CARI Adaptation of the KDIGO Transplant Guidelines

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On behalf of the CARI Adaptation Team

DNT, Cypress Lakes, 2011
The KDIGO Clinical Practice Guidelines for the Care of Kidney Transplant Recipients

Jeremy R. Chapman

The clinical guideline for care of renal transplant recipients was written by a committee of 15 people from nine countries, supported by an evidence review team. The scope of the review was care of the patient after a renal transplant—not evaluation or selection of recipients and donors, focusing on the issue specific to the immunosuppressed transplant patient. A total of 12,327 articles comprising 3168 randomized controlled trials, 7543 cohort studies, and 1609 reviews were selected by a formal search. Each article was formally evaluated for the quality of the data from A to D. A consistent set of statements were based on the strength of the evidence. Level 1 evidence: “we recommend” means that if you were a patient, most people would want to do this; if a clinician, you should recommend this course of action to most patients; and if a policy maker, you should adopt this as a reasonable standard. Level 2 evidence: “we suggest” means the majority of patients would want to do this; to the clinician, it means that different solutions may well be needed for different patients; whereas to the health policy maker, this is a strong warning to engage stakeholders in the creation of a particular local policy. Because 69% of the advice is “suggested” on the basis of level C or D evidence, one outcome of this work is to make it clear where the current evidence for clinical decisions runs out of data.

Keywords: Evidence-based medicine, Consensus, Chronic Kidney Disease.

(Transplantation 2010;89: 644–645)
CARI Adaptation – What is it and why do it???

What:
200+ pages, 12,000+ papers

Why:
CARI ran out of other subjects for guidelines
Team in need of publications for CV
Couldn’t remember the right dose of cyclosporine
Lawyers needed a yardstick for malpractice in Tx
RRT Australia, 12/08

Transplant 7109

Dialysis 9642

2,311 incident RRT

69 LD

202 LD

546 Tx

344 DD

2242

16,751 RRT

151 deaths

2.2/100yrs

1,452 deaths

15.4/100yrs

1,603 deaths
History of transplant immunosuppression

Improving short term graft survival

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<tr>
<th>Year</th>
<th>Patient Survival</th>
<th>Graft Survival</th>
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<tr>
<td>1960</td>
<td>60%</td>
<td>20%</td>
</tr>
<tr>
<td>1970</td>
<td>90%</td>
<td>60%</td>
</tr>
<tr>
<td>1980</td>
<td>95%</td>
<td>90%</td>
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Drugs:
- Belatacept
- Sotrastaurin
- Tasocitinib
- Eculizumab
- IVIG
- Mycophenolate mofetil
- Mycophenolate sodium
- Basiliximab
- Daclizumab
- Muromonab OKT-3
- Polyclonal Antilymphocyte Antibodies
- Cyclosporin
- Cyclosporine ME
- Tacrolimus
- Sirolimus
- Everolimus
- Azathioprine
- Steroids
Intervention in the immunology of rejection

Depletion – ALGs, OKT3, Campath
Signal 1 – CsA, FK506, PKC
Signal 2 – CTLA41g - belatacept
Signal 3 – aCD25, PSIs, JAK3
Late – MMF, AZA, Pred
B & Ab – rituximab, IVIG

APC

MHC

TCR

Ag

B7 CD28

CD40 CD40L

belatacept

ATG Thymo

CSA FK506 PKC

IL2

IL2R

CD25

antiCD25

mTOR-I, JAK

MMF AZA

Proliferation

Activation

Pred

rituximab IVIG

B cells/Ab MØ NK & CD8

SC 2008
CVD is the main cause of death with a functioning graft: ANZDATA 1980-2007

Adjusted RR 0.61 (CI 0.38–0.96; \(p=0.034\)) for 2005–2007 compared to 1980–1984

Adjusted death rates in kidney transplant recipients per 100 patient years

Pilmore HL, H Dent, S McDonald, S Chadban. In press: Transplantation 2009
Outcomes after Transplantation according to recipient age - ANZDATA

Death-censored graft failure

Death with functioning graft

Recipient age (years)

Graphs by gloss

Lim, Chang, et al, NDT 2010
Symphony - Time to Withdrawal

H Ekberg et al, NEJM 2007
CARI Adaptation – What is it and why do it???

