The Kidney Health Australia-Caring for Australasians with Renal Impairment (KHA-CARI) Guidelines

Adaptation of the KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients

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Guideline Authors

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INTRODUCTION

KHA-CARI has been developing guidelines de novo for an Australian & New Zealand target audience since 1999. 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 organisations and to efficiently use the available expertise and resources. As a consequence KHA-CARI have committed to adapting selected KDIGO guidelines to meet Australian and New Zealand circumstances and requirements rather than producing separate guidelines.

This guideline is an adaptation of the KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients [1] and includes an overview of the adaptation methodology, the adapted recommendations and suggestions for each sub-topic and the rationale for any changes made as part of the adaptation. A summary of the adapted guideline has been published separately in the journal Nephrology. 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 [2].

Adaptation Process

The process used for the adaptation has been based on the ADAPTE framework (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 have 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 (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, organisational 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 Recommendations

The overall approach followed by KDIGO (and in the KHA-CARI adaptation) in grading both
evidence and recommendations follows the GRADE framework (www.gradeworkinggroup.org). In
completing the adaptation KHA-CARI have 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.

Table 1 provides a description of the overall grades applied to an evidence profile. Evidence
profiles are assessed on an outcome basis (e.g. mortality, graft failure, acute rejection etc.)
following a framework and set of rules defined by GRADE. The final evidence grade relevant to a
recommendation does, inevitably, rely on judgement, however, GRADE states that the final grade
must be 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 e.g. surrogate
measures of kidney function, then the evidence profile quality may be evaluated as being low even
though there are many RCTs and systematic reviews.

The strength of recommendations are 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 have followed this
approach, however “ungraded” statements have been denoted as “Ungraded Suggestions for
Clinical Care” and shown separately from the recommendations, thereby 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.
### Table 1. Final grade for overall quality of evidence (KDIGO Table 38)

<table>
<thead>
<tr>
<th>Overall Evidence Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td><em>High quality of evidence.</em> We are confident that the true effect lies close to that of the estimate of the effect.</td>
</tr>
<tr>
<td>B</td>
<td><em>Moderate quality of evidence.</em> The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.</td>
</tr>
<tr>
<td>C</td>
<td><em>Low quality of evidence.</em> The true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td>D</td>
<td><em>Very low quality of evidence.</em> The estimate of effect is very uncertain, and often will be far from the truth.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Grade</th>
<th>Implications</th>
<th>Patients</th>
<th>Clinicians</th>
<th>Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1 “We recommend”</td>
<td></td>
<td></td>
<td></td>
<td>The recommendation can be adopted as a policy in most situations</td>
</tr>
<tr>
<td></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></td>
<td></td>
</tr>
<tr>
<td>Level 2 “We suggest”</td>
<td></td>
<td></td>
<td></td>
<td>The recommendation is likely to require debate and involvement of stakeholders before policy can be determined</td>
</tr>
<tr>
<td></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></td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Determinants of strength of recommendations (KDIGO Table 41)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance between desirable and undesirable effects</td>
<td>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.</td>
</tr>
<tr>
<td>Quality of the evidence</td>
<td>The higher the quality of evidence, the more likely a strong recommendation is warranted.</td>
</tr>
<tr>
<td>Values and preferences.</td>
<td>The more variability in values and preferences, or more uncertainty in values and preferences, the more likely a weak recommendation is warranted</td>
</tr>
<tr>
<td>Costs (resource allocation)</td>
<td>The higher the costs of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.</td>
</tr>
</tbody>
</table>

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 pre-transplant 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 KDIGO guideline provides recommendations and suggestions across 27 sub-topics, of which 20 have been addressed in the KHA-CARI adaptation. The subtopics excluded from the adaptation and the reasons for omission are as follows:

- **Strategies to reduce drug costs.** The focus of this topic is on drug costs borne by individuals and consequent limitation to access. Due to Government subsidies this topic is not relevant in Australia and New Zealand.

- **Transplant bone disease.** This is based on the KDIGO CKD-MBD guideline and addressed separately to the transplant guidelines.

- **Haematological complications.** The adaptation working group deemed that insufficient evidence was available to underpin guidelines in this area in an ANZ context.

- **Hyperuricaemia and gout.** The adaptation working group deemed that insufficient evidence was available to underpin guidelines in this area in an ANZ context.

- **Growth and development.** Growth and Development will be referred to the KHA-CARI Nutrition and Growth in Kidney Disease Group for inclusion in the next update of these guidelines.
Sexual function and fertility. Relevant evidence from which to base recommendations and suggestions in relation to sexual function and fertility in KTRs is limited and has therefore not been addressed in the adaptation. In respect of male and female fertility guidelines reference should be made back to the KDIGO guidelines.

Lifestyle. Lifestyle factors in relation to diet and weight have been addressed separately in the KHA-CARI Nutrition in Kidney Transplant Recipients guideline and has not been addressed in the adaptation.

Mental health. Relevant evidence from which to base recommendations and suggestions in relation to mental health in KTRs is limited and has therefore not been addressed in the adaptation.

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 [3]. All transplant procedures performed and subsequent recipient outcomes are reported to the ANZDATA registry (http://www.anzdata.org.au/). Deceased donor procedures utilising 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 whilst 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 whilst T-cell depleting induction is used in less than 5% of cases. Maintenance immunosuppression consists predominantly of triple-therapy with a calcineurin inhibitor, most commonly tacrolimus, plus a mycophenolate plus steroids with withdrawal of steroids being uncommon. Currently mTOR-inhibitors are used in less than 10% of recipients. Universal health care coverage is provided by the respective Governments and transplant procedures, hospitalisations and medications are highly subsidised 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. due to death with function or graft failure in similar proportions.

