Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines on kidney transplantation: a European Renal Best Practice (ERBP) position statement

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Abstract

KDIGO (Kidney Disease: Improving Global Outcomes) is an international independent body aiming to ‘improve the care and outcomes of kidney disease patients worldwide, through the development and implementation of clinical practice guidelines’. Recently, the KDIGO work group has produced comprehensive clinical practice guidelines for the care of kidney transplant recipients (KTrrs). The guideline makes recommendations for immunosuppression, graft monitoring, as well as prevention and treatment
of infection, cardiovascular disease, malignancy and other complications that are common in KTRs, including haematological and bone disorders. Because most guidelines were ‘soft’ rather than ‘strong’, and because global guidelines need to be adapted and implemented into the regional context where they are used, the European Renal Best Practice (ERBP) Advisory Board appointed a work group of transplant nephrologists and surgeons to review the newest KDIGO guideline and comment on its relevance and applicability for European KTRs. In this article, we concentrate only on those guidelines which we considered worth amending or adapting. All guidelines not mentioned are fully endorsed.

**Keywords:** donor management; ERBP; KDIGO; kidney transplantation; post-transplant care

**Introduction**

KDIGO (Kidney Disease: Improving Global Outcomes) as a guidance body aims to ‘improve the care and outcomes of kidney disease patients worldwide, through the development and implementation of clinical practice guidelines’. While KDIGO since its institution has been focusing on global guidelines for worldwide use about broad topics, they still left an opening for local or regional adaptation, guidance irrespective of low evidence and/or specific niches not dealt with by KDIGO. European Renal Best Practice (ERBP) was founded in 2008 to generate viewpoints and guidance specific to the European condition on topics conforming with the areas left open by KDIGO mentioned above.

Recently, the KDIGO work group has generated guidelines for the care of kidney transplant recipients (KTRs). This was a timely initiative, as previous guidelines for transplant patients produced by the European Best Practice Guidelines (EBPG) Group [1,2] and by the American Society of Transplantation [3–7] had been published already a decade ago. The KDIGO guideline makes recommendations for immunosuppression, graft monitoring, as well as prevention and treatment of infection, cardiovascular disease, malignancy and other complications that are common in KTRs, including haematological and bone disorders. KDIGO used the Grades of Recommendation Assessment, Development and Evaluation system to rate the level of evidence and the strength of recommendations. Due to overall paucity of evidence in the field, only 21% of the 243 recommendations/statements were graded ‘1’ (we recommend), 61% were graded ‘2’ (we suggest) and 18% were ungraded statements. Altogether, only 2% of recommendations reached the ‘A’ level of quality of evidence. Because most guidelines were ‘soft’ rather than ‘strong’, and because global guidelines need to be adapted and implemented into the regional context where they are used, the ERBP Advisory Board appointed a work group of transplant nephrologists and surgeons to review the newest KDIGO guideline and comment on its relevance and applicability for European KTRs.

In what follows, we will concentrate only on those guidelines which we considered worth amending or adapting. All guidelines not mentioned are fully endorsed.

**Induction therapy**

1.1: We recommend starting a combination of immunosuppressive medications before, or at the time of, kidney transplantation. (1A)

1.2: We recommend including induction therapy with a biologic agent as part of the initial immunosuppressive regimen in KTRs. (1A)

1.2.1: We recommend that an (IL-2 receptor antagonist) IL2-RA be the first-line of induction therapy. (1B)

1.2.2: We suggest using a lymphocyte-depleting agent, rather than an IL2-RA, for KTRs at high immunologic risk. (2B)

Immunosuppression is essential for the success of transplantation for which optimally a combination of drugs is needed. With regard to induction therapy, a meta-analysis of >5000 patients enrolled in prospective randomized trials confirmed lower rates of acute rejection and improved graft survival in patients treated with IL-2RA [8] without major differences between basiliximab and daclizumab [9,10]. In the trials considering therapeutic schemes based on the combination of the latter two drugs, a benefit was not as obvious. Gralla et al. analysed retrospectively data obtained from 28686 patients of the US Renal Data System (USRDS) transplanted between 2000 and 2008, treated with tacrolimus and mycophenolic acid (MPA). Although the rate of acute rejection was marginally lower in patients treated with IL-2RA as compared to those patients not receiving induction treatment, the overall rate of survival at 1, 3 and 5 years was identical [10]. Along the same line, Willoughby [11] observed that addition of IL2-RA to patients receiving tacrolimus and MPA had only minimal impact on 6-month rates of acute rejection and graft loss if patients were on maintenance steroids.

