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Original Article

KHA-CARI guideline: KHA-CARI adaptation of the KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients

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SUMMARY AT A GLANCE

The latest Caring for Australians with Renal Impairment (CARI) guideline detailing renal transplant care, developed as a local modification of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines.

Kidney Health Australia Caring for Australians with Renal Impairment (KHA-CARI) has been developing guidelines de novo for an Australian & New Zealand target audience since 1999. Kidney Disease Improving Global Outcomes (KDIGO) was set up in 2002 to explore the possibility of developing international chronic kidney disease (CKD) guidelines. The science and evidence-based care of those with CKD are universal and independent of geographical location/national borders. It is important to avoid duplication of effort by organizations and to efficiently use the available expertise and resources. As a consequence KHA-CARI has committed to adapting selected KDIGO guidelines to meet Australian and New Zealand circumstances and requirements rather than producing separate guidelines.

This summary guideline is an adaptation of the KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients.[1] The summary includes a brief description of the adaptation methodology and the adapted recommendations and suggestions for each sub-topic. The complete KHA-CARI adapted guideline can be accessed at the KHA-CARI website (http://www.cari.org.au). The ultimate purpose of the adapted guideline is to provide a comprehensive listing of recommendations relevant to Australian and New Zealand practice following a detailed review and update of the KDIGO guidelines.

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ADAPTATION PROCESS

The process used for the adaptation has been based on the ADAPTE framework (http://www.adapte.org). The ADAPTE framework has been developed to facilitate review of multiple guidelines for evaluation and synthesis into a single adapted guideline for local use. In this case the adaptation is of a single guideline only. As a consequence KHA-CARI has used the following simplified approach:

Step 1: Assess guideline currency.

- Review search strategy and update to ensure evidence base is complete and current.
- Identify recommendations that may be invalid on the basis of additional evidence.
- Identify recommendations that require modification on the basis of additional evidence.
- Identify additional recommendations that may be warranted on the basis of additional evidence.

Step 2: Assess guideline consistency.

- Rate quality of the evidence according to the GRADE (http://www.gradeworkinggroup.org) evidence evaluation framework (see below).
- Evaluate consistency between the selected evidence and the summary of the evidence.
- Evaluate the consistency between the interpretation of the evidence and the recommendations.
- Assess coherence between the evidence and recommendations.

Step 3: Assess applicability of the recommendations with respect to Australia and New Zealand.

- Does the population studied match the population for which the adapted Australian and New Zealand guideline would apply?
- Does the intervention meet patient views and preferences in the context of Australia and New Zealand?
- Are the intervention and/or equipment available in the context of use in Australia and New Zealand?
- Are there any constraints, organizational barriers, legislation, policies and/or resources in the Australian and New Zealand health care setting that would impeded the implementation of the recommendation?
- Is the recommendation compatible with the culture and values in Australia and New Zealand?

Step 4: Prepare an adapted guideline document with recommendations and suggestions reflecting assessments made in Steps 1 to 3.

GRADING OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

The overall approach followed by KDIGO (and in the KHA-CARI adaptation) in grading both evidence and recommendations follows the GRADE framework. In completing the adaptation, KHA-CARI has relied on a review of the adequacy of the KDIGO search strategy and evidence profiles rather than independently developing evidence profiles. The review has sometimes resulted in changes to the KDIGO grades in the KHA-CARI adaptation. Changes to the grades may also reflect the inclusion of additional studies found by the update searches.

A description of the overall grades applied to an evidence profile is shown in Table 1. Evidence profiles are assessed on an outcome basis (e.g. mortality, graft failure and acute rejection) following a framework and set of rules defined by GRADE. The final evidence grade is based on the most critical outcome for a given question. As critical outcomes such as mortality are often supported by poorer quality evidence than less critical outcomes, for example, surrogate measures of kidney function, then the evidence profile may be evaluated as being of low quality even though there are many randomized controlled trials (RCT) and systematic reviews of RCT.

The strength of recommendations is indicated by a 1 or 2 thus giving 8 possible grades. A description of the meaning of the strength of a recommendation is given in Table 2, while Table 3 describes the determinants of the strength of a recommendation. In addition, KDIGO use 'We recommend. . . .' and 'We suggest . . .' to denote strength (i.e. 1 and 2 respectively as used by GRADE) which has been adopted by KHA-CARI. KDIGO also provide 'ungraded' statements (or consensus driven statements) that reflect clinically relevant advice that is not supported by the evidence base for the question. In undertaking the adaptation, KHA-CARI has followed this approach; however, 'ungraded' statements have been denoted as 'Ungraded suggestions for clinical care' and shown separately from the recommendations, thereby

Table 1 Final grade for overall quality of evidence (KDIGO table 38)

Overall evidence grade	Description
A	*High quality of evidence.* We are confident that the true effect lies close to that of the estimate of the effect.
B	*Moderate quality of evidence*. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	*Low quality of evidence.* The true effect may be substantially different from the estimate of the effect.
D	*Very low quality of evidence.* The estimate of effect is very uncertain, and often will be far from the truth.