Overall Search Strategy

The overall approach to the search strategy was to provide an update to that used by KDIGO (refer to Table 32 in the Appendix of the KDIGO guideline). The KHA-CARI update search is to November 2010. For some topics additional key papers have been identified by the writers and searches have been extended beyond November 2010, this is noted under the search strategy for each sub topic.
Topic 1. Induction Therapy

Author: S Cohney and K Wiggins

GUIDELINES

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

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

c. We recommend an interleukin-2 receptor antagonist (IL-2RA) 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 IL-2RA as an induction agent. (2B)

f. We suggest that kidney transplant recipients with a donor specific anti-HLA antibody be considered for peri-transplant plasmapheresis and/ or high dose intravenous immunoglobulin pre-transplant. (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)

UNGRADED SUGGESTIONS FOR CLINICAL CARE

None made.

IMPLEMENTATION AND AUDIT

The use of antibody therapy for induction immunosuppression is captured by the ANZDATA registry and is available at the web site and in each annual report. This data should be periodically examined in relation to outcomes including acute rejection rates, incidence of malignancy, patient and graft survival. Prospective collection of this data by larger units to record outcomes not captured by ANZDATA, such as specific infections and development of donor specific antibodies, may provide additional insights,

BACKGROUND

The following background has been based on that provided in the KDIGO guideline and edited to reflect review conducted for the adaptation.
Acute rejection is a significant cause of renal allograft dysfunction in the early post-transplant period with the potential to reduce long-term graft survival. In severe cases acute rejection can cause early graft loss.

Induction agents are biological agents used in the peri-transplant period. Induction therapy aims to reduce the incidence of acute rejection, and improve graft and patient survival. Induction may also permit reduction of other immunosuppressive agents, such as calcineurin inhibitors (CNIs) or corticosteroids. These benefits need to be weighed against potential side effects.

The most widely used induction agents in Australia and New Zealand are interleukin-2 receptor antagonists (IL-2RA), with lymphocyte-depleting antibodies rarely employed. Basiliximab is the only available IL-2RA; it binds the CD25 antigen (IL2 receptor α-chain) at the surface of activated T-lymphocytes thereby competitively inhibiting IL2-mediated lymphocyte activation, a crucial phase in cellular immune response of allograft rejection. Available lymphocyte-depleting agents include antithymocyte globulin (ATG) and antilymphocyte globulin (ALG). Several formulations of ATG are available, including Fresenius ATG and thymoglobulin (both rabbit ATG), and Atgam (equine ATG). The apparent benefit of lymphocyte depletion in reducing acute cellular rejection (ACR) in high immunological risk patients needs to be weighed against the potentially increased risk of infection, malignancy and death.

Clinical studies of induction therapy have focused predominantly on ACR, but as rates of ACR have fallen, antibody mediated rejection (AbMR) now constitutes a significant percentage of acute rejection episodes, with or without accompanying ACR. In addition to this relative increase in AbMR, there has also been an absolute increase in the number of cases of AbMR as a result of the growing number of sensitised patients and the growth in transplant operations performed deliberately in the presence of blood group incompatibility and donor specific anti-HLA Abs (DSAb). In patients identified to be at high risk of AbMR, due to the presence of DSAb, +/- a positive cross-match, combinations of high dose intravenous immunoglobulin (IVIG), and/or plasma exchange are used to remove antibody or, in the case of IVIG, with the intent of some immunomodulation. In the context of ABO blood group incompatible (ABOi) kidney transplantation, removal of anti-blood group antibody is also essential to reduce the antibody to a level that will avert graft threatening AbMR. The anti-blood group antibody level should be lowered to a titre known to avoid AbMR according to the specific institution’s assay(s).

The objective of this guideline is to evaluate currently available evidence regarding the benefits and harms associated with induction therapy in renal transplantation. A particular emphasis is placed on the applicability to clinical practice in Australia and New Zealand.

SEARCH STRATEGY

The search strategy was an update of that used by KDIGO (refer to Table 32 in the Appendix of the KDIGO guideline). Additional key papers have been identified the authors that were published after the KHA-CARI update search.

Databases searched: Medline, Central, Cochrane database of systematic reviews.

Date of searches: November 2010.

ADEQUACY OF KDIGO SEARCH STRATEGY

The KDIGO search strategy was comprehensive and included a large number of trials. A number of additional trials were identified in the updated search performed by KHA-CARI. These included an updated Cochrane review of IL-2RA as induction therapy. Several other additional trials of IL-2RA and lymphocyte-depleting antibodies were identified but were generally small and did not
substantially alter the conclusions drawn by the KDIGO Guideline authors. One trial of induction therapy with rituximab was found.

The KDIGO guideline did not address induction therapy for patients at high risk of AbMR (ABO blood group incompatible transplants and patients with donor specific antibody and/ or positive cross match), or rituximab. Information regarding these therapies has been included in this guideline, as such transplants are being performed with increasing frequency and are therefore applicable to local practice.

The evidence base for the benefits of IL-2RA includes a large number of RCTs as well as a Cochrane review, and is quite strong. Conclusive evidence is less extensive for lymphocyte-depleting agents, but there are some RCTs and a meta-analysis. The available evidence regarding alemtuzumab as an induction agent is poor.

**APPLICABILITY OF KDIGO RECOMMENDATIONS AND SUGGESTIONS**

There are a number of general considerations that have the potential to reduce the applicability of available evidence, hence these guidelines, to current practice in Australia and New Zealand (as well as in other developed nations). The majority of trials have been conducted in patients at low immunological risk. The significance of studies of “high risk” patients is unclear, as advances in both knowledge and technology have led to changes in the immunological evaluation of transplant recipients. These include routine use of DTT or heat treatment in cross-matches to avoid false positive B cell crossmatches caused by autoantibodies, and use of solid phase assays to identify anti-HLA antibodies and in particular those with donor specificity DSAb. Historically studies relied on measures such as panel reactive antibody (PRA) to stratify patients without taking into account specificity or false positives and negatives. There are currently no published randomised studies comparing outcomes of patients receiving kidneys in the presence of a positive crossmatch on different forms of induction therapy. However, in published series of patients with DSAb (and varying crossmatch results), rates of AbMR and graft loss tend to be the same regardless of the type of induction. Non-randomised studies of patients with DSAb have not suggested a benefit for lymphocyte depleting agents [4-6].