What:
1st Adaptation of a KDIGO guideline – ADAPTE
Context: ANZ
Evidence base – updated searches, evidence re-grade
Condensed output including summary
Currently undergoing external review - CARI website

Why:
Patient demographics, medications, funding differ
Much of KDIGO Guideline “opinion” based
Adaptation reduces workload over new guideline
Canadian Society of Transplantation and Canadian Society of Nephrology Commentary on the 2009 KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients

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AJKD 2010;56:219-46
CARI Adaptation Team

Transplant Clinicians with particular interests
  - second reviewer of their choosing
Steve Chadban
  - chair
  - coordination

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  - evidence search updates
  - compilation of chapters
  - evidence grading
  - coordination

Jonathan Craig and Jeremy Chapman
  - authors of KDIGO Guidelines

Martin Gallagher
  - CARI
## CARI Adaptation Team

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<td>Kate Wiggins</td>
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<td>Kate Wyburn</td>
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# Rating the evidence base: GRADE

<table>
<thead>
<tr>
<th>Overall Evidence Grade</th>
<th>Description</th>
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</table>
| 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. |
## Strength of recommendations

<table>
<thead>
<tr>
<th>Grade</th>
<th>Patients</th>
<th>Clinicians</th>
<th>Policy</th>
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<tr>
<td><strong>Level 1 “We recommend”</strong></td>
<td>Most people in your situation would want the recommended course of action and only a small proportion would not</td>
<td>Most patients should receive the recommended course of action</td>
<td>The recommendation can be adopted as a policy in most situations</td>
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<tr>
<td><strong>Level 2 “We suggest:”</strong></td>
<td>The majority of people in your situation would want the recommended course of action, but many would not</td>
<td>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</td>
<td>The recommendation is likely to require debate and involvement of stakeholders before policy can be determined</td>
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</table>
Guidelines under GRADE system

The overall implication of the above grading process is that a strong recommendation may be made on the basis of low quality evidence (i.e. a 1D grade). eg. Pre-transplant vaccination against varicella

Similarly a suggestion only may be made even though there is high quality evidence (i.e. 2A). eg. DIRECT study, RCT, cyclosporin equally efficacious but less diabetogenic than tacrolimus

This differs to the approach previously taken by CARI whereby “Guidelines” were only made where Level 1 or 2 evidence (i.e. systematic reviews or RCTs) was available.
### Topic 1. Induction Therapy

a. We recommend that a combination of immunosuppressive medications should be started before, or at the time of, kidney transplantation (IA)

b. We recommend Induction therapy with a biologic agent as part of the initial immunosuppression regimen in kidney transplant recipients (IB)

c. We recommend that an interleukin-2 receptor antagonist should be the first-line induction therapy (1B)

d. In KTRs at high immunological risk of acute cellular rejection consideration can be given to the use of a lymphocyte-depleting agent in place of an IL-2RA (2B)

e. We suggest that in KTRs at high risk of antibody-mediated rejection, induction therapy should be given that may include at least one of IVIG, plasma exchange or rituximab (2C)

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**KDIGO**

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 IL2-RA be the first line 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)
**Topic 2. Initial Maintenance**

**Immunosuppressive Medications**

a. We recommend using a combination of immunosuppressive medication as maintenance 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 mTOR inhibitors are used, they not be started until graft function is established and wounds are healed. (1B)

d. **We suggest that tacrolimus be first-line for higher risk patients.** (2A)
   
i. 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 tac; 2B csa)

e. We suggest that, in patients who are at low immunological risk and who receive induction therapy, corticosteroids could be minimised early after transplantation. (2B)

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**KDIGO**

2.1: We recommend using a combination of immunosuppressive medications as maintenance therapy including a CNI and an antiproliferative agent, with or without corticosteroids. (1B)

2.2: We suggest that tacrolimus be the first-line CNI used. (2A)
   
   2.2.1: We suggest that tacrolimus or CsA be started before or at the time of transplantation, rather than delayed until the onset of graft function. (2D tacrolimus; 2B CsA)

2.3: We suggest that mycophenolate be the first-line antiproliferative agent. (2B)

2.4: We suggest that, in patients who are at low immunological risk and who receive induction therapy, corticosteroids could be discontinued during the first week after transplantation. (2B)

2.5: We recommend that if mTOR inhibitors are used, they should not be started until graft function is established and surgical wounds are healed. (1B)
**Topic 3: Long-Term Maintenance Immunosuppressive Medications**

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

b. We suggest that calcineurin inhibitors 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)

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**KDIGO**

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 CNIs be continued rather than withdrawn. (2B)

3.2: If prednisone is being used beyond the first week after transplantation, we suggest prednisone be continued rather than withdrawn. (2C)
Ch 5. Monitoring Immunosuppressive Medications - KDIGO:

5.1: We recommend measuring CNI blood levels (1B), and suggest measuring at least:
   a. every other day during the immediate postoperative period until target levels are reached (2C);
   b. whenever there is a change in medication or patient status that may affect blood levels (2C);
   c. whenever there is a decline in kidney function that may indicate nephrotoxicity or rejection. (2C)

5.1.1: We suggest monitoring CsA using 12-h trough (C0), 2-h post-dose (C2) or abbreviated AUC. (2D)

5.1.2: We suggest monitoring tacrolimus using 12-h trough (C0). (2C)

5.2: We suggest monitoring MMF levels. (2D)

5.3: We suggest monitoring mTORi levels. (2C)
Topic 5 Monitoring Immunosuppressive Medications - CARI