KDIGO, Kidney Disease Improving Global Outcomes.

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Table 2 Nomenclature and description for grading recommendations (KDIGO table 40)

Grade	Implications		
	Patients	Clinicians	Policy
Level 1 'We recommend'	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be adopted as a policy in most situations.
Level 2 'We suggest'	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require debate and involvement of stakeholders before policy can be determined.

KDIGO, Kidney Disease Improving Global Outcomes.

Table 3 Determinants of strength of recommendations (KDIGO table 41)

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is warranted. The narrower the gradient, the more likely a weak recommendation is warranted.
Quality of the evidence	The higher the quality of evidence, the more likely a strong recommendation is warranted.
Values and preferences	The more variability in values and preferences, or more uncertainty in values and preferences, the more likely a weak recommendation is warranted.
Costs (resource allocation)	The higher the costs of an intervention – that is, the more resources consumed – the less likely a strong recommendation is warranted.

KDIGO, Kidney Disease Improving Global Outcomes.

making it clear to the reader that these are opinion based statements.

Following this approach, where the benefits or harms of not following a particular intervention or practice are clear as well as being important and applicable to all patients, yet specific evidence in kidney transplant recipients is limited, a recommendation may be given a 1D grade. Similarly a suggestion may be made even though there is high quality evidence (i.e. 2A) where the decision to adopt an intervention may vary between patients depending on individual values, preferences or risk factors.

SCOPE OF GUIDELINE

This guideline addresses issues relevant to the care of kidney transplant recipients in Australia and New Zealand. The guideline does not address issues related to pretransplant assessment or care of candidates for kidney transplantation or the assessment and care of donors. In addition, the guideline does not address returning to dialysis, graft nephrectomy or withdrawal of immunosuppression in the event of declining function or failure of the graft.

THE TRANSPLANT ENVIRONMENT IN AUSTRALIA AND NEW ZEALAND

There have been over 20 000 kidney transplant operations performed on approximately 18 500 patients in Australia and New Zealand over the period 1963 to 2009.[2] All transplant procedures performed and subsequent recipient outcomes are reported to the ANZDATA Registry (Australia and New Zealand Dialysis and Transplantation Registry; http://www.anzdata.org.au/). Deceased donor procedures using deceased brain donors and deceased cardiac donors represent approximately 50% of transplants performed on an annual basis, with live donor transplants comprising a similar proportion. Less than 1% of all transplants received by residents of Australia and New Zealand are performed outside the two countries. In both countries the ethnicity of donors and recipients is dominantly Caucasian. Asians and Indigenous groups are numerically significant minorities while Hispanic and African ethnicities are rare (<1%). Glomerulonephritis is the commonest primary kidney disease leading to transplantation, followed by polycystic kidney disease and diabetes. In current practice, induction with anti-CD25 antibodies occurs in approximately 95% of all transplants in Australia and around 50% of all transplants in New Zealand while T-cell depleting induction is used in less than 5% of cases. Maintenance immunosuppression consists predominantly of triple-therapy with a calcineurin inhibitor (CNI), most commonly tacrolimus, plus a mycophenolate plus steroids with withdrawal of steroids being uncommon. Currently mammalian target of rapamycin inhibitors (mTORi) are used in less than 10% of recipients. Universal health care coverage is provided by the respective Governments and transplant procedures, hospitalizations and medications are highly subsi-

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dized by Government. Current outcomes are equal to or better than most leading centre's globally. Acute rejection occurs in 15–20% of first graft recipients. Current 1 year patient and graft survival rates are 97% and 93% for recipients of a first deceased donor graft and 99% and 96% for recipients of a first live donor graft. Beyond the first year, grafts are lost at a rate of approximately 5% p.a. because of death with function or graft failure in similar proportions.

GUIDELINE RECOMMENDATIONS

1. Induction therapy

a. We recommend that a combination of immunosuppressive medications start before, or at the time of, kidney transplantation. (1A)
b. We recommend induction therapy with a biologic agent as part of initial immunosuppression in kidney transplant recipients. (1B)
c. We recommend an interleukin-2 receptor antagonist as first-line induction therapy. (1B)
d. We suggest that induction with loading doses of a mycophenolate be considered. (2B)
e. In kidney transplant recipients at high risk of acute cellular rejection we suggest that consideration may be given to the use of a T-lymphocyte-depleting agent in place of an interleukin-2 receptor antagonist as an induction agent. (2B)
f. We suggest that kidney transplant recipients with a donor specific anti-human leukocyte antigen antibody be considered for peri-transplant plasmapheresis and/or high-dose intravenous (IV) immunoglobulin pretransplant. (2C)
g. We suggest that patients undergoing ABO incompatible transplantation should undergo plasmapheresis or immunoadsorption to reach an anti-blood group titre known to be acceptable at that institution with consideration of post-transplant antibody removal depending on the baseline titre. (2A)