Historically graft loss may have been to unrecognised factors such as BK virus nephropathy, which is now screened for and is less common as a cause of allograft failure. Similarly practices such as increased duration of CMV prophylaxis may modify events associated with induction therapy.

Recent changes to maintenance immunosuppression with associated reduction in ACR also impact on the applicability of trial results to current practice in developed countries such as Australia and New Zealand. Specifically, the greater use of tacrolimus and mycophenolate, and lower target tacrolimus levels. The specific incremental improvement attributable to induction therapy in these combinations is unclear.

Most studies of conventional induction therapy have not included AbMR as an outcome. There is no evidence to suggest that any form of induction therapy reduces AbMR or that rates differ according to what form of induction patients receive [7, 8]. Some studies have suggested an increased rate of AbMR in patients receiving lymphocyte depleting induction [9]. A randomised study comparing thymoglobulin with Daclizumab in sensitised patients with DSAb showed a greater incidence of AbMR and persistence of DSAb in those receiving Thymoglobulin. Rates of ACR in this study were significantly greater in the Daclizumab arm [10].

Differences in clinical practice and drug availability also affect applicability of these guidelines to Australia and New Zealand. Use of lymphocyte depleting agents is common in the United States. In contrast in Australia lymphocyte-depleting agents are used as induction therapy in less than 5% of all transplants [11]. Rituximab, the subject of only one randomised controlled trial (in unsensitised patients and compared with placebo) is not licenced for use in transplantation. Many
trials from the United States include African American and Hispanic patients. The applicability of results from such studies to the Australian population is unclear in light of the difference in outcomes between Caucasian patients and other ethnicities.

Interuption of the terminal complement pathway through inhibition of C5a has demonstrated a clinically significant reduction in the incidence of AbMR in comparison to historical controls matched for level of DSAb, and immunological risk [12]. A prospective randomised study with eculizumab is planned to commence soon (Clinical Trials.gov NCT00670774).

OVERVIEW OF THE EVIDENCE

The following provides an overview of the evidence as identified in the KDIGO guidelines and the update searches conducted by KHA-CARI as part of the adaptation process.

Summary of findings

- Induction therapy is generally associated with a lower risk of rejection when used in combination with historical maintenance regimens
- Lymphocyte depleting agents are associated with a lower risk of rejection than IL2RA, but there is no difference in graft survival

IL-2 receptor antagonists vs. placebo/no therapy

IL2-RAs (compared to placebo or no therapy) have been shown to reduce rates of acute rejection and death-censored graft loss in a number of studies. These findings were confirmed in a recently published Cochrane review of 71 RCTs and 10,537 [13] participants. This review considered trials in which IL-2RA were compared to placebo, no induction, other induction agents or other IL-2RA. At one year use of IL-2RA, compared to placebo or no treatment, was associated with decreases in graft loss including death with a functioning graft (RR 0.75 [95% CI 0.62–0.90], 24 studies), biopsy-proven rejection (RR 0.72 [0.64–0.81], 14 studies) and CMV disease (RR0.81 [0.68–0.97], 13 studies). There was no difference in graft loss beyond one year. At six months the risk of early malignancy was decreased and serum creatinine was lower, but these changes were not persistent. No differences between basiliximab and daclizumab were observed. The use of IL2-RA has been shown to be cost [14] effective.

Lymphocyte-depleting agents vs. placebo/no therapy

The evidence for safety and efficacy of lymphocyte depleting antibodies is more limited than that for IL2-RA. A meta-analysis of seven RCTs (N = 794) comparing lymphocyte-depleting agents with placebo or no treatment reported a reduction in graft failure (RR 0.66, 0.45–0.96) [15]. In an individual patient meta-analysis of five of these same trials (N = 628), the reduction in graft loss at 2 years was greater in patients with high panel-reactive antibody (PRA) levels (RR 0.12, 0.03–0.44), compared to the reduction in risk for patients without high PRA (RR 0.74, 0.50–1.09) [16].

Since publication of these meta-analyses, a single-centre RCT has been published, in which sensitized patients were randomized to induction with ATG or no induction. Patients treated with ATG had a reduction in acute rejection and improvement in graft survival [17]. In a three-arm RCT, the incidence of biopsy-proven acute rejection at 6 months was highest in deceased-donor kidney transplant recipients receiving tacrolimus, azathioprine and prednisone without induction (25.4%, N = 185) compared to a group receiving tacrolimus, azathioprine, prednisone and ATG (15.1%, N = 184) and a group receiving cyclosporine A (CsA), azathioprine, prednisone and ATG (21.2%, N = 186) [18]. However, CMV infection occurred in 16%, 24% and 28% of the patients in these groups, respectively (p=0.012). Similarly, leukopenia, thrombocytopenia, fever and serum sickness were all more common in the two groups receiving antithymocyte induction [18].
Induction therapy with lymphocyte depleting antibodies increases the incidence of serious adverse effects. For kidney transplant recipients treated with depleting antibodies, a reduction in the incidence of acute rejections must be balanced against an increase in major infections. This balance may favour the use of depleting agents in some, but not all, patients. Logic would suggest that the chances of a favourable balance between benefits and harm could be maximized by limiting the use of lymphocyte-depleting agents to patients at increased risk for acute rejection. A potential advantage of lymphocyte depletion in lower risk patients is that it may allow for a reduction in CNI (as a strategy for delayed graft function but not yet substantiated by evidence) or in either/both CNI and steroid. Use of lymphocyte induction to enable steroid avoidance/withdrawal complicated issue that cannot be adequately covered here [19].

