 1 mg and 5 mg. **Indications:** ADVAGRAF and PROGRAF: Prophylaxis of transplant rejection in adult liver or kidney allograft recipients and treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products. **Posology and Administration:** ADVAGRAF and PROGRAF therapy require careful monitoring by adequately qualified and equipped personnel. Either drug should only be prescribed, and changes in immunosuppressive therapy initiated, by physicians experienced in immunosuppressive therapy and the management of transplant patients. Dosage recommendations given below should be used as a guideline. ADVAGRAF or PROGRAF are routinely administered in conjunction with other immunosuppressive agents in the initial post-operative period. The dose may vary depending on the immunosuppressive regimen chosen. Dosing should be based on clinical assessments of rejection and tolerability aided by blood level monitoring. To suppress graft rejection immunosuppression must be maintained so no limit to the duration of oral therapy can be given. The daily dose of ADVAGRAF capsules should be taken once daily in the morning with fluid (preferably) water at least 1 hour before or 2-3 hours after a meal. PROGRAFcapsules should be taken as for ADVAGRAF, in two divided doses. ADVAGRAF: In stable patients converted from PROGRAF (twice daily) to ADVAGRAF (once daily) on a 1:1 (mg:mg) total daily dose basis the systemic exposure to tacrolimus for ADVAGRAF was approximately 10% lower than for PROGRAF. The relationship between tacrolimus trough levels (C_{24}) and systemic exposure (AUC_{0-24}) for ADVAGRAF is similar to that of PROGRAF. When converting from PROGRAF capsules to ADVAGRAF trough levels should be measured before and within two weeks after conversion. In de novo kidney and liver transplant patients AUC_{0-24} of tacrolimus for ADVAGRAF on Day 1 was 30% and 50% lower respectively, when compared with that for the immediate release capsules (PROGRAF) at equivalent doses. By Day 4, systemic exposure as measured by trough levels is similar for both kidney and liver transplant patients with both formulations. Race: In comparison to Caucasians, black patients may require higher tacrolimus doses to achieve similar trough levels. **Prophylaxis of transplant rejection** – liver and kidney: Initial dose of ADVAGRAF and PROGRAF capsules is 0.10-0.20 mg/kg/day for liver transplantation and 0.20-0.30 mg/kg/day for kidney transplantation starting approximately 12-18 hours for ADVAGRAF and 12hrs for PROGRAF after completion of liver or within 24 hours of completion of kidney transplant surgery. Dose adjustment post-transplant: ADVAGRAF and PROGRAF doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy leading to ADVAGRAF monotherapy or PROGRAF dual therapy or monotherapy. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments. Dose recommendations – Conversion to ADVAGRAF. Patients maintained on twice daily PROGRAF requiring conversion to once daily ADVAGRAF should be converted on a 1:1 (mg:mg) total daily dose basis. Following conversion, tacrolimus trough levels should be monitored and if necessary dose adjustments made. Care should be taken when converting patients from ciclosporin-based to tacrolimus-based therapy. Initiate ADVAGRAF after considering ciclosporin blood concentrations and clinical condition of patient. Delay dosing in presence of elevated ciclosporin blood levels. Monitor ciclosporin blood levels following conversion. Dose recommendations – Rejection therapy. Increased doses of tacrolimus, supplemental corticosteroid therapy and introduction of short courses of mono-/polyclonal antibodies have all been used. If signs of toxicity are noted the dose may need to reduced. For conversion to PROGRAF, treatment should begin with the initial oral dose recommended for primary immunosuppression. For conversion of kidney and liver recipients from other immunosuppressants to once daily ADVAGRAF, begin with the respective initial dose recommended for rejection prophylaxis. In adult heart transplant recipients converted to ADVAGRAF, an initial oral dose of 0.15 mg/kg/day should be administered once daily in the morning. For other allografts, see SPC. Therapeutic drug monitoring: Blood trough levels for ADVAGRAF should be drawn approximately 24 hours post-dosing, just prior to the next dose, for PROGRAF approximately 12 hours post-dosing. Frequent trough level monitoring in the early transplant period is recommended, with periodic monitoring during maintenance therapy. Monitoring is also recommended following conversion from PROGRAF to ADVAGRAF, dose