General
• Target concentration range for immunosuppressants should be individualised depending on recipient immunological and toxicity risk status and co-therapy administered. (2C)

• When interpreting concentrations of immunosuppressants, it is recommended that attention be paid to whether high performance liquid chromatography (HPLC) or immunoassay technology is employed. Immunoassays can be biased by cross-reactivity with metabolites and therefore typically provide a higher reading than HPLC which is specific for the parent compound. (1B)
Calcineurin inhibitor (CNI) monitoring - CARI

• We recommend cyclosporine and tacrolimus blood drug concentrations should be measured (1C):
  a. frequently in the immediate post-operative period (e.g. second daily) until target levels are reached and stability of therapeutic concentrations has been demonstrated;
  b. following a dose change;
  c. whenever there is a significant change in clinical parameters, concomitant immunosuppression or medications that may affect drug concentrations;
  d. when there is concern regarding over- or under-immunosuppression. (2C)
• Cyclosporine can be monitored using 12-hour trough (C0) or 2-hour 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)
• C0 concentrations can be used for tacrolimus monitoring as there is a lack of evidence for a superior monitoring strategy. (2D)
Mycophenolate mofetil (MMF) monitoring - CARI

• We suggest consideration should be given to MMF monitoring:
  • in high immunological risk recipients;
  • when there is a significant change in clinical parameters, concomitant immunosuppression or medications that may affect drug concentrations;
  • when there is concern regarding over- or under-immunosuppression. (2D)

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

• A mycophenolic acid (MPA) AUC0-12 target range of 30 to 60 mg·h/L is suggested for the early post-transplant period. There is no data available regarding an appropriate MPA AUC0-12 target in patients a distance post-transplant. (2C)
Mammalian target of rapamycin inhibitor monitoring

• We recommend mTORi concentrations should be monitored (1C). The following monitoring strategy is suggested:
  • after initiation of therapy or a change in dose;
  • with suspected drug interactions;
  • when there is concern regarding over- or under-immunosuppression. (2C)

• It is suggested that C0 concentrations can be used for mTOR inhibitor monitoring, however we note that mTORi target concentrations may vary by drug, perceived risk of rejection, and time post-transplant. (2C)
**Topic 6. Treatment of Acute Rejection**

a. We recommend biopsy before treating AR, unless the biopsy will substantially delay Rx (1C)

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

c. We recommend using pulsed steroids for initial treatment of acute cellular rejection. (1D)

i. We suggest adding or restoring maintenance prednisone if ARE whilst steroid free (2D)

ii. We suggest using lymphocyte-depleting antibodies for resistant or vascular AR (Banff II or higher) (2C)

a. We suggest consideration be given to treating ABMR with plasma exchange and/or IVIG (2C)

b. If ARE, we suggest increasing immunosuppression (e.g. switching azathioprine to mycophenolate, add, increase or change CNI; switching an mTORi to a CNI; or increasing the dose of agents being used (2D).

**KDIGO**

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 mycophenolate if the patient is not receiving mycophenolate or azathioprine, or switching azathioprine to mycophenolate. (2D)
## Topic 7 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 CAI and histological evidence of calcineurin inhibitor (CNI) toxicity, we suggest reducing, withdrawing, or replacing CNI (2C)

i. For patients with eGFR >40 mL/min/1.73 m², and urine total protein excretion <50 mg/mmol creatinine (or equivalent proteinuria by other measures), we suggest replacing the CNI with a mammalian target of rapamycin inhibitor (mTORi) (2D)

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### KDIGO

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 CAI and histological evidence of CNI toxicity, we suggest reducing, withdrawing, or replacing the CNI. (2C)

7.2.1: For patients with CAI, eGFR >40 mL/min/1.73 m², and urine total protein excretion <500 mg/g creatinine (or equivalent proteinuria by other measures), we suggest replacing the CNI with a mTORi. (2D)
**Topic 8 Monitoring Kidney Allograft Function**

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

b. We suggest monitoring urine PCR on a random urine intermittently. A suggested minimum test schedule: (2C)
   i. once in the first month (baseline) (2D)
   ii. 3 monthly during the first year; (2D)
   iii. annually, thereafter. (2D)

c. We recommend assessing graft function by monitoring serum creatinine (1B). Frequency should balance probability of acute complications, need for early detection and patient inconvenience. A suggested minimum (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;
   vi. every 2–3 months, thereafter.