**IL-2RA vs. lymphocyte depleting agents**

There have been a number of RCTs comparing IL2-RA with lymphocyte-depleting agents. Most of these trials have been small and of low quality. The recently published Cochrane review by Webster et al [13] evaluated 18 studies with 1844 participants in which IL-2RA were compared to ATG. ATG was associated with a decrease in biopsy-proven acute rejection at one year, with 30% increased risk in patients treated with IL2-RA (RR 1.30 [1.01-1.67], 8 studies) with no difference in graft loss. Benefits of IL-2RA included lower rates of malignancy (RR 0.25 [0.07-0.87], 7 studies) and CMV disease (RR 0.68 [0.50-0.93], 13 studies). The serum creatinine was lower after 6 months in patients treated with IL-2RA, but not at other time points. Analyses were performed to consider the influence of type of maintenance immunosuppression (tacrolimus or cyclosporine, mycophenolate or azathioprine) and baseline risk of rejection. These did not influence the results. Thus, there is moderate quality evidence for trade-offs between IL2-RA and depleting antibodies; depleting antibodies are superior to prevent acute rejection, but there is uncertainty whether this corresponds to improved graft outcomes. Depleting antibodies are associated with more infections and malignancy.

**Different lymphocyte depleting agents**

In one trial comparing thymoglobuline and Atgam, conducted in 72 patients with 10 years of follow-up, thymoglobuline was associated with lower rates of rejection but similar patient and graft survival [20]. Rates of infection and malignancy were similar between groups. However, overall there have been few head-to-head comparisons of different lymphocyte-depleting agents and in meta-analyses there do not appear to be obvious differences in the effects of different lymphocyte-depleting agents on acute rejection or graft survival.

**Alemtuzumab**

Alemtuzumab (Campath 1H) is a humanized anti-CD52 monoclonal antibody that depletes lymphocytes. There have been a few small RCTs examining the use of alemtuzumab as an induction agent in kidney transplant recipients. All of these RCTs lack statistical power to examine the effects of alemtuzumab on patient survival, graft survival or acute rejection. In many of the RCTs, there were differences between the comparator groups other than alemtuzumab, making it difficult to discern the effects of alemtuzumab alone. For example, in a single-centre RCT, 65 deceased-donor kidney transplant recipients received alemtuzumab induction with delayed tacrolimus monotherapy and were compared to 66 kidney transplant recipients treated with no induction, mycophenolate mofetil (MMF) and corticosteroids. At 12 months, the rate of biopsy-proven acute rejection was 20% vs. 32% in the two groups, respectively (p = 0.09) [21]. In 21 high immunological-risk kidney transplant recipients randomized to alemtuzumab plus tacrolimus vs. four doses of ATG (plus tacrolimus, MMF and steroids), there were two vs. three acute rejections, respectively [22]. Among 20 patients randomized to alemtuzumab plus low-dose CsA vs. 10 patients on CsA plus azathioprine and prednisone, there were biopsy-proven acute rejections in 25% vs. 20%, respectively [23]. Ninety deceased-donor kidney transplant recipients were randomly...
allocated to ATG, alemtuzumab or daclizumab induction, with those receiving alemtuzumab also receiving a lower tacrolimus target, MMF 500 mg twice daily and no maintenance prednisone, while those in the other two groups received MMF 1000mg twice daily and prednisone. After 2 years of follow-up, acute rejections occurred in 20%, 23% and 23% in the three groups, respectively, but there was borderline worse death-censored graft survival in the alemtuzumab group (p = 0.05), and more chronic allograft nephropathy (CAN) (p = 0.008) [24, 25]. A recently published study of 474 patients reported that alemtuzumab, in combination with an initial 5 day course of prednisone and ongoing mycophenolate mofetil and tacrolimus reduced rates of acute cellular rejection in the first 12 months post-transplant when compared to either basiliximab or rabbit ATG. However, the rates of ACR occurring 12 to 36 months post-transplant were higher in patients who received alemtuzumab. This difference was statistically significant in the basiliximab subgroup (3 vs. 8%, P=0.03) but not the rabbit anti-thymocyte globulin group (3 vs. 8%, P=0.12) [26]. Altogether, these studies fail to clearly demonstrate that the benefits outweigh the harm of alemtuzumab induction in kidney transplant recipients.

**Other agents**

**Mycophenolate**

Inosine monophosphate dehydrogenase inhibitors (mycophenolate mofetil and mycophenolate sodium) are frequently used in maintenance immunosuppression. These agents are metabolised to mycophenolic acid (MPA). There is evidence that achieving an adequate MPA level on day 3 post-transplant is associated with a lower risk of acute rejection [27, 28]. These observations indicate that use of high dose mycophenolate in the early post-transplant period may reduce rejection rates. In the CellCept Loading Dose in Early Post-transplant Period in Renal Allograft Recipients (CLEAR) Study 135 patients were randomised to receive 3g of MMF per day for the first 5 days post-transplant, then 2g/ day, or to receive 2g/ day from the time of transplant [29]. There were less cases of suspected and treated acute rejection cases within the first 3 months in the 3g/day group, although the difference did not reach statistical significance (11.8% vs. 28.4%, P=0.0546). There was no difference in renal function at 6 months. Results of a post-hoc analysis of the Fixed Dose vs. Concentration Controlled (FDCC) Study indicated that early achievement of an adequate MPA level reduced the risk of rejection in patients deemed to be at high risk of acute rejection (at least one of delayed graft function, second or third transplant, panel reactive antibody >15%, 4 or more HLA mismatches, black race), but not patients at low risk of rejection [30].