Thus, with an immunosuppressant consisting of tacrolimus and MPA, the benefits of IL-2RA may not justify the additional costs in all cases. In addition, one must be careful when applying the recommendation to patients aged >65 years as these patients were mostly excluded from randomized controlled trials on immunosuppression. Thus, we would downgrade the recommendation 1.2 from 1A to 1B.

In a recent meta-analysis [8], IL2-RA was compared to anti-thymoglobuline (ATG) (16 studies, 2211 participants). The patients enrolled were primarily at low immunological risk [first grafts, no anti-human leucocyte antigen (HLA) antibodies]. There was no difference in graft loss at any time point, or for acute rejection diagnosed clinically. While there was a marginal benefit of ATG therapy over IL2-RA for biopsy-proven acute rejection at 1 year, it came at the cost of a 75% increase in malignancy [primarily post-transplant lymphoproliferative disease (PTLD)] and a 32% increase in cytomegalovirus (CMV) disease. ATG patients experienced significantly more fever, cytokine release syndrome and other adverse reactions to drug administration.
and more leucopenia but not thrombocytopenia. There were no significant differences in outcomes according to cyclosporine or tacrolimus use, azathioprine or MPA or to the study populations baseline risk for acute rejection. There was no evidence that effects were different according to whether equine or rabbit ATG was used. Thus, in cases of induction in low-risk patients, IL2-RA appeared to be preferable to ATG.

The picture is likely to be different in high-risk transplant recipients, where two randomized prospective trials, one enrolling mainly patients at high risk for delayed graft function [12], the other being devoted to high-immunological risk patients [13], showed a significantly lower risk for acute rejection with ATG as compared to IL2-RA. Therefore, the ERBP endorses recommendation 1.2.2 and proposes that rejection with ATG as compared to IL2-RA. Therefore, the ERBP endorses recommendation 1.2.2 and proposes that high risk might be defined as high panel reactive antibody, transplantation across a donor-specific antibody barrier, multiple previous transplants or a previous transplant lost to immunological reasons, 5–6 HLA mismatches, donation after cardiac death and cold ischaemia >24 h.

**Long-term maintenance immunosuppressive medications**

3.1: We suggest using the lowest planned doses of maintenance immunosuppressive medications by 2–4 months after transplantation, if there has been no acute rejection. 
(2C)

3.2: We suggest that calcineurin inhibitors (CNIs) be continued rather than withdrawn. (2B)

3.3: If prednisone is being used beyond the first week after transplantation, we suggest prednisone be continued rather than withdrawn. (2C)

The data on long-term maintenance immunosuppression is extremely limited and do not necessarily reflect real-life situations. Furthermore, as local practice, risk profiles, donor types and induction therapy vary to a large degree, the suggestions 3.1 and 3.2 are reasonable but weak. However, with regard to recommendation 3.3, ERBP believes there is no particular risk to withdraw steroids after the first week, as stated above, in cases where a tacrolimus–MPA combination is applied [14]. Based on a recent meta-analysis, a withdrawal at any given time after transplantation increases the risk of immediate rejection. However, there seems to be no long-term effects on function or graft survival [15]. The risk of rejection seems to be most pronounced in patients treated with cyclosporine rather than tacrolimus. As the cessation of steroids is associated with a reduction of side effects, there are certainly reasons to justify a reduction or withdrawal of steroids even after the first week [16]. On the other hand, there are patients who depend on steroids in order to prevent graft rejection. However, due to a lack of data describing the phenotype of the patients, we assume those to be at a high risk of rejection (see above) or who have developed a severe rejection after transplantation. Thus, ERBP considers that selected patients may benefit from steroid withdrawal at any time after transplantation and does not see stringent reasons to strictly adhere to recommendation 3.3, stressing the need for steroid withdrawal within the first week after transplantation.