8.1: We suggest measuring urine volume (2C):
   - every 1–2 hours for at least 24 hours after transplantation (2D);
     - daily until graft function is stable. (2D)

8.2: We suggest measuring urine protein excretion, (2C) at least:
   - once in the first month to determine a baseline (2D);
   - every 3 months during the first year (2D);
   - annually, thereafter. (2D)

8.3: We recommend measuring serum creatinine, (1B) at least:
   - daily for 7 days or until hospital discharge, whichever occurs sooner (2C);
   - two to three times per week for weeks 2–4 (2C);
   - weekly for months 2 and 3 (2C);
   - every 2 weeks for months 4–6 (2C);
   - monthly for months 7–12 (2C);
   - every 2–3 months, thereafter. (2C)

8.3.1: We suggest estimating GFR whenever serum creatinine is measured, (2D) using:
   - one of several formulas validated for adults (2C); or
   - the Schwartz formula for children and adolescents. (2C)

8.4: We suggest including a kidney allograft ultrasound examination as part of the assessment of kidney allograft dysfunction. (2C)
**Topic 9 Kidney Allograft Biopsy**

a. We suggest kidney allograft biopsy when there is a persistent, unexplained increase in serum creatinine. (2C)

b. We suggest kidney allograft biopsy when serum creatinine has not returned to baseline after treatment of acute rejection. (2D)

c. We suggest allograft biopsy when there is:
   i. new onset of proteinuria (2C);
   ii. unexplained proteinuria ≥100 mg/mmol creatinine or ≥1.0 g per 24 hours. (2C)

a. We suggest kidney allograft biopsy every 5–10 days during delayed function. (2C)

b. We suggest kidney allograft biopsy if expected kidney function is not achieved within the first 1–2 months after transplantation. (2D)

c. We suggest a surveillance renal allograft biopsy at 3 months post-transplant for patients on cyclosporine and azathioprine maintenance immunosuppression. (2C)

d. We suggest a surveillance renal allograft biopsy at 12 months post-transplantation. (2D)

**KDIGO**

9.1: We recommend kidney allograft biopsy when there is a persistent, unexplained increase in serum creatinine. (1C)

9.2: We suggest kidney allograft biopsy when serum creatinine has not returned to baseline after treatment of acute rejection. (2D)

9.3: We suggest kidney allograft biopsy every 7–10 days during delayed function. (2C)

9.4: We suggest kidney allograft biopsy if expected kidney function is not achieved within the first 1–2 months after transplantation. (2D)

9.5: We suggest kidney allograft biopsy when there is:
   - new onset of proteinuria (2C);
   - unexplained proteinuria ≥3.0 g/g creatinine or ≥3.0 g per 24 hours. (2C)
**Topic 10 Recurrent Kidney Disease**

a. We suggest screening kidney transplant recipients with primary FSGS for proteinuria (2C). A reasonable approach would be to screen, using dipstick or spot urine albumin creatinine ratio (ACR) or protein creatinine ratio (PCR):
   - weekly for 4 weeks (2D);
   - every 3 months, for the first year (2D);
   - if oedema or graft dysfunction occur (2D).

b. We suggest screening kidney transplant recipients with potential recurrence of primary kidney disease from IgAN, MPGN, anti-GBM disease, or ANCA associated vasculitis for microhematuria and proteinuria. A reasonable approach would be to perform dipstick urinalysis OR spot urine or plus urine microscopy (2C):
   - every 3 months during the first year (2D);
   - annually, thereafter (2D);
   - any time that graft dysfunction or symptoms of recurrent systemic disease occurs (2D).

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**KDIGO**

10.1: We suggest screening KTRs with primary kidney disease caused by 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, MPGN, anti-GBM disease, or ANCA-associated vasculitis for microhematuria, (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 HUS, we suggest screening for thrombotic microangiopathy (e.g. with platelet count, peripheral smear for blood cell morphology, plasma haptoglobin, and serum lactate dehydrogenase). (2D)
**Topic 10 Recurrent Kidney Disease**

a. During episodes of graft dysfunction in patients with primary HUS, we suggest screening for thrombotic microangiopathy (e.g. with platelet count, blood film, haptoglobin, LDH (2D).

b. When screening tests or clinical features suggest possible recurrent disease, we suggest obtaining an allograft biopsy for histology by light and EM. (2C).

c. Treatment of recurrent kidney disease:
   i. We suggest plasma exchange if a biopsy shows minimal change disease or FSGS in those with primary FSGS (2D).
   ii. We suggest high-dose corticosteroids and cyclophosphamide, with or without plasmapheresis, if recurrent ANCA-associated vasculitis or anti-GBM disease (2D).
   iii. For KTRs 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).

10.4: 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 ACE-I or an 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)
### Topic 11 Preventing, Detecting, and Treating Nonadherence

a. It is suggested that nonadherence to immunosuppressive medication be reviewed in a non-judgemental manner on an individual basis. (2C)

b. It is suggested that the reasons for nonadherence be discussed on an individual basis and that strategies be identified that may assist in overcoming any practical problems raised. (2C)

### KDIGO

11.1: Consider providing all KTRs and family members with education, prevention, and treatment measures to minimize nonadherence to immunosuppressive medications. (Not Graded)