**Rituximab**

Rituximab is a monoclonal antibody with activity against CD20 that depletes B cells. Rituximab induction was compared to placebo in a prospective, randomised, double-blinded multicentre trial involving 136 participants in [31] Sweden. Recipients received a single dose of rituximab 375 mg/m² or placebo within 24 hours of revascularisation. Maintenance immunosuppression consisted of prednisolone, tacrolimus and mycophenolate mofetil. Exclusion criteria included a PRA >50% in the preceding 6 months, recipients of HLA-identical grafts, third or subsequent transplants and multiple organ transplants. The treatment arms were well matched with the exception of a higher number of live donor recipients in the placebo arm (25/68 vs. 19/68) and more recipients of a first graft in the rituximab group (62/68 for placebo vs. 68/68 for rituximab). There were more episodes of BPAR in the placebo group (17.6% vs. 11.6% for rituximab) but the difference was not statistically different (P=0.317). There were 5 episodes of steroid resistant rejection in the placebo group and 2 in the rituximab group. In each group there was one patient death and 1 graft loss unrelated to rejection. Patient and death-censored graft survival rates at 6 months were 98.5% in both groups. Rituximab appeared to be associated with minimal harm, and was not associated with an increased risk of infection. Severe leucopaenia (WCC <10⁹ cells/L) occurred in 3 patients who received rituximab, and in all cases responded to temporary withdrawal of mycophenolate mofetil. A RCT of induction therapy with rituximab vs. daclizumab was commenced in the United Kingdom. However, this study was terminated early after recruitment of
13 patients due to a high rate of ACR in the rituximab group (5 of 6 patients (83%) compared to 14% in the daclizumab group)[32].

**ABO incompatible transplantation**

The presence of anti-blood group antibodies in the setting of ABO blood group incompatibility will usually lead to graft loss from severe acute AbMR [33, 34]. A small number of successful ABOi have been performed (some inadvertently) attributable to low level antibody in the recipient [35]. A number of case series reporting successful ABOi transplantation have been published [36-38]. Induction therapies used in these reports include various combinations of splenectomy, rituximab, IVIG and plasma exchange. More recent reports indicate that ABOi transplants can be performed successfully without splenectomy or rituximab [39], or in some cases without any additional treatment beyond standard immunosuppression [40]. The majority of case series reported has also used induction therapy in the form of IL-2RA. Rates of acute cellular rejection have generally been similar, or slightly better, than those of the overall transplant population. The greatest incremental improvement in ABOi outcomes has coincided with the general improvement in transplant results [41]. Reduction in rates of AbMR have been associated with the addition of antibody removal post-transplant whether by immunoadsorpton with blood group specific columns [38, 42], or by plasmapheresis [40, 43, 44]. The use of lymphocyte depletion with either thymoglobulin [45-48] or alemtuzumab [49, 50] has been associated with significantly higher rates of AbMR of up to 37%, and increased graft loss [48-50].

**Transplants performed across a positive CDC cross-match and/or in the presence of DSA**

The risk of AbMR is increased and graft survival decreased when a kidney transplant is performed in the presence of a positive B cell CDC cross-match, and/or when donor specific anti-HLA antibodies (donor specific antibody; DSAb) are present pre-transplant. For such transplants there are several case series reporting moderate success with regimens built around plasma exchange and/or high dose IVIG. This has been in combination with thymoglobulin, campath and IL2r blockade with no apparent benefit from lymphocyte depletion [4, 6].

There is a paucity of RCTs of induction therapy (conventional or antibody depleting) in both ABOi and transplants otherwise considered high risk for AbmR.

**SUMMARY OF EVIDENCE**

The evidence base for the benefits of IL-2RA includes a large number of RCTs as well as a Cochrane review, and is quite strong. Conclusive evidence is less extensive for lymphocyte-depleting agents, but there are some RCTs and a meta-analysis. The available evidence regarding alemtuzumab as an induction agent is poor. Overall the evidence indicates induction therapy to be generally associated with a lower risk of rejection when used in combination with historical maintenance regimens and lymphocyte depleting agents to be associated with a lower risk of rejection than IL2RA. However, there is no difference in graft survival. Overall there have been few head-to-head comparisons of different lymphocyte-depleting agents and in meta-analyses there do not appear to be obvious differences in the effects of different lymphocyte-depleting agents on acute rejection or graft survival.

There are a number of general considerations that have the potential to reduce the applicability of available evidence, to current practice in Australia and New Zealand (as well as in other developed nations). The majority of trials have been conducted in patients at low immunological risk. The significance of studies of “high risk” patients is unclear, as advances in both knowledge and technology have led to changes in the immunological evaluation of transplant recipients.

Recent changes to maintenance immunosuppression with associated reduction in ACR also impact on the applicability of trial results to current practice in Australia and New Zealand.
Specifically, the greater use of tacrolimus and mycophenolate, and lower target tacrolimus levels. The specific incremental improvement attributable to induction therapy in these combinations is unclear.

Most studies of conventional induction therapy have not included AbMR as an outcome. There is no evidence to suggest that any form of induction therapy reduces AbMR or that rates differ according to what form of induction patients receive. In published series of patients with DSAb (and varying crossmatch results), rates of AbMR and graft loss tend to be the same regardless of the type of induction. Non-randomised studies of patients with DSAb have not suggested a benefit for lymphocyte depleting agents. There is a paucity of RCTs of induction therapy (conventional or antibody depleting) in both ABOi and transplants otherwise considered high risk for AbmR.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: None

UK Renal Association: None

Canadian Society of Nephrology: None

European Best Practice Guidelines: [51]

Guideline III.3
A. Prophylactic immunosuppression with antibodies may be administered to renal transplant recipients as an optional therapy to reduce the number and severity of acute rejections during the first 3-6 months after renal transplantation. However, these benefits must be balanced against the risks of over-immunosuppression with increased susceptibility to opportunistic viral infections and post-transplant lymphoproliferative disorder.

B. Classical “induction therapy” with polyclonal (ALG, ATG) or monoclonal (muromonab-CD3) antibodies administered during the perioperative period for a limited time (1-3 weeks) does not consistently improve graft survival at 3 years post-transplant in unselected recipients.