2. Initial maintenance of immunosuppressive medication

a. We recommend using a combination of immunosuppressive medication as maintenance therapy including a CNI and an antiproliferative agent, with or without corticosteroids. (1B)
b. We recommend that mycophenolate be the first-line antiproliferative agent. (1B)
c. We recommend that if mTORi are used, they not be started until graft function is established, surgical wounds are healed and the patient is free from rejection. (1B)
d. We suggest that tacrolimus be the first-line CNI used for higher-risk patients. (2A)
e. We suggest that tacrolimus or cyclosporine be started before or at the time of transplantation, rather than delayed until the onset of graft function. (2D tacrolimus; 2B cyclosporine)
f. We suggest that, in patients who are at low immunological risk and who receive induction therapy, corticosteroids could be minimized or withdrawn early after transplantation. (2B)

3. Long-term maintenance immunosuppressive medications

a. We recommend low-level exposure to maintenance immunosuppressive medications by 4 months after transplantation, as was used in the Symphony Trial (tacrolimus trough concentrations 3–7 ng/mL, mycophenolate 1–2 g daily and prednisone 5 mg daily[3]) for patients who have not experienced acute rejection. (1B)
b. We suggest that CNI be continued rather than withdrawn. (2B)
c. If prednisolone is being used beyond the first week after transplantation, we suggest prednisolone be continued rather than withdrawn. (2C)

4. Monitoring immunosuppressive medications

General

a. We suggest that the target concentration range for immunosuppressants be individualized depending on recipient immunological and toxicity risk status and co-therapy administered. (2C)
b. When interpreting concentrations of immunosuppressants, we recommend that attention be paid to whether high performance liquid chromatography or immunosassay technology is employed. Immunoassays can be biased by cross-reactivity with metabolites and therefore typically provide a higher reading than high performance liquid chromatography which is specific for the parent compound. (1B)

Calcineurin inhibitor monitoring

c. We recommend that cyclosporine and tacrolimus concentrations in blood should be measured (1C):
   i. frequently in the immediate postoperative period (e.g. second daily) until target concentrations are reached and stability of therapeutic concentrations has been demonstrated;
   ii. following a dose change;
   iii. whenever there is a significant change in clinical parameters, concomitant immunosuppression or medications that may affect drug concentrations; and
   iv. when there is concern regarding over- or under-immunosuppression. (2C)
d. We suggest that cyclosporine be monitored using 12 h trough (C0) or 2 h post-dose (C2) concentrations, or a validated limited sampling strategy (LSS) for estimation of the full-dose interval area under the concentration time curve (AUC0–12). (2C)

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e. We suggest that C0 concentrations be used for tacrolimus monitoring. (2D)

Mycophenolate mofetil monitoring

f. While routine monitoring cannot be recommended, we suggest consideration be given to mycophenolate mofetil monitoring in selected clinical scenarios:

i. in high immunological risk recipients;
ii. when there is a significant change in clinical parameters, concomitant immunosuppression or medications that may affect drug concentrations;
iii. when there is concern regarding over- or under-immunosuppression; and
iv. unless a loading dose strategy has been used. (2D)

g. We suggest that mycophenolate mofetil be monitored using a multiple regression derived LSS or Bayesian estimators for AUC0–12. To ensure reliable predictions, LSS and Bayesian estimators should ideally be validated in the population of interest prior to their use in that population. (2C)

h. We suggest a mycophenolic acid AUC0–12 target range of 30 to 60 mg·h/L for the early post-transplant period. There is no data available regarding an appropriate mycophenolic acid AUC0–12 target in patients more than 12 months post transplant. (2C)

Mammalian target of rapamycin inhibitor monitoring

i. We recommend mTORi concentrations in blood should be monitored. (1C) The following monitoring strategy is suggested (2C):

i. after initiation of therapy or a change in dose;
ii. with suspected drug interactions; and
iii. when there is concern regarding over- or under-immunosuppression.

j. We suggest that C0 concentrations can be used for mTORi monitoring; however, we note that mTORi target concentrations may vary by drug, perceived risk of rejection and time post transplant. (2C)

5. Treatment of acute rejection

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

b. We suggest treating subclinical and borderline cellular rejection. (2D)

c. We recommend using short-duration high-dose corticosteroids for the initial treatment of acute cellular rejection. (1D)

i. We suggest adding or restoring maintenance prednisone in patients not on steroids who have a rejection episode. (2D)
ii. We suggest using lymphocyte-depleting antibodies for resistant acute cellular rejection episodes and for acute cellular rejection episodes with a vascular component (BANFF Grade II or greater). (2C)

d. We suggest consideration be given to treating antibody-mediated acute rejection with plasma exchange and/or IV immunoglobulin. (2C)

e. For patients who have a rejection episode, we suggest increasing the baseline immunosuppression (e.g. adding mycophenolate if the patient is not receiving mycophenolate or azathioprine, or switching azathioprine to mycophenolate). Additional or alternative strategies include: adding a CNI if the patient is not taking this; switching cyclosporine to tacrolimus; switching an mTORi to a CNI; or increasing the dose of any of the immunosuppressive agents being used. (2D)