11.2: Consider providing KTRs at increased risk for nonadherence with increased levels of screening for nonadherence. (Not Graded)
**Topic 12 Vaccination**

a. We recommend giving all KTRs approved, inactivated vaccines according to recommended schedules for the general population (1D)

b. We suggest hepatitis B virus (HBV) vaccination (ideally prior to transplantation) and measurement to confirm development of protective antibody (HBsAb) titres 6–12 weeks after vaccination series (2D)

i. We suggest annual HBsAb titres thereafter (2D)

ii. We suggest revaccination if the antibody titres fall below 10mIU/ml (2D)

a. We suggest avoiding live vaccines in kidney transplant recipients (2C)

b. We suggest avoiding vaccinations, except influenza vaccination, in the first 6 months after kidney transplantation (2C)

c. We suggest giving all kidney transplant recipients, who are at least one month post transplant, influenza vaccination prior to the onset of the annual influenza season regardless of status of immunosuppression (2C).

12.1: We recommend giving all KTRs approved, inactivated vaccines, according to recommended schedules for the general population, except for HBV vaccination. (1D)

12.1.1: We suggest HBV vaccination (ideally prior to transplantation) and HBsAb titers 6–12 weeks after completing the vaccination series. (2D)

12.1.1.1: We suggest annual HBsAb titers. (2D)

12.1.1.2: We suggest revaccination if the antibody titer falls below 10mIU/mL. (2D)

12.2: We suggest avoiding live vaccines in KTRs. (2C)

12.3: We suggest avoiding vaccinations, except influenza vaccination, in the first 6 months following kidney transplantation. (2C)

12.3.1: We suggest resuming immunizations once patients are receiving minimal maintenance doses of immunosuppressive medications. (2C)

12.3.2: We recommend giving all KTRs, who are at least 1-month post-transplant, influenza vaccination prior to the onset of the annual influenza season, regardless of status of immunosuppression. (1C)

12.4: We suggest giving the following vaccines to KTRs who, due to age, direct exposure, residence or travel to endemic areas, or other epidemiological risk factors are at increased risk for the specific diseases:

- rabies, (2D)
- tick-borne encephalitis, (2D)
- Japanese B encephalitis—inactivated, (2D)
- Meningococcus, (2D)
- Pneumococcus, (2D)
- Salmonella typhi—inactivated. (2D)

12.4.1: Consult an infectious disease specialist, a travel clinic or public health official for guidance on whether specific cases warrant these vaccinations. (Not Graded)
**Topic 13.1 BK Polyoma Virus**

a. We suggest screening high risk KTRs for BKV with quantitative plasma NAT. Frequency of screening is not clear however the risk is higher in the early post transplant period (2C):
   i. monthly for M3–6 post-Tx (2D);
   ii. then months 3, 6, 9, 12 (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 BKV plasma nucleic acid testing (NAT) is persistently greater than 10,000 copies/ml (10x7 copies/L) unless there is a contra-indication (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 BKN (2C).

**KDIGO**

13.1.1: We suggest screening all KTRs for BKV with quantitative plasma 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 greater than 10,000 copies/mL (107 copies/L). (2D)
<table>
<thead>
<tr>
<th><strong>Topic 13.2 Cytomegalovirus</strong></th>
<th>13.2.1: 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–depletion (1C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Cytomegalovirus (CMV) prophylaxis: We recommend that kidney transplant recipients (except when donor and recipient both negative) receive chemoprophylaxis for CMV infection with oral ganciclovir or valganciclovir for at least the first 3 post-Tx months or after T cell Ab (1C).</td>
<td>13.2.2: In patients with CMV disease, we suggest weekly monitoring of CMV by NAT or pp65 antigenemia. (2D)</td>
</tr>
<tr>
<td>b. Pre-emptive treatment of CMV infection is recommended as it significantly reduces the risk of CMV disease compared to placebo (1C)</td>
<td>13.2.3: CMV treatment:</td>
</tr>
<tr>
<td>c. We recommend that all patients with serious (including most patients with tissue invasive) CMV disease be treated with IV ganciclovir. (1D)</td>
<td>13.2.3.1: We recommend that all patients with serious (tissue invasive) CMV disease be treated with intravenous ganciclovir. (1D)</td>
</tr>
<tr>
<td>d. In patients with CMV disease, we suggest weekly monitoring of CMV by NAT or pp65 antigenemia (2D). To monitor response to treatment we suggest continuing therapy until CMV is no longer detectable by NAT or pp65 antigenemia (2D)</td>
<td>13.2.3.2: We recommend that CMV disease in adult KTRs that is not serious (e.g. mild clinical symptoms) be treated with either intravenous ganciclovir or oral valganciclovir. (1D)</td>
</tr>
<tr>
<td>e. We recommend that CMV disease in adult KTRs that is not serious (e.g. mild clinical symptoms) be treated with either intravenous ganciclovir or oral valganciclovir (1D).</td>
<td>13.2.3.3: We recommend that all CMV disease in pediatric KTRs be Rx with IV ganciclovir. (1D)</td>
</tr>
<tr>
<td>f. We recommend that all CMV disease in paediatric KTRs be treated with IV ganciclovir (1D)</td>
<td>13.2.3.4: We suggest continuing therapy until CMV is no longer detectable by plasma NAT or pp65 antigenemia. (2D)</td>
</tr>
<tr>
<td>g. We suggest reducing immunosuppressive medication in life-threatening CMV disease and CMV disease that persists (2D).</td>
<td>13.2.4: 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)</td>
</tr>
<tr>
<td>h. We suggest monitoring graft function closely during CMV disease (2D).</td>
<td>13.2.4.1: We suggest monitoring graft function closely during CMV disease. (2D)</td>
</tr>
</tbody>
</table>
**Topic 13.3 Epstein –Barr Virus and Post-Transplant Lymphoproliferative Disease**