C. Recipients with delayed graft function, recipients with low and high panel reactive antibodies directed to HLA may benefit from classical induction therapy with polyclonal ALG, ATG or monoclonal antibodies (OKT3 or muromonab-CD3).

D. The biological agents ALG, ATG, OKT3 and muromonab-CD3 used for classical induction therapy show equivalent efficacy.

E. Recently, safe and effective prophylactic therapy has been achieved with high affinity humanised or chimeric monoclonal antibodies (daclizumab and basiliximab respectively) which target the interleukin-2 (IL2) receptor.

SUGGESTIONS FOR FUTURE RESEARCH

1. Future trials of induction therapy that reflect current clinical practice incorporating maintenance regimens including mycophenolate mofetil and tacrolimus, and practices such as MMF “front loading”. These trials may be impractical given the large numbers that would be required to show a difference in hard endpoints such as ACR, graft survival and even renal function. Prevention of de novo DSAb as observed in a recent trial of Belatacept vs. standard therapy may be a component of a composite endpoint that may be helpful. Trials examining the prevention of AbMR in the presence of pre-existing DSAb are necessary.
CONFLICT OF INTEREST

S Cohney has a Level II conflict of interest according to the conflict of interest statement set down by KHA-CARI.

K Wiggins has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by KHA-CARI.
Topic 2. Initial Maintenance Immunosuppressive Medication

Author: Josette Eris and Kate Wyburn

GUIDELINES

a. We recommend using a combination of immunosuppressive medication as maintenance therapy including a calcineurin inhibitor (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 mammalian target of rapamycin inhibitors (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 minimised or withdrawn early after transplantation. (2B)

UNGRADED SUGGESTIONS FOR CLINICAL CARE

None made.

IMPLEMENTATION AND AUDIT

The use of initial maintenance immunosuppression is captured by the ANZDATA registry and is available at the web site and in each annual report. Audit of initial maintenance immunosuppression and consequences for patient and graft outcomes may be undertaken to better understand usage patterns and to generate hypotheses about relationships with outcomes including patient and graft survival which could subsequently be tested by RCT.

BACKGROUND

The following background has been based on that provided in the KDIGO guideline and edited to reflect review conducted for the adaptation.

Maintenance immunosuppressive medication is a long-term treatment to prevent acute rejection and deterioration of graft function. Treatment is started before or at the time of transplantation, and the initial medication may or may not be used with induction therapy. Agents are used in combination to achieve sufficient immunosuppression, while minimizing the toxicity associated with individual agents. Since the risk for acute rejection is highest in the first 3 months after
transplantation, higher doses are used during this period, and then reduced thereafter in stable patients to minimize toxicity. In these guidelines, antiproliferative agents refer specifically to azathioprine or mycophenolate (either MMF or enteric-coated mycophenolate sodium [EC-MPS]).

Corticosteroids have traditionally been a mainstay of maintenance immunosuppression in kidney transplant recipients. However, adverse effects of corticosteroids have led to attempts to find maintenance immunosuppression regimens that do not include corticosteroids. Terminology has often been confusing, but ‘steroid avoidance’ is used here to refer to protocols that call for the initial use of corticosteroids, which are then withdrawn sometime during the first week after transplantation. In contrast, ‘steroid-free’ protocols do not routinely use corticosteroids as initial or maintenance immunosuppression. ‘Steroid withdrawal’ refers to protocols that discontinue corticosteroids after the first week post-transplant. Similar definitions have been applied to the use of CNIs.

**Rationale**

- Used in combination and at reduced doses, drugs that have different mechanisms of action may achieve additive efficacy with limited toxicity.
- The earlier that therapeutic blood levels of a CNI can be attained, the more effective the CNI will be in preventing acute rejection.
- There is no reason to delay the initiation of a CNI, and no evidence that delaying the CNI prevents or ameliorates DGF.
- Compared to CsA, tacrolimus reduces the risk of acute rejection and improves graft survival during the first year of transplantation.
- Low-dose tacrolimus reduces the risk of new-onset diabetes after transplantation (NODAT) compared to higher doses of tacrolimus.
- Compared with placebo and azathioprine, mycophenolate reduces the risk of acute rejection.
- Minimising the use of maintenance corticosteroids beyond the first week after kidney transplantation in recipients who have received induction therapy or are at low immunological risk, reduces adverse effects without affecting graft survival.
- Mammalian target of rapamycin inhibitors (mTORi) have not been shown to improve patient outcomes when used either as replacement for antiproliferative agents or CNIs, or as add-on therapy.

**SEARCH STRATEGY**

The search strategy was an update of that used by KDIGO (refer to Table 32 in the Appendix of the KDIGO guideline).

**Databases searched:** Medline, Central, Cochrane database of systematic reviews.

**Date of searches:** November 2010.

**ADEQUACY OF KDIGO SEARCH STRATEGY**

The KDIGO search strategy was considered to be appropriate for the topic.

**APPLICABILITY OF KDIGO RECOMMENDATIONS AND SUGGESTIONS**

The KDIGO recommendations and suggestions for ‘Initial Maintenance Immunosuppressive Medications’ are generally applicable to the Australia and New Zealand setting. Steroid avoidance was a prominent theme in the KDIGO guidelines and is probably less broadly practiced in Australia and New Zealand.
OVERVIEW OF THE EVIDENCE

The following provides an overview of the evidence as identified in the KDIGO guidelines and the update searches conducted by KHA-CARI as part of the adaptation process.