6. Treatment of chronic allograft injury

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

b. For patients with chronic allograft injury (CAI) and histological evidence of CNI toxicity, we suggest reducing, withdrawing, or replacing the CNI. (2C)

i. For patients with CAI, estimated glomerular filtration rate (eGFR) > 40 mL/min per 1.73 m^2, and urine total protein excretion <50 mg/mmol creatinine (or equivalent proteinuria by other measures), we suggest replacing the CNI with an mTORi. For patients with CAI and an eGFR < 40 mL/min per 1.73 m^2, a switch to mTORi is not recommended. (2D)

7. Monitoring kidney allograft function

a. We suggest monitoring urine protein : creatinine ratio (PCR) or albumin : creatinine ratio (ACR) on a random urine intermittently. A suggested minimum test schedule is at least: (2C)

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

b. We recommend assessing graft function by monitoring serum creatinine frequently after transplantation. (1B) Frequency of measurement should balance probability of acute complications affecting graft function, need for early detection and patient inconvenience. A suggested minimum test schedule is at least (2C):

i. daily for 7 days or until hospital discharge;
ii. two to three times per week for weeks 2–4;
iii. weekly for months 2 and 3;
iv. every 2 weeks for months 4–6;
v. monthly for months 7–12; and
vi. every 2–3 months, thereafter.

c. We suggest including a kidney allograft ultrasound examination as part of the assessment of kidney allograft dysfunction. (2C)

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8. Kidney allograft biopsy

a. We recommend kidney allograft biopsy when there is a persistent, unexplained increase in serum creatinine. (1C)
b. We suggest kidney allograft biopsy when serum creatinine has not returned to baseline after treatment of acute rejection. (2D)
c. We suggest kidney allograft biopsy when there is:
   i. new onset of proteinuria (2C); and
   ii. unexplained proteinuria (≥100 mg/mmol PCR or ≥1.0 g per 24 h.). (2C)
d. We suggest kidney allograft biopsy every 5–10 days during delayed function. (2C)
e. We suggest kidney allograft biopsy if expected kidney function is not achieved within the first 1–2 months after transplantation. (2D)
f. We suggest a surveillance kidney allograft biopsy be performed within the first year after transplant for all recipients (2D), and ideally at 3 months post transplant for patients receiving cyclosporine and azathioprine for maintenance immunosuppression. (2C)

9. Recurrent kidney disease

a. We suggest screening kidney transplant recipients with primary kidney disease caused by focal segmented glomerulosclerosis (FSGS) for proteinuria. (2C) A reasonable approach would be to screen, using dipstick or spot urine ACR or PCR:
   i. weekly for 4 weeks (2D);
   ii. every 3 months, for the first year (2D); and
   iii. any time that oedema or graft dysfunction occurs. (2D)
b. We suggest screening kidney transplant recipients with potential recurrence of primary kidney disease from immunoglobulin A nephropathy, membranoproliferative glomerulonephritis, anti-glomerular basement membrane disease, or antineutrophil cytoplasmic autoantibody associated vasculitis for microhematuria and proteinuria. A reasonable approach would be to perform dipstick urinalysis or spot urine ACR or PCR plus urine microscopy (2C):
   i. every 3 months during the first year (2D);
   ii. annually, thereafter (2D); and
   iii. any time that graft dysfunction or symptoms of recurrent systemic disease occurs. (2D)
c. 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 dehydrogenase). (2D)
d. When screening tests or clinical features suggest possible recurrent disease, we suggest obtaining an allograft biopsy for histological assessment by light and electron microscopy. (2C)
e. Treatment of recurrent kidney disease:
   i. We suggest plasma exchange if a biopsy shows minimal change disease or FSGS in those with FSGS as their primary kidney disease. (2D)
   ii. We suggest high-dose corticosteroids and cyclophosphamide, with or without plasmapheresis, in patients with recurrent antineutrophil cytoplasmic autoantibody associated vasculitis or anti-glomerular basement membrane disease. (2D)
   iii. For kidney transplant recipients with primary hyperoxaluria, we suggest appropriate measures to prevent oxalate deposition until plasma and urine oxalate levels are normal, including high fluid intake, intensive haemodialysis and pyridoxine. (2C)

10. Preventing, detecting and treating non-adherence

a. We suggest that non-adherence to immunosuppressive medication be reviewed in a non-judgemental manner on an individual basis. (2C)
b. We suggest that the reasons for non-adherence is discussed on an individual basis and that strategies be identified that may assist in overcoming any practical problems raised. (2C)

11. Vaccination

a. We recommend giving all kidney transplant recipients approved, inactivated vaccines according to recommended schedules for the general population. (1D)
b. We recommend pretransplant vaccination with varicella for potential transplant recipients who are non-immune. (1D)
c. We suggest hepatitis B virus (HBV) vaccination (ideally prior to transplantation) and measurement to confirm development of protective titres of antibody to hepatitis B surface antigen (anti-HBs) 6–12 weeks after completing the vaccination series. (2D)
   i. We suggest annual anti-HBs titres thereafter (2D); and
   ii. We suggest revaccination if the antibody titres fall below 10 mIU/mL. (2D)
d. We suggest avoiding live vaccines in kidney transplant recipients. (2C)
e. We suggest avoiding vaccination, except influenza vaccination, in the first 6 months after kidney transplantation. (2C)
f. We suggest giving all kidney transplant recipients, who are at least 1 month post transplant, influenza vaccination prior to the onset of the annual influenza season regardless of status of immunosuppression. (2C)