a. We suggest monitoring high-risk (D+R-) KTRs for EBV by NAT be considered (2D). The frequency and duration of monitoring is unclear, but the peak incidence of EBV related 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.

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 recommend that patients with Epstein-Barr Virus (EBV) disease, including Post-Transplant Lymphoproliferative Disease (PTLD), have a reduction/cessation of immunosuppression (2C).

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

f. Rituximab may have a role in primary treatment or rescue treatment of CD20+ PTLD (2D).

**UNGRADED SUGGESTIONS FOR CLINICAL CARE**

a. We suggest KTRs with PTLD are managed by a team including a haematologist (ungraded).

**KDIGO**

13.3.1: We suggest monitoring high-risk (donor 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)
**Topic 13.4 Herpes Simplex Virus 1,2 and Varicella Zoster Virus**

a. We suggest KTRs who develop a superficial HSV 1, 2 infection be treated with acyclovir, valaciclovir or famciclovir until all lesions have resolved (2D).

b. We suggest KTRs with systemic HSV 1, 2 infection be treated with intravenous acyclovir and a reduction in immunosuppressive medication. (2D).

  i. We suggest 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 can be fatal in KTRs.** We suggest that primary VZV infection (chickenpox) in kidney transplant recipients be treated with IV acyclovir and a temporary reduction in immunosuppression (2D).

  i. We suggest that treatment be continued until all lesions have scabbed (2D).

e. We suggest that uncomplicated herpes zoster (2D) (shingles) be treated with oral acyclovir (2C) or valacyclovir at least until all lesions scabbed (2D).

f. 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).

g. We suggest that prevention of primary VZV be instituted in Varicella susceptible patients after exposure to individuals with active varicella zoster infection (2D):

  - VZV immunoglobulin or IVIG <96hrs (2D)
  - If above not available, 7 ds oral acyclovir (2D).

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13.4.1: We recommend that KTRs who develop a superficial HSV 1, 2 infection be treated (1B) with an appropriate oral antiviral agent (e.g. acyclovir, valacyclovir, or famciclovir) until all lesions have resolved. (1D)

13.4.2: We recommend that KTRs with systemic HSV 1, 2 infection be treated (1B) with intravenous acyclovir and a reduction in immunosuppressive medication. (1D)

  13.4.2.1: We recommend that intravenous acyclovir continue until the patient has a clinical response, (1B) 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)

13.4.3: We suggest using a prophylactic antiviral agent for KTRs experiencing frequent recurrences of HSV 1,2 infection (2D)

13.4.4: We recommend that primary VZV infection (chickenpox) in KTRs be treated (1C) with either intravenous or oral acyclovir or valacyclovir; and a temporary reduction in amount of immunosuppressive medication. (2D)

  13.4.4.1: We recommend that treatment be continued at least until all lesions have scabbed. (1D)

13.4.5: We recommend that uncomplicated herpes zoster (shingles) be treated (1B) with oral acyclovir or valacyclovir (1B), at least until all lesions have scabbed. (1D)

13.4.6: We recommend that disseminated or invasive herpes zoster be treated (1B) with intravenous acyclovir and a temporary reduction in the amount of immunosuppressive medication (1C), at least until all lesions have scabbed. (1D)

13.4.7: We recommend that prevention of primary varicella zoster be instituted in varicella-susceptible patients after exposure to individuals with active varicella zoster infection (1D):

  - varicella zoster immunoglobulin (or intravenous immunoglobulin) within 96 hours of exposure (1D);
  - if immunoglobulin is not available or more than 96 h have passed, a 7-day course of oral acyclovir begun 7–10 days after varicella exposure. (2D)
**Topic 13.5 Hepatitis C Virus**

a. We suggest HCV infected KTRs be treated only when the benefits of treatment clearly outweigh the risk of allograft rejection due to interferon-based therapy (e.g. fibrosing cholestatic hepatitis, life-threatening vasculitis). (2D)

b. We suggest interferon monotherapy for KTRs in whom the benefits of antiviral treatment clearly outweigh the risks. (2D)

c. We suggest that all conventional induction and maintenance immunosuppressive regimens can be used in HCV infected patients. (2D)

d. We suggest that all patients with HCV associated glomerulopathy not receive interferon. (2D)