Calcineurin Inhibitors

Timing of initiation

In theory, the earlier that therapeutic blood levels of a CNI can be attained, the more effective the CNI is likely to be in preventing acute rejection. However, there are also theoretical reasons that the early use of CNIs might increase the incidence and severity of DGF. As a result, RCTs have compared early vs. delayed CNI initiation after transplantation. In three RCTs (N = 338), there was no difference in the incidence of DGF with early vs. delayed CsA initiation. In five RCTs (N = 620), there were no differences in acute rejection, graft failure or kidney function in early vs. delayed CsA initiation. Altogether, these RCTs suggest that there is no reason to delay the initiation of CsA. There are no similar studies using tacrolimus, but it is suggested that, with a regimen including induction and reduced-dose tacrolimus, the risk for early CNI nephrotoxicity is minimized and optimal prevention of acute rejection can be achieved. There is moderate-quality evidence that, in CsA-containing regimens, there is no net benefit or harm of early vs. delayed CsA; the evidence is of low quality for CNIs in general, because of a lack of data for tacrolimus-containing regimens (refer to Evidence Profile and accompanying evidence in Supporting Tables 11–13 of the KDIGO guidelines).

Tacrolimus vs. cyclosporine

A meta-analysis of RCTs reported reduced acute rejection and better graft survival with tacrolimus compared to CsA [52]. For every 100 patients treated for the first year with tacrolimus rather than CsA, 12 would be prevented from having acute rejection, two would be prevented from having graft failure, but five would develop NODAT. The RCTs in the meta-analysis combined studies of patients receiving the original CsA preparation and cyclosporine A microemulsion (CsA-ME). This study also showed an inverse linear relationship between levels of tacrolimus exposure and relative risk of graft loss and NODAT, such that lower levels were consistently beneficial compared with higher levels. Randomized controlled trials comparing tacrolimus with CsA-ME using concomitant azathioprine and corticosteroids, but no induction, have shown reduced acute rejection with tacrolimus; for example 22% vs. 42% at 12 months, respectively (p < 0.001) [53]. The difference in acute rejection between the two CNIs could no longer be observed with concomitant induction and MMF instead of azathioprine; for example 4% vs. 6%, for tacrolimus vs. CsA-ME, respectively [54]. The DIRECT study showed no difference in efficacy between tacrolimus and CsA at comparable levels of exposure, in recipients with a PRA not exceeding 50%, with acute rejection episodes of 7% vs. 10% at 6 months, respectively [55] when C2 monitoring of CsA was also employed. There is no data comparing tacrolimus and CsA efficacy in recipients with higher PRAs. Furthermore, there is evidence that subclinical rejection (acute rejection changes in protocol biopsy not indicated by a change in kidney function) is more effectively prevented by tacrolimus and MMF compared to CsA and MMF; 15% vs. 39% (p < 0.05) [56]. A very large multicentre RCT in de novo kidney transplant recipients (n = 1645; the Symphony study) showed superior graft function, better prevention of acute rejection (12.3%) and superior graft survival (96.4%) at 12 months with daclizumab induction and low-dose tacrolimus (C0 3–7 ng/mL). The comparator groups included low-dose CsA and low-dose sirolimus, both with daclizumab induction and standard-dose CsA without induction. All patients received MMF (2 g/day) and corticosteroids [57]. There is no uniform definition of NODAT used in the literature. Therefore, the reported incidences of NODAT vary to a great extent. Studies reporting a difference between tacrolimus and CsA in the incidence of NODAT, impaired glucose tolerance, or the use of antidiabetic treatment, favour CsA; for example 17% vs. 9% (p < 0.01; tacrolimus vs. CsA) [55].
Others have found lower incidences and no significant difference [54, 58]. One reason for the variation in findings may be differences in the use of corticosteroids as maintenance medication and treatment of acute rejection. Indeed, use of a steroid-free regimen has been associated with a lower incidence of NODAT [59]. Overall, there is moderate-quality evidence for a net benefit of tacrolimus vs. CsA (refer to Evidence Profile and accompanying evidence in Supporting Tables 8–10 of the KDIGO guidelines). There is no clear evidence of differences in terms of patient mortality, incidence of malignancy, infection, delayed onset of graft function or blood pressure. There is evidence that cholesterol, low-density lipoprotein cholesterol (LDL-C) (but not high-density lipoprotein cholesterol [HDL-C]), acute rejection and graft loss are higher with CsA vs. tacrolimus. However, there is also evidence that NODAT is more common with tacrolimus than CsA, so that there is clear trade-off in the different patient-relevant outcomes with these two CNIs.

Dosing of CNI

Dosing of CNI is important, but is a relatively under researched area. There are few trials that compare the effects of different doses or target levels of the same drugs in which baseline immunosuppression is kept constant across both arms. Indirect comparisons and case series have shown that high doses might increase adverse events and low doses might increase acute rejection. Standard dose tacrolimus may be defined as it is recommended by the producer (Astellas Pharma, Tokyo, Japan); the dose achieving 12-h trough levels (C0) of 10 (5–15) ng/mL. A low dose tacrolimus has recently been introduced in the Symphony study and was defined as C0 of 5 (3–7) ng/mL [60]. Standard-dose CsA may be defined as the dose achieving C0 of 200 (150–300) ng/mL [61] or C2 1400–1800 ng/mL early and 800–1200 ng/mL later after transplantation [55]. Low-dose CsA has been used in some recent clinical studies [60, 61] and was defined as achieving C0 of 75 (50–100) ng/mL.

Mycophenolate Mofetil

Randomized controlled trials have shown that MMF (2 or 3 g, but not 1 g daily) is significantly better in preventing acute rejection than placebo. This was seen in studies using steroids as concomitant medication and either tacrolimus or CsA (31,32). For example, acute rejection at 6 months was reduced from 55% with placebo to 30% and 26% with MMF 2 and 3 g daily doses [62]. There were 5–7% improvements of graft survival at 12 months with MMF, but the studies were not powered to evaluate this difference. There were no significant differences in patient survival, graft function, malignancy, NODAT, infection rates or gastrointestinal adverse events such as diarrhoea, although there might be evidence that higher doses of MMF cause more diarrhoea than lower doses of MMF. More bone marrow suppression was seen with MMF compared to placebo. Overall, there is moderate-quality evidence of a net benefit of MMF over placebo to prevent acute rejection, but low-quality evidence for all graft and patient outcomes overall (refer to Evidence Profile and accompanying evidence in Supporting Tables 14–15 of the KDIGO guidelines).