12. Viral diseases

12.1 BK polyoma virus

a. We suggest screening high risk kidney transplant recipients for BK polyoma virus with quantitative plasma nucleic

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acid testing. The frequency of screening is not clear; however, the risk is higher in the early post-transplant period. (2C) The frequency of screening suggested by KDIGO is a reasonable option as follows:

i. monthly for the first 3–6 months after transplantation (2D);
ii. then every 3 months until the end of the first post-transplant year (2D);
iii. whenever there is an unexplained rise in serum creatinine (2D); and
iv. after treatment for acute rejection. (2D)

b. We suggest reducing immunosuppressive medications when BK polyoma virus plasma nucleic acid testing is persistently greater than 10 000 copies/mL (107 copies/L) unless there is a contraindication. (2D)

c. We suggest performing a renal biopsy in the event of a deterioration in renal allograft function in order to establish the presence of BK nephropathy or other pathology. (2C)

12.2 Cytomegalovirus

a. Cytomegalovirus (CMV) prophylaxis: We recommend that kidney transplant recipients (except when donor and recipient both have negative CMV serologies) receive chemoprophylaxis for CMV infection with oral ganciclovir or valganciclovir for at least the first 3 post-transplant months or after receiving T-cell depleting antibody. (1C)

b. Pre-emptive treatment of CMV infection is recommended as it significantly reduces the risk of CMV disease compared with placebo. (1C)

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

d. In patients with CMV disease, we suggest weekly monitoring of CMV by quantitative PCR or pp65 antigenaemia. (2D) To monitor response to treatment we suggest continuing therapy until CMV is no longer detectable by plasma PCR or pp65 antigenaemia. (2D)

e. We recommend that CMV disease in adult kidney transplant recipients that is not serious (e.g. episodes that are associated with mild clinical symptoms) be treated with either IV ganciclovir or oral valganciclovir. (1D)

f. We recommend that all CMV disease in paediatric kidney transplant recipients be treated with IV ganciclovir. (1D)

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

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

12.3 Epstein–Barr virus and post-transplant lymphoproliferative disease

a. We suggest monitoring high-risk (donor Epstein–Barr virus (EBV) seropositive/recipient seronegative) kidney transplant recipients for EBV by PCR be considered. (2D) The frequency and duration of monitoring is unclear on current evidence, but the peak incidence of EBV-related post-transplant lymphoproliferative disease (PTLD) occurs in the first 2 years following transplantation. There is no reliable evidence that patient outcomes are different in the presence or absence of viral load monitoring. Additional testing may be appropriate after any increases in immunosuppressive load, such as after treatment for acute rejection.

b. We suggest that EBV-seronegative patients with a persistently increasing EBV load have immunosuppressive medication reduced. (2D)

c. We suggest that EBV load alone should not be used to diagnose EBV disease. (2D)

d. We suggest that patients with EBV disease, including PTLD, have a reduction or cessation of immunosuppressive medications. (2C)

e. Use of prophylactic antiviral drugs may have some benefit in preventing EBV-related PTLD in kidney transplant recipients, and we suggest they be considered for high risk patients (EBV seronegative at transplant). (2C)

f. We suggest that rituximab be considered for primary treatment or rescue treatment of PTLD that is positive for CD20 by immunostaining. (2D)

Ungraded suggestion for clinical care

g. Kidney transplant recipients with suspected or proven PTLD should be managed by a clinical team including expertise in haematoncology. (ungraded)

12.4 Herpes simplex virus 1, 2 and varicella zoster virus

a. We suggest that kidney transplant recipients who develop a superficial herpes simplex virus (HSV) 1 or HSV 2 infection be treated with an appropriate oral antiviral agent (e.g. acyclovir, valaciclovir or famciclovir) until all lesions have resolved. (2D)

b. We suggest that kidney transplant recipients with systemic HSV 1 or HSV 2 infection be treated with IV acyclovir and a reduction in immunosuppressive medication. (2D)

i. We suggest that IV acyclovir continue until the patient has a clinical response then switch to an appropriate oral antiviral agent (e.g. acyclovir, valacyclovir or famcyclovir) to complete a total treatment duration of 14–21 days. (2D)

c. We suggest using a prophylactic antiviral agent for kidney transplant recipients experiencing frequent recurrences of HSV 1, 2 infection. (2D)

d. Primary varicella zoster virus (VZV) can be fatal in kidney transplant recipients. We suggest that primary VZV infection (chickenpox) in kidney transplant recipients be treated with IV acyclovir and a temporary reduction in the amount of immunosuppresive medication. (2D)