**Treatment of acute rejection**

6.1: We recommend biopsy before treating acute rejection, unless the biopsy will substantially delay treatment. (1C)

6.2: We suggest treating subclinical and borderline acute rejection. (2D)

6.3: We recommend corticosteroids for the initial treatment of acute cellular rejection. (1D)

6.3.1: We suggest adding or restoring maintenance prednisone in patients not on steroids who have a rejection episode. (2D)

6.3.2: We suggest using lymphocyte-depleting antibodies or OKT3 for acute cellular rejections that do not respond to corticosteroids and for recurrent acute cellular rejections. (2C)

6.4: We suggest treating antibody-mediated acute rejection with one or more of the following alternatives, with or without corticosteroids (2C):

- plasma exchange;
- intravenous immunoglobulin;
- anti-CD20 antibody;
- lymphocyte-depleting antibody.

6.5: For patients who have a rejection episode, we suggest adding MPA if the patient is not receiving MPA or azathioprine to steroids in this situation. (2D)

To first perform a biopsy in cases of suspected acute rejection and then treat with steroids is common practice in most transplant centres. If steroids fail in the treatment of cellular rejection, lymphocyte-depleting antibodies are the second line. These approaches can be easily endorsed. Although there are basically no studies which analyse in a randomized way the treatment of antibody-mediated rejection, most centres also add other forms of immunosuppression such as MPA or azathioprine to steroids in this condition. So, this line of treatment is also endorsed [17]. It may, however, be mentioned that a switch to tacrolimus is also an option in the treatment of humoral and acute cellular rejection [18–21].

**Treatment of chronic allograft injury**

7.1: We recommend kidney allograft biopsy for all patients with declining kidney function of unclear cause, to detect potentially reversible causes. (1C)

7.2: For patients with chronic allograft injury (CAI) and histological evidence of CNI toxicity, we suggest reducing, withdrawing or replacing the CNI. (2C)
7.2.1: For patients with CAI, estimated glomerular filtration rate >40 mL/min/1.73m², and urine total protein excretion <500 mg/g creatinine (or equivalent proteinuria by other measures), we suggest replacing the CNI with an mammalian target of rapamycin (mTOR) inhibitor. (2D)

In order to clarify the reason for a decline in kidney function, routine examinations have to be performed such as ultrasound to exclude arterial or post-renal problems, and a physical examination to exclude non-renal reasons for a decline in renal function such as dehydration or cardiac insufficiency.

Only when extrinsic causes have been excluded, a biopsy should be performed.

If CNI toxicity can be identified in a kidney biopsy, reduction, withdrawal or replacement of the CNI should be considered. Data are scarce on the advantage of mTOR inhibitors in this particular setting. One could argue as well for a switch to MPA or azathioprine in patients not yet receiving one of those particular drugs [22–26].

Recurrent kidney disease

10.1: We suggest screening KTRs with primary kidney disease caused by focal segmental glomerulosclerosis (FSGS) for proteinuria (2C) at least:

• daily for 1 week (2D);
• weekly for 4 weeks (2D);
• every 3 months, for the first year (2D);
• every year, thereafter. (2D)

10.2: We suggest screening KTRs with potentially treatable recurrence of primary kidney disease from IgA nephropathy, membrano proliferative glomerulopathy (MPGN), anti-glomerular basement membrane (GBM) disease or anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis for microhaematuria (2C) at least:

• once in the first month to determine a baseline (2D);
• every 3 months during the first year (2D);
• annually, thereafter. (2D)

10.3: During episodes of graft dysfunction in patients with primary haemolytic uraemic syndrome, we suggest screening for thrombotic microangiopathy (e.g. with platelet count, peripheral smear for blood cell morphology, plasma haptoglobin and serum lactate dehydrogenases). (2D)

10.4: When screening suggests possible treatable recurrent disease, we suggest obtaining an allograft biopsy. (2C)

10.5: Treatment of recurrent kidney disease:

10.5.1: We suggest plasma exchange if a biopsy shows minimal change disease or FSGS in those with primary FSGS as their primary kidney disease. (2D)