**UNGRADED SUGGESTION FOR CLINICAL CARE**

a. Measure ALT if HCV+ monthly for the first 6 months and every 3–6 months, thereafter. Perform imaging annually to look for cirrhosis and hepatocellular carcinoma. (Not Graded)

b. Test HCV infected patients at least every 3–6 months for proteinuria. (Not Graded)

c. For patients who develop new onset proteinuria, perform an allograft biopsy with immunofluorescence and EM for HCV related MPGN has developed. (Not Graded)

d. We strongly suggest discussion with a hepatologist in all cases (Not Graded)

13.5.1: We suggest that HCV-infected KTRs be treated only when the benefits of treatment clearly outweigh the risk of allograft rejection due to interferon-based therapy (e.g. fibrosing cholestatic hepatitis, life-threatening vasculitis). (2D) [Based on KDIGO Hepatitis C Recommendation 2.1.5.]

13.5.2: We suggest monotherapy with standard interferon for HCV-infected KTRs in whom the benefits of antiviral treatment clearly outweigh the risks. (2D) [Based on KDIGO Hepatitis C Recommendations 2.2.4 and 4.4.2.]

13.5.3: We suggest that all conventional current induction and maintenance immunosuppressive regimens can be used in HCV infected patients. (2D) [Based on KDIGO Hepatitis C Recommendation 4.3.]

13.5.4: Measure ALT 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. (Not Graded) [Based on KDIGO Hepatitis C Recommendation 4.4.1.] (See Recommendation 19.3.)

13.5.5: Test HCV-infected patients at least every 3–6 months for proteinuria. (Not Graded) [Based on KDIGO Hepatitis C Recommendation 4.4.4.]

13.5.5.1: For patients who develop new onset proteinuria (either urine protein/creatinine ratio >1 or 24-hour urine protein >1 g on two or more occasions), perform an allograft biopsy with immunofluorescence and electron microscopy. (Not Graded) [Based on KDIGO Hepatitis C Recommendation 4.4.4.]

13.5.6: We suggest that patients with HCV associated glomerulopathy not receive interferon. (2D) [Based on KDIGO Hepatitis C Recommendation 4.4.5.]
**Topic 13.6 Hepatitis B Virus**

a. We suggest that any current induction and maintenance immunosuppressive Mx can be used in Hepatitis B Virus infected KTRs. (2D)

b. We suggest that interferon treatment should generally be avoided in HBV infected KTRs. (2D)

c. We suggest that all HBsAg positive kidney transplant recipients should receive prophylaxis with tenofovir, entecavir, or lamivudine. (2D)

d. We suggest treatment with adefovir or tenofovir for KTRs with lamivudine resistance (>5 log10 copies/ml rebound of HBV DNA). (2D)

**UNGRADED SUGGESTION FOR CLINICAL CARE**

a. Tenofovir or entecavir are preferable to lamivudine, to minimise the development of potential drug resistance, unless medication cost requires that lamivudine be used. (Not Graded)

b. During therapy with antivirals, measure HBV DNA and ALT levels every 3 months to monitor efficacy and to detect drug resistance. (Not Graded)

c. Screen Hepatitis B surface antigen (HBsAg) positive patients with cirrhosis for hepatocellular carcinoma every 12 months with liver ultrasound and alpha feto-protein. (Not Graded)

d. We suggest that patients who are negative for HBsAg and have antibody to Hepatitis B surface antigen (HBsAb) titre <10 mIU/ml receive booster vaccination to raise the titre to ≥100mIU/ml.

e. We suggest discussion with a hepatologist in all Hepatitis B infected KTRs(Not Graded)
**Topic 13.7 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**

a. We suggest that HIV infection is not a contra-indication for transplantation, but should be considered along with other co-morbidities in determining whether to proceed with transplantation and, if so, in determining appropriate immune-suppression and adjunctive therapies (ungraded).

13.7.1: If not already done, screen for HIV infection. (Not Graded)

13.7.2: To determine antiretroviral therapy, refer HIV-infected KTRs to an HIV specialist, who should pay special attention to drug–drug interactions and appropriate dosing of medications. (Not Graded)
**Topic 14.1 Urinary Tract Infection**

a. We recommend that all kidney transplant recipients receive urinary tract infection prophylaxis with daily trimethoprim–sulfamethoxazole in the early post transplant period unless contraindicated. (1B)

b. We suggest patients with allograft pyelonephritis be hospitalised for initial treatment with intravenous antibiotics (2C)

14.1.1: We suggest that all KTRs receive UTI prophylaxis with daily trimethoprim–sulfamethoxazole for at least 6 months after transplantation. (2B)

14.1.2: For allograft pyelonephritis, we suggest initial hospitalization and treatment with intravenous antibiotics. (2C)
**Topic 14.2 Pneumocystis Jirovecii Pneumonia (previously PCP)**

a. We recommend that all kidney transplant recipients receive PCP prophylaxis with trimethoprim-sulfamethoxazole for 3 – 6 months after transplantation (1B).

b. We suggest that all kidney transplant recipients receive PCP prophylaxis with daily 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 intravenous trimethoprim-sulfamethoxazole, and a reduction in immunosuppressive medications (1C).

d. We suggest treatment with corticosteroids for kidney transplant recipients with moderate to severe (as defined by PaO2 <70 mmHg in room air or an alveolar gradient of >35 mmHg) PCP (2C).