Randomized controlled trials comparing outcomes between MMF vs. azathioprine have shown some important inconsistencies. In a recent meta-analysis of 19 trials and 3143 patients, MMF was associated with less acute rejection (RR 0.62, 95% confidence interval [CI] 0.55–0.87) and improved graft survival (RR 0.76, 0.59–0.98) [63]. However, there were no differences in patient survival or kidney function [63]. There were also no differences in major adverse effects (e.g. infections, CMV, leucopenia, anaemia and malignancies) between MMF and azathioprine, but diarrhoea was more common with MMF (RR 1.57; 95% CI 1.33–28.6) [63]. In several RCTs, MMF reduced the incidence of acute rejection at 6 months; for example from 36% with azathioprine (100–150 mg/day) to 20% with MMF (2 g/day) using CsA and steroids as concomitant medication [64] and from 38% to 20% with the addition of concomitant induction [65]. Also, a reduction from 29% to 7% was seen with concomitant tacrolimus, steroids and induction in using MMF 2 g, but not 1 g [66]. Conversely, another study showed a smaller reduction in acute rejection at 6 months from 23% with azathioprine (100–150 mg/day) to 18% with MMF (2 g/day), a difference that was not statistically significantly [67]. These patients were also treated with CsA-ME and steroids.
However, using the same concomitant medication, including CsA-ME, other investigators found a significant reduction of acute rejection at 12 months from 27% with azathioprine to 17% with MMF 2 g [68]. In a third arm of this latter study, patients received MMF from day 0 to day 90 and thereafter azathioprine, and the acute rejection rate was the same, 17%, as for those receiving MMF for the entire study period of 12 months. Thus, high-quality evidence finds a net benefit of MMF over azathioprine to prevent acute rejection, but moderate-quality evidence exists for patient-level outcomes. Because of the substantially increased cost of MMF compared with azathioprine and increased side effects compared with azathioprine, there is no clear net benefit, but a decision based upon trade-offs is required (refer to Evidence Profile and accompanying evidence in Supporting Tables 16–18 in the KDIGO guidelines).

Analyses of observational registry data have shown either a small 4% improvement in graft survival with MMF vs. azathioprine [69] or, more recently, no improvement in graft survival [70]. However, for a number of reasons, the results of retrospective analyses of observational registry data need to be interpreted cautiously [71].

**MMF Compared to EC-MPS**

One RCT compared MMF 2 g daily vs. EC-MPS 1.44 g daily with CsA-ME, steroids, with or without induction [72]. There were no significant differences in acute rejection (24% vs. 23%), patient or graft survival or rates of malignancy or infection. There was no difference in rates of gastrointestinal disorders (80% vs. 81%) despite the fact that the potential reduction of gastrointestinal adverse events has been the incentive for the development of EC-MPS. Another study [73] tested the crossover between the two formulations and also found no differences in any of the outcome parameters. A summary of the RCTs on MMF vs. EC-MPS is available in Supporting Tables 25–26 of the KDIGO guidelines.

**Steroid avoidance or withdrawal**

The rationale for minimizing corticosteroid exposure is compelling and provided by well-established risks of osteoporosis, avascular necrosis, cataracts, weight gain, diabetes, hypertension and dyslipidaemia. Such risk is not constant, and varies with comorbidities such as pre-existing metabolic syndrome and age. On the other hand, corticosteroids have been the mainstay of immunosuppression for kidney transplant recipients for decades, and trial data evaluating minimization of steroid exposure are sparse compared to the large number of trials that have included steroids in the regimens being evaluated. In addition, many of the adverse effects attributed to corticosteroids were observed with high doses. Whether or not low doses (e.g. 5 mg prednisone per day) that are commonly used for long-term maintenance immunosuppression are associated with major adverse effects is less clear.

Randomized controlled trials have shown that the withdrawal of corticosteroids from maintenance immunosuppressive medication regimens, when carried out weeks to months after transplantation, is associated with a high risk of acute rejection [74, 75]. More recent studies have examined whether steroid avoidance (discontinuing corticosteroids within the first week after transplantation) can be done safely. These studies have generally shown higher rates of acute rejection, but lower rates of long-term adverse effects [19, 59, 76-78]. Unfortunately, these trials have had design limitations that make the interpretation of their results difficult. Overall, there is moderate-quality evidence for trade-offs between steroid avoidance or withdrawal compared to steroid maintenance, with a higher rate of steroid-sensitive acute rejections but avoidance of steroid-related adverse effects (refer to Evidence Profile and accompanying evidence in Supporting Tables 19–21 of the KDIGO guidelines).
**Mammalian target of rapamycin inhibitor(s)**

Regimens using the mTORi sirolimus or everolimus have been compared to a number of different regimens in clinical trials in kidney transplant recipients, for example as replacement for azathioprine, MMF or CNIs, and in combination with CNIs (both at high and low dose). The use of mTORi in the setting of chronic allograft injury (CAI) is described in the Topic 7: Treatment of Chronic Allograft Injury. mTORi have a number of adverse effects that limit their use, including dyslipidaemia and bone marrow suppression [79-86]. Although they have been compared with many other regimens in RCTs, in none of these RCTs was there an improvement in graft or patient survival.

**mTORi as replacement for antiproliferative agents**

In a meta-analysis of 11 RCTs with 3966 kidney transplant recipients evaluating mTORi as replacement for azathioprine or MMF, there were no differences in graft or patient survival [86]. mTORi appear to reduce the risk of acute rejection (RR 0.84, 95% CI 0.71–0.99; p = 0.04), but graft function and LDL-C outcomes were generally better with azathioprine or MMF [86].

**mTORi as replacement for CNIs**

In a meta-analysis of eight RCTs with 750 patients evaluating mTORi as replacement for CNIs, there were no differences in acute rejection, CAN, graft survival or patient survival [86]