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e. We suggest that treatment be continued until all lesions have scabbed. (2D)
f. We suggest that uncomplicated herpes zoster (2D) (shingles) be treated with oral acyclovir (2C) or valacyclovir at least until all lesions have scabbed. (2D)
g. We suggest that disseminated herpes zoster (2B) be treated with IV acyclovir (2C) and a temporary reduction in immunosuppression at least until all lesions have scabbed. (2D)
h. We suggest that prevention of primary VZV be instituted in varicella susceptible patients after exposure to individuals with active VZV infection: (2D)
   i. VZV immunoglobulin or IV immunoglobulin within 96 h of exposure (2D); and
   ii. If immunoglobulin is not available or more than 96 h have passed, a 7 day course of oral acyclovir begun 5–10 days after VZV exposure. (2D)

12.5 Hepatitis C virus

a. We suggest that hepatitis C virus (HCV)-infected kidney transplant recipients be treated only when the benefits of treatment clearly outweigh the risk of allograft rejection because of interferon-based therapy (e.g. fibrosing cholestatic hepatitis, life threatening vasculitis). (2D)
b. We suggest monotherapy with standard interferon for HCV-infected kidney transplant recipients in whom the benefits of antiviral treatment clearly outweigh the risks. (2D)
c. We suggest that all conventional current induction and maintenance immunosuppressive regimens can be used in HCV-infected patients. (2D)
d. We suggest that interferon is not an appropriate treatment for patients with HCV associated transplant glomerulopathy. (2D)

Ungraded suggestion for clinical care
e. Measure alanine transferase in HCV-infected patients monthly for the first 6 months and every 3–6 months, thereafter. Perform imaging annually to look for cirrhosis and hepatocellular carcinoma. (ungraded)
f. Test HCV-infected patients at least every 3–6 months for proteinuria. (ungraded)
g. For patients who develop new onset proteinuria (either urine protein/creatinine ratio >1 or 24 h urine protein >1 g on two or more occasions), perform an allograft biopsy with immunofluorescence and electron microscopy to determine whether HCV-related membranoproliferative glomerulonephritis has developed. (ungraded)
h. Patients with hepatitis C after transplantation should be managed in consultation with a hepatologist. (ungraded)
   i. For hepatitis C-infected patients being considered for transplantation, consideration be given to antiviral treatment with ribavirin and interferon in a bid to eradicate the virus prior to transplantation. (ungraded)

12.6 Hepatitis B virus

a. We suggest that any currently available induction and maintenance immunosuppressive medication can be used in HBV-infected kidney transplant recipients. (2D)
b. We suggest that interferon treatment should generally be avoided in HBV-infected kidney transplant recipients. (2D)
c. We suggest that all hepatitis B surface antigen (HBsAg)-positive kidney transplant recipients should receive prophylaxis with tenofovir, entecavir or lamivudine. (2D)
d. We suggest treatment with adefovir or tenofovir for kidney transplant recipients with lamivudine resistance (>5 log 10 copies/mL rebound of HBV DNA). (2D)

Ungraded suggestion for clinical care
e. Tenofovir or entecavir are preferable to lamivudine, to minimize the development of potential drug resistance, unless medication cost requires that lamivudine be used. (ungraded)
f. During therapy with antivirals, measure HBV DNA and alanine transferase levels every 3 months to monitor efficacy and to detect drug resistance. (ungraded)
g. Screen HBsAg-positive patients with cirrhosis for hepatocellular carcinoma every 12 months with liver ultrasound and alpha feto-protein. (ungraded)
h. Patients who are negative for HBsAg and have a titre <10 mIU/mL for anti-HBs should receive booster vaccination to raise the titre to ≥100 mIU/mL. (ungraded)
i. We strongly suggest discussion with a hepatologist in all patients with hepatitis B after transplantation. (ungraded)

12.7 Human immunodeficiency virus

a. We suggest that all potential kidney transplant recipients be screened for human immunodeficiency virus (HIV) infection. (2D)
b. To determine antiretroviral therapy, we suggest referral of HIV-infected kidney transplant recipients to an HIV specialist who should pay special attention to drug–drug interactions and appropriate dosing of medication. (2D)

Ungraded suggestion for clinical care
c. HIV infection should not be considered a contraindication for transplantation, but should be considered along with other comorbidities in determining whether to proceed with transplantation and, if so, in determining appropriate immunosuppression and adjunctive therapies. (ungraded)

13. Other infections

13.1 Urinary tract infection

a. We recommend that all kidney transplant recipients receive urinary tract infection prophylaxis with

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trimethoprim-sulfamethoxazole in the early post-transplant period unless contraindicated. (1B)
b. We suggest patients with allograft pyelonephritis be hospitalized for initial treatment with IV antibiotics. (2C)

13.2 Pneumocystis jirovecii pneumonia

a. We recommend that all kidney transplant recipients receive pneumocystis jirovecii pneumonia (PCP) prophylaxis with trimethoprim-sulfamethoxazole for 3–6 months after transplantation. (1B)
b. We suggest that all kidney transplant recipients receive PCP prophylaxis with trimethoprim-sulfamethoxazole for at least 6 weeks during and after treatment for acute rejection. (2C)
c. We recommend that kidney transplant recipients with PCP be treated with high-dose IV trimethoprim-sulfamethoxazole, and a reduction in immunosuppressive medications. (1C)
d. We suggest treatment with corticosteroids for kidney transplant recipients with moderate to severe PCP (as defined by PaO2 < 70 mmHg on room air on an alveolar gradient of >35 mmHg). (2C)