adjustment, changes in the immunosuppressive regimen, or co-administration of substances which may alter tacrolimus whole blood concentrations (see 'Warnings and Precautions' and 'Interactions'). Adjustments to the ADVAGRAF and PROGRAF dose regimen may take several days before steady state is achieved. Most patients can be managed successfully if tacrolimus blood concentrations are maintained below 20 ng/mL. In clinical practice, whole blood trough levels have been 5-20 ng/mL in liver transplant recipients and 10-20 ng/mL in kidney transplant recipients early post-transplant, and 5-15 ng/mL during maintenance therapy. Dose adjustments in specific populations: See SPC. **Contraindications**: Hypersensitivity to tacrolimus or other macrolides or any excipient. **Warnings and Precautions**: Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations, have led to serious adverse events, including graft rejection, or other side effects which could be a consequence of either under- or over-exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist. ADVAGRAF only limited experience in non-Caucasian patients and those at elevated immunological risk. ADVAGRAF is not recommended for use in children below 18 years due to limited data on safety and efficacy. ADVAGRAF and PROGRAF: During the initial period routinely monitor blood pressure, ECG, neurological and visual status, fasting blood glucose, electrolytes (particularly potassium), liver and renal function tests, haematology parameters, coagulation values, and plasma protein determinations; consider adjusting the immunosuppressive regimen if clinically relevant changes are seen. Monitor tacrolimus levels when co-administering strong inducers or inhibitors

of CYP3A4. Herbal preparations, including those containing St. John's Wort, should be avoided. Extra monitoring of tacrolimus concentrations is recommended during episodes of diarrhoea. Avoid concomitant administration of ciclosporin. Ventricular hypertrophy or hypertrophy of the septum (reported as cardiomyopathy) have been reported, occurring with tacrolimus blood trough concentrations much higher than the recommended maximum tacrolimus blood trough concentrations levels. Other risk factors for these conditions include pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema. Echocardiography or ECG monitoring pre- and post-transplant is advised in high-risk patients, and dose reduction or a change of immunosuppressive agent should be considered if abnormalities develop. Tacrolimus may prolong the QT interval. Exercise caution in specific patients – see SPC.. Patients are at increased risk of all opportunistic infections including BK Virus associated nephropathy and JC Virus associated progressive multifocal leukoencephalopathy (PML); consider in patients with deteriorating renal function or neurological symptoms. Patients have been reported to develop posterior reversible encephalopathy syndrome (PRES), if so radiological tests should be performed. If PRES is diagnosed, control blood pressure and seizures and immediately discontinue tacrolimus. Epstein Barr Virus (EBV)-associated lymphoproliferative disorders have been reported: concomitant use of other immunosuppressives such as antilymphocytic antibodies increase the risk. EBV-Viral Capsid Antigen (VCA)- negative patients have been reported to have increased risk of lymphoproliferative disorders; EBV-VCA serology should be ascertained before starting tacrolimus treatment. During treatment, careful monitoring with EBV-PCR is recommended. Exposure to sunlight and UV light should be limited. The risk of secondary cancer is unknown. Dose reduction may be necessary in patients with severe liver impairment. Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. All patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease or concomitant medications associated with PRCA. The printing ink used to mark ADVAGRAF capsules contains soya lecithin. In patients who are hypersensitive to peanut or soya, the risk and severity of hypersensitivity should be weighed against the benefit of using ADVAGRAF. Capsules contain lactose. **Interactions**: See SPC. Tacrolimus is metabolised by CYP3A4. Concomitant use of CYP3A4 inhibitors/inducers may increase/decrease tacrolimus blood levels. Monitoring of tacrolimus blood levels, renal function,side effects and QT prolongation is strongly recommended during concomitant use. Interrupt/adjust tacrolimus dose as necessary to maintain similar tacrolimus exposure. Tacrolimus is a CYP3A4 inhibitor; concomitant use with products metabolised by this enzyme may affect