10.5.2: We suggest high-dose corticosteroids and cyclophosphamide in patients with recurrent ANCA-associated vasculitis or anti-GBM disease. (2D)

10.5.3: We suggest using an angiotensin converting enzyme-1 or an angiotensin receptor blocker (ARB) for patients with recurrent glomerulonephritis and proteinuria. (2C)

10.5.4: For KTRs with primary hyperoxaluria, we suggest appropriate measures to prevent oxalate deposition until plasma and urine oxalate levels are normal (2C), including:

• pyridoxine (2C);
• high calcium and low oxalate diet (2C);
• increased oral fluid intake to enhance urinary dilution of oxalate (2C);
• potassium or sodium citrate to alkalinize the urine (2C);
• orthophosphate (2C);
• magnesium oxide (2C);
• intensive hemodialysis to remove oxalate. (2C)

The recommendations on the treatment of recurrent diseases are based on the medical knowledge for the original diseases. Whether the same methods of management are applicable for patients after transplantation and possibly dialysis as well is unknown. Thus, in principle, the recommendations are suggestions guided by educated guesses. Apart from animal data, which are very convincing, so far only one large trial in transplanted patients analysed the benefits of ARB’s, without differentiating between recurrent disease and chronic allograft failure[27]. Thus, recommendation 10.5.3. can be supported; however, differences in local practice based on personal experience or a different interpretation of animal or human data are acknowledged and remain for the time being with the current evidence acceptable.

Viral diseases

13.1: BK polyoma virus

13.1.1: We suggest screening all KTRs for BK polyoma virus (BKV) with quantitative plasma nucleic acid testing (NAT) (2C) at least:

• monthly for the first 3–6 months after transplantation (2D);
• then every 3 months until the end of the first post-transplant year (2D);
• whenever there is an unexplained rise in serum creatinine (2D) and
• after treatment for acute rejection. (2D)
13.1.2: We suggest reducing immunosuppressive medications, when BKV plasma NAT is persistently >10000 copies/mL (10^7 copies/L). (2D)

It is unclear why BK virus nephropathy affects primarily KTRs although ∼50–90% of the general population is positive for the virus [28]. It has been suggested that the degree of immunosuppression is responsible, but this has been demonstrated in case series only. In some published cases, a reduction of the immunosuppressive load decreased the viral burden and was associated with an improvement of kidney function. In other cases, leflunomide or ciprofloxacin achieved the same results [29–31]. So far, there are no convincing data from randomized trials suggesting a clear therapeutic strategy. In lung transplantation, BK virus was apparent in the urine of ∼40% of the patients, but, although immunosuppression is markedly higher than for kidney transplantation, no significant impact on kidney function could be detected [32]. The same results were obtained in recipients of non-renal organs [33]. To check for BK virus is certainly of high scientific value, but the practical consequence of its positivity is limited to imposing a careful evaluation of immunosuppression, which, however, may induce a rejection and therefore should be applied with utmost caution.

There is no clear-cut threshold with regard to viral load above which immunosuppression has to be lowered. Furthermore, determination methods and their sensitivity differ from centre to centre making it difficult to impose universal cut-offs. Centres should apply testing methods with which they have most expertise (plasma NAT, urine NAT or decoy cells). Cut-off levels for reduction of immunosuppression should be decided per individual unit or method. Kidney biopsies in search of polyoma virus-associated nephropathy should be considered on a case-by-case basis.

13.2: Cytomegalovirus

13.2.1: Cytomegalovirus (CMV) prophylaxis: We recommend that KTRs (except when donor and recipient both have negative CMV serologies) receive chemoprophylaxis for CMV infection with oral ganciclovir or valganciclovir for at least 3 months after transplantation (1B) and for 6 weeks after treatment with a T-cell-depleting antibody. (1C)

13.2.2: In patients with CMV disease, we suggest weekly monitoring of CMV by NAT or pp65 antigenaemia. (2D)

13.2.3: CMV treatment:

13.2.3.1: We recommend that all patients with serious (including most patients with tissue invasive) CMV disease be treated with intravenous ganciclovir. (1D)

13.2.3.2: We recommend that CMV disease in adult KTRs which are not serious (e.g. episodes that are associated with mild clinical symptoms) be treated with either intravenous ganciclovir or oral valganciclovir. (1D)