13.3 Mycobacterium tuberculosis

a. We suggest that Mycobacterium tuberculosis prophylaxis and treatment regimens be the same in kidney transplant recipients as would be used in the local, general population who require therapy. (2D)
b. We suggest monitoring CNI and mTORi blood concentrations in patients receiving rifampicin. (2C)

13.4 Candida prophylaxis

a. We suggest oral and oesophageal Candida prophylaxis in the early post-transplantation period and after treatment with anti-lymphocyte antibody. (2D)
b. We suggest close monitoring of CNI dosing when using anti-fungals that inhibit the cytochrome P450 pathway. (2D)

14. Diabetes mellitus

14.1 Screening for new-onset diabetes after transplantation

a. We recommend screening all nondiabetic kidney transplant recipients for the development of new-onset diabetes after transplantation (NODAT) with fasting and/or post-prandial plasma glucose (1C) at least:

i. weekly for 4 weeks (2D);
ii. every 3 months for 1 year (2D);
iii. annually thereafter (2D); and
iv. after starting, or substantially increasing the dose of CNI, mTORi or corticosteroids. (2D)

b. Fasting and post-prandial plasma glucose are useful screening tests for NODAT, while the diagnosis should be made according to WHO criteria (see below). HbA1c is not a useful diagnostic test during the first 3 months post transplant. (2D)

Ungraded suggestion for clinical care
c. Consideration be given to screening for NODAT by oral glucose tolerance testing at 3 months after transplantation. (ungraded)

14.2 Managing new-onset diabetes or diabetes present at transplantation

Insufficient evidence available for provision of graded recommendations or suggestions.

Ungraded suggestion for clinical care
a. If NODAT develops, consider modifying the immunosuppressive drug regimen to reverse or ameliorate diabetes, after weighing the risk of rejection and other potential adverse effects. (ungraded)
b. Consider using diet and exercise, and if required hypoglycaemic medications, to target HbA1c $\leq$ 7.0, unless the patient is at high risk of hypoglycaemia (e.g. hypoglycaemic unawareness, autonomic neuropathy, severe macrovascular disease). (ungraded)

15. Hypertension, dyslipidaemia, tobacco use and obesity

15.1 Hypertension

a. We suggest regular assessment and treatment of hypertension be undertaken in kidney transplant recipients. (2C)
b. Although there is no RCT evidence to guide target blood pressure in this population, we suggest blood pressure be maintained at <130 mmHg systolic and <80 mmHg diastolic in adults and less than the 90th percentile for sex, age and height if under 18 years of age. As in the CKD population, tighter blood pressure control (<125/75) is suggested for patients with significant proteinuria (>1 g per day). (2C)
c. We suggest the use of a calcium channel blocker as first line therapy, although this should be balanced against each patient's comorbidity and the presence of proteinuria. CNI concentrations should be monitored closely in patients starting calcium channel blocker therapy, as a CNI dose reduction may be required. (2B)

Ungraded suggestion for clinical care
d. In patients with uncontrolled or refractory hypertension, underlying causes of hypertension should be sought, particularly transplant renal artery stenosis. (ungraded)

15.2 Dyslipidaemia

a. We recommend lipid lowering therapy with statins in kidney transplant recipients on the basis that such therapy is

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safe and leads to lowered total cholesterol, triglycerides and low density lipoprotein cholesterol (LDL-C). (1B) Statin therapy is likely to be associated with a reduction in cardiovascular events and mortality; however, caution should be taken regarding drug–drug interactions with immunosuppressive therapy. (1C)

Ungraded suggestion for clinical care

b. Complete lipid profiles should be measured in the first 2–3 months post transplant, 2–3 months after any alteration in treatment or immunosuppression, and annually thereafter. (ungraded)

c. A diet rich in whole grains, and high fibre carbohydrates with a low glycaemic index should be recommended to adult kidney transplant recipients with abnormal lipid profiles (refer to the KHA-CARI guidelines Nutrition in Kidney Transplant Recipients at http://www.cari.or.au).

d. There is no evidence to suggest a target LDL-C in kidney transplant recipients. However, the Study of Heart and Renal Protection (SHARP) trial in CKD patients found a 19% risk reduction of atherosclerotic events for every 1 mmol/L reduction in LDL-C. Combination therapy with statins and ezetimibe may be considered in order to achieve the National Heart Foundation guidelines of an LDL-C < 2 mmol/L for high-risk patients. (ungraded)

e. There are no randomized controlled trials to guide measurement or treatment of dyslipidaemias in paediatric kidney transplant recipients. (ungraded)

15.3 Tobacco use

a. We recommend that all kidney transplant recipients be questioned and counselled regarding tobacco use at or before initial hospitalization and at least annually thereafter. (1D)