the metabolism of these products. **Pregnancy and lactation**: Tacrolimus can be considered in pregnant women when there is no safer alternative. Cases of spontaneous abortion have been reported. In case of in utero exposure, monitoring of the newborn for the potential adverse events of tacrolimus is recommended . Women should not breast feed whilst receiving tacrolimus, see SPC. **Undesirable effects**: Infections: Cases of BK Virus associated nephropathy, as well as cases of JC Virus associated PML have been reported. Neoplasms: Increased risk of malignancies. Malignant neoplasms including EBV-associated lymphoproliferative disorders and skin malignancies have been reported. Cases of pure red cell aplasia have been reported. Very Common (≥1/10): Hyperglycaemic conditions, diabetes mellitus, hyperkalaemia, insomnia, tremor, headache, hypertension, diarrhoea, nausea, renal impairment, infections, liver function test abnormal, Common (≥1/100 to <1/10): Haematological abnormalities, electrolytes decreased, fluid overload, hyperuricaemia, appetite decreased, , metabolic acidoses, lipid disorders, hypophosphataemia, anxiety symptoms, mental disorders, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, seizures, disturbances in consciousness, paraesthesias and dysaesthesias, peripheral neuropathies, dizziness, writing impaired, vision blurred, photophobia, eye disorders, tinnitus, ischaemic coronary artery disorders, tachycardia, haemorrhage, thromboembolic and ischaemic events, vascular hypotensive disorders, peripheral vascular disorders, dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis, cough, nasal congestion and inflammations, gastrointestinal inflammatory conditions, gastrointestinal ulceration and perforation, gastrointestinal haemorrhages, stomatitis, ascites, vomiting, gastrointestinal disorders, bile duct disorders,, cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis, pruritus, rash, alopecias, acne, sweating increased, arthralgia, muscle spasms, limb and back pain, renal failure, oliguria, renal tubular necrosis, nephropathy toxic, urinary abnormalities, bladder and urethral symptoms, asthenic conditions, febrile disorders, pain, discomfort, oedema, blood alkaline phosphatase increased, weight increased, body temperature perception disturbed, primary graft dysfunction. Uncommon (≥1/1000 to <1/100): Coagulopathies, coagulation and bleeding analyses abnormal, pancytopenia, hypoproteinaemia, hyperphosphataemia, hypoglycaemia, dehydration, coma, central nervous system haemorrhages and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language disorders, amnesia, cataract, arrhythmias, cardiac arrest, heart failures, cardiomyopathies, ECG investigations abnormal, pulse investigations abnormal, weight decrease, ventricular hypertrophy, palpitations, infarction, deep venous thrombosis, shock, respiratory failures, respiratory tract disorders, asthma, paralytic ileus, peritonitis, acute and chronic pancreatitis, amylase increased, blood lactate dehydrogenase increased, gastrooesophageal reflux disease, impaired gastric emptying, anuria, haemolytic uraemic syndrome, uterine bleeding, psychotic disorder, multi-organ failure. Rare (≥1/10,000 to <1/1000): Thrombotic thrombocytopenic purpura, blindness, neurosensory deafness, pericardial effusion, acute respiratory distress syndrome, subileus, pancreatic pseudocyst, hepatic artery thrombosis, venoocclusive liver disease, toxic epidermal necrolysis (Lyell's syndrome), mobility decreased, fall, ulcer, chest tightness, thirst. Very rare (<1/10,000): ECG abnormal, ECG QT prolonged, Torsades de Pointes, hepatic failure, Stevens Johnson syndrome, nephropathy, cystitis haemorrhagic. Not known: Pure red cell aplasia, agranulocytosis, haemolytic anaemia. Consult the SPC for complete information on side effects and full prescribing information. **Packs and prices:**

Country-specific. **Legal Classification:** POM. **MA Number:** PROGRAF: Country specific. ADVAGRAF: EU/1/07/387/001-26. **Date of Revision:** November 2015. Further information available from Astellas Pharma Europe Ltd, 2000 Hillswood Drive, Chertsey, Surrey, KT16 0RS, UK. ADVAGRAF and PROGRAF are registered trademarks. ADV/11/0030/EUc(4). **Adverse events should be reported. UK residents: Reporting form and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Astellas Pharma Ltd. on 0800 783 5018. Non-UK residents:Report adverse events to Astellas Pharma Europe by email to safety-eu@astellas.com, by facsimile to +31 (0)71-545 5208, or contact your local Astellas office (www.astellas.eu/contact/locations/).**