13.2.3.3: We recommend that all CMV disease in paediatric KTRs be treated with intravenous ganciclovir. (1D)

13.2.3.4: We suggest continuing therapy until CMV is no longer detectable by plasma NAT or pp65 antigenaemia (2D)

13.2.4: We suggest reducing immunosuppressive medication in life-threatening CMV disease, and CMV disease which persists in the face of treatment, until CMV disease has resolved. (2D)

13.2.4.1: We suggest monitoring graft function closely during CMV disease. (2D)

The benefits of CMV prophylaxis have been documented in recent trials [34]. In addition, two recent randomized controlled trials demonstrated lower rates of infections in D+/R− combinations if prophylaxis was extended to 6 months instead of 3 [35,36]. However, in the most recent studies, there was neither a difference between ganciclovir versus valganciclovir nor valganciclovir versus pre-emptive treatment [37–41]. Thus, if proper testing for CMV is available, pre-emptive treatment may be as efficient as prophylaxis. However, it is not clear, how frequently such testing should be applied. Exceptions depend on the relative risk profile of the recipient with regard to donor status or immunosuppressive therapy; e.g. in patients having received lymphocyte-depleting antibodies, particularly in a situation where the donor is positive and the recipient negative, prophylaxis might be superior.

There are some articles on the economic differences between pre-emptive treatment and prophylaxis with antiviral drugs. However, the data is not conclusive as the cost benefit ratio always depends on the surrounding conditions. Specifically, it is difficult to outweigh the cost of medication in comparison to that of hospitalization. This ratio varies markedly from country to country, so that such an evaluation can only be made on a country basis.

Apart from pre-emptive therapy, a treatment of CMV is essential in tissue invasive disease. Given close monitoring, this can be done intravenously or orally under permanent control of the viral load. As an acute rejection is rather frequent after the resolve of CMV disease, we strongly support intensified graft monitoring during and after the disease.

13.3: Epstein-Barr virus and PTLD

13.3.1: We suggest monitoring high-risk [donor Epstein-Barr virus (EBV) seropositive/recipient seronegative] KTRs for EBV by NAT (2C):

• once in the first week after transplantation (2D);
• then at least monthly for the first 3–6 months after transplantation (2D);
• then every 3 months until the end of the first post-transplant year (2D) and
• additionally after treatment for acute rejection. (2D)

13.3.2: We suggest that EBV-seronegative patients with an increasing EBV load have immunosuppressive medication reduced. (2D)

13.3.3: We recommend that patients with EBV disease, including PTLD, have a reduction or cessation of immunosuppressive medication. (1C)
PTLD occurs in 0.5–2% of KTR and is most often driven by EBV. EBV-negative recipients of EBV-positive donors are at a special risk. In order to limit the incidence of PTLD, it may be useful to avoid this combination, particularly in children. On the other hand, questions may be raised about the added value of routine EBV testing after transplantation. Currently, there are no data from randomized trials as to whether an asymptomatic patient with positive polymerase chain reaction should be treated or whether the level of immunosuppression should be lowered. However, as a consequence of such testing, one might be more careful with regard to lymphocyte-depleting drugs or a more intense immunosuppressant.

Regarding the issue of testing donor and recipient for EBV or not, there is a lack of consistency in attitudes within the European transplant community. In most countries, EBV is tested in donors and recipients. However, as >90% of adult donors and recipients are positive for EBV, a matching based on the EBV status would markedly limit the chances of an EBV-negative recipient to receive a proper organ. Thus, in adults such a matching is not practicable.

However, as the rate of EBV-positive recipients is much lower and the risk to develop a PTLD is most pronounced in children, in some countries such as Switzerland, donor testing is mandatory and has an influence on organ allocation in children but not in adults. Given proper donor rates, this is a reasonable approach. However, if the number of EBV-negative donors is lower than the number of EBV-negative children on the waiting list, this approach puts EBV-negative children at a disadvantage prolonging their waiting time. As a prolongation of waiting time is also associated with reduced survival, such a policy has to be considered with care but no general rule encompassing all countries can be formulated.