Ungraded suggestion for clinical care

b. Treatment/counselling should be offered to all patients who use tobacco to facilitate smoking cessation. (ungraded)

15.4 Obesity

a. We suggest obesity should be assessed at each visit, given the association between obesity after renal transplant and diabetes mellitus, inferior graft survival and inferior patient survival. (2C)

Ungraded suggestion for clinical care

b. Diet and behaviour modification are likely to be safe in kidney transplant recipients; however, they are likely to only reduce weight in the short term. In addition, giving simple advice may be ineffective. (ungraded)

c. The KHA-CARI guidelines for Nutrition in Kidney Transplant Recipients (http://www.cari.or.au) should be adopted. Briefly, overweight kidney transplant recipients should have a diet that is individually planned with a moderate energy restriction of about 30% of energy expenditure, with monthly follow up with a dietician. (ungraded)

16. Atherosclerotic cardiovascular disease management

a. Unless there are contraindications, we suggest that aspirin is appropriate in kidney transplant patients with demonstrated atherosclerotic cardiovascular disease (CVD). (2B) This is based on the increased risk of CVD in kidney transplant patients and because the use of low-dose aspirin (65–100 mg/day) has been shown to be effective in the general population in reducing atherosclerotic CVD events in patients with known CVD. (2B)

Ungraded suggestion for clinical care

b. The principles of management of complications of atherosclerotic CVD are unlikely to be different in kidney transplant recipients compared with the general population and the population of patients with CKD. Thus, in the absence of specific randomized controlled trial evidence in renal transplant recipients for the benefit of modification of traditional atherosclerotic risk factors, there is little reason to believe that the benefits of lifestyle modification would not exceed the harms in kidney transplant recipients, especially those with established CVD. (ungraded) (See also KHA-CARI guidelines – 'Cardiovascular Risk Factors'.)

17. Cancer of the skin and lip

a. We recommend kidney transplant recipients especially those with previous history of skin cancer, fair skin, occupation requiring sun exposure or other significant sun exposure be told that their risk of skin and lip cancer is high. (1C)

b. We recommend kidney transplant recipients be advised to minimize excessive sun exposure, and use appropriate ultraviolet blocking strategies (sunscreens and clothing). (1D)

c. We recommend kidney transplant recipients with a history of skin cancer be offered treatment with oral Acitretin if there are no contraindications and the therapy is tolerated. (1C)

d. We suggest that kidney transplant recipients perform regular skin and lip self-examination and report new lesions to health care providers. (2D)

e. We suggest that a health care specialist with expertise in skin cancer diagnosis, examine the skin and lips of kidney transplant recipients annually, especially those with previous history of skin cancers. (2D)

f. We suggest that kidney transplant recipients who are smokers be told that they are at high risk of developing lip cancer. (2C)

g. We suggest that alteration of maintenance immunosuppression be considered for kidney transplant recipients at

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high risk of skin cancer, and after a skin cancer diagnosis. The benefit of mTORi remains uncertain, given that the evidence is conflicting, in particular whether the potential benefits outweigh the potential harms of therapy. (2D)

18. Non-skin malignancies

Insufficient evidence available for provision of graded recommendations or suggestions.

Ungraded suggestion for clinical care

a. Develop an individualized screening programme for each kidney transplant recipient that takes into account past medical and family history, tobacco use, projected life expectancy, other competing risk factors for death and the test performance characteristics of the screening test methodology. (ungraded)

b. Screening for the following cancers as per local guidelines for the general population should be undertaken (ungraded):

i. Women: cervical, breast and colorectal cancer.

ii. Men: colorectal and prostate cancer.

c. Targeted screening for renal cancer by ultrasound should be considered for kidney transplant recipients at higher risk, such as those with a past or family history of renal cell carcinoma or prior history of analgesic nephropathy. (ungraded)

d. Hepatic ultrasound and alpha feto-protein should be obtained every 12 months in patients with compensated cirrhosis. (ungraded)

19. Managing cancer with reduction of immunosuppressive medication

a. We suggest consideration be given to reducing immunosuppressive medications for kidney transplant recipients once diagnosed with cancer. (2C) Important factors for consideration include:

i. The staging of cancer at diagnosis.

ii. Whether the cancer is likely to be exacerbated by immunosuppression.

iii. The therapies available for cancer.

iv. Whether immunosuppressive medications interfere with the ability to administer the standard chemotherapy.

v. The wishes of the patient, once appropriately informed of the diagnosis, prognosis and therapeutic options and their effects.

b. For patients with Kaposi sarcoma we suggest consideration of an mTORi along with a reduction in overall immunosuppression. (2C)

CONFLICT OF INTEREST

K Barraclough, C Clark, N Cross, L Henderson, M Howell, N Isbel, J Kanellis, S Kotwal, P Manley, W Mulley, K Murali, A Webster and K Wiggins have no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by KHA-CARI.

S Chadban, S Campbell, S Cohney, J Eris, H Pilmore and G Russ, have a Level II conflict of interest according to the conflict of interest statement set down by KHA-CARI.

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