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14.2.1: We recommend that all KTRs receive PCP prophylaxis with daily trimethoprim–sulfamethoxazole for 3–6 months after transplantation. (1B)

14.2.2: We suggest that all KTRs receive PCP prophylaxis with daily trimethoprim–sulfamethoxazole for at least 6 weeks during and after treatment for acute rejection. (2C)

14.2.3: We recommend that KTRs with PCP diagnosed by bronchial alveolar lavage and/or lung biopsy be treated with high-dose intravenous trimethoprim–sulfamethoxazole, corticosteroids, and a reduction in immunosuppressive medication. (1C)

14.2.4: We recommend treatment with corticosteroids for KTRs with moderate to severe PCP (as defined by PaO2 <70 mm Hg in room air or an alveolar gradient of >35 mm Hg). (1C)
**Topic 14.4 Candida prophylaxis**

a. We suggest oral and oesophageal Candida prophylaxis in the early post-transplantation period and after treatment with antilymphocyte antibody (2D).

b. We suggest close monitoring of calcineurin inhibitor (CNI) dosing when using anti-fungals that inhibit the cytochrome P450 pathway (2D).

14.4.1: We suggest oral and esophageal Candida prophylaxis with oral clotrimazole lozenges, nystatin, or fluconazole for 1–3 months after transplantation, and for 1 month after treatment with an antilymphocyte antibody. (2C)
**Topic 15.1 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:
   - weekly for 4 weeks (2D);
   - every 3 months for 1 year (2D);
   - annually thereafter (2D); and
   - after starting, or substantially increasing the dose of calcineurin inhibitors (CNI), mammalian target of rapamycin inhibitors (mTORi), or corticosteroids. (2D).

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

c. We suggest consideration be given to screening for NODAT by oral glucose tolerance testing at 3 months after transplantation (2D) [Note: whilst HbA1c is an acceptable screening test among the general population, its role in screening for, or diagnosing, NODAT remains to be confirmed].

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15.1.1: We recommend screening all nondiabetic KTRs with fasting plasma glucose, oral glucose tolerance testing, and/or HbA1c (1C) at least:
   - weekly for 4 weeks (2D);
   - every 3 months for 1 year (2D); and
   - annually thereafter. (2D)

15.1.2: We suggest screening for NODAT with fasting glucose, oral glucose tolerance testing, and/or HbA1c after starting, or substantially increasing the dose, of CNIs, mTORi, or corticosteroids. (2D)
**Topic 15.2 Managing NODAT or Diabetes Present at Transplantation**

*INSUFFICIENT EVIDENCE AVAILABLE FOR PROVISION OF GRADED GUIDELINES. UNGRADED SUGGESTION FOR CLINICAL CARE*

a. If new-onset diabetes after transplantation (NODAT) develops, consider modifying the immunosuppressive drug regimen to reverse or ameliorate diabetes, after weighing the risk of rejection and other potential adverse effects. (Not Graded)

b. Consider using diet and exercise, and if required hypoglycaemic medications, to target HbA1c ≤ 7.0, unless the patient is at high risk of hypoglycaemia (e.g. hypoglycaemic unawareness, autonomic neuropathy, severe macrovascular disease) (Not Graded)

15.2.1: 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. (Not Graded)

15.2.2: Consider targeting HbA1c 7.0–7.5%, and avoid targeting HbA1c ≤ 6.0%, especially if hypoglycemic reactions are common. (Not Graded)

15.2.3: We suggest that, in patients with diabetes, aspirin (65–100 mg/day) use for the primary prevention of CVD be based on patient preferences and values, balancing the risk for ischemic events to that of bleeding. (2D)
CARI Adaptation of KDIGO Guidelines— conclusion

Outcomes
Facilitate management of KTRs in ANZ context
  approx. 30% different to KDIGO
Targets nephrologists, physicians, KTRs, providers
Current to mid 2010 – will require periodic updates
Summarises existing evidence base – plus deficits
Currently undergoing external review

For CARI – Adapte saved approx. 50% vs new guideline
Acknowledgements - CARI Adaptation Team

KDIGO Team – 15 reviewers plus support team
Transplant Clinicians with particular interests
- second reviewer of their choosing
Steve Chadban
- chair
- coordination
Martin Howell
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- compilation of chapters
- evidence grading
- coordination
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Martin Gallagher
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