Furthermore, most patients currently receive prophylactic treatment with ganciclovir or valganciclovir against CMV. This treatment has additional effects against EBV. It is currently unclear whether this strategy additionally lowers the incidence of PTLD and, thus, influences the clinical impact of EBV.

In summary, considering the limitations mentioned above, we believe that the level of guideline 13.3.3. should be lowered to Grade 2D.

Furthermore, immunosuppression in all recipients should be reduced as much as possible. Thus, this approach has to be considered as relevant for the entire transplant population and is not specific to EBV-negative recipients receiving an EBV-positive organ. While a higher amount of immunosuppression may increase the risk of PTLD in these patients, a lower amount of immunosuppression may enhance the risk of graft loss. The proper way can only be decided case by case. If the titre of EBV load increases, it sounds reasonable to reduce the immunosuppressive load. However, whether this approach has any effect on the incidence of PTLD has never been demonstrated in a clinical trial. On the other hand, there are data which suggest that the EBV load by itself is not a very good indicator for the later occurrence of PTLD [42,43]. Altogether, recommendation 13.3.2 (Grade 2D) and 13.3.3 are endorsed by the ERBP working group, with the only addition that in fact recommendation 13.3.3 applies to the entire transplant population.

Hypertension, dyslipidaemia, tobacco use and obesity

16.2: Dyslipidaemias (These recommendations are based on KDOQI Dyslipidaemia Guidelines and are thus Not Graded)

16.2.1: Measure a complete lipid profile in all adult (≥18 years old) and adolescent (puberty to 18 years old) KTRs (based on KDOQI Dyslipidaemia Recommendation 1):

- 2–3 months after transplantation;
- 2–3 months after a change in treatment or other conditions known to cause dyslipidaemias;
- at least annually, thereafter.

16.2.2: Evaluate KTRs with dyslipidaemias for secondary causes (based on KDOQI Dyslipidaemia Recommendation 3)

16.2.2.1: For KTRs with fasting triglycerides ≥500 mg/dL (≥2.59 mmol/L) that cannot be corrected by removing an underlying cause, treat with:

- Adults: therapeutic lifestyle changes and a triglyceride-lowering agent (based on KDOQI Recommendation 4.1);
- Adolescents: therapeutic lifestyle changes (based on KDOQI Recommendation 5.1).

16.2.2.2: For KTRs with elevated LDL-C:

- Adults: If low density lipoprotein cholesterol (LDL-C) ≥100 mg/dL (≥2.59 mmol/L), treat to reduce LDL-C to <100 mg/dL (<2.59 mmol/L) (based on KDOQI Guideline 4.2);
- Adolescents: If LDL-C ≥130 mg/dL (≥3.36 mmol/L), treat to reduce LDL-C to <130 mg/dL (<3.36 mmol/L) (based on KDOQI Guideline 5.2).

16.2.2.3: For KTRs with normal LDL-C, elevated triglycerides and elevated non-high density lipoprotein (HDL)-C:

- Adults: If LDL-C <100 mg/dL (<2.59 mmol/L), fasting triglycerides ≥200 mg/dL (≥2.26 mmol/L) and non-HDL-C ≥130 mg/dL (≥3.36 mmol/L), treat to reduce non-HDL-C to <130 mg/dL (<3.36 mmol/L) (based on KDOQI Guideline 4.3);
Conclusions

The KDIGO guidelines on transplantation resulted in a holistic set of recommendations offering advice in the treatment of graft recipients after their intervention in a global perspective. The present position statement endorses the majority of these recommendations, offering a number of amendments, essentially from a European perspective.

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Disclaimer. The present text is based upon the information available to the work group at the moment of the preparation of this publication. It has been designed to provide information and assist decision making, but is not intended to define a standard of care or to improve an exclusive course of diagnosis, prevention or treatment. Individual decision making is essential in the approach to any disease and thus also transplantation. Variations in practice are inevitable when physicians take into account individual patient needs, available resources and limitations specific for a geographic area, country, institution or type of practice. In addition, evidence may change over time as new information becomes available, so that practice may be modified subsequently. Every practitioner using this text is responsible for its application to any particular clinical situation. The work group members involved in the development of the present text have disclosed all actual and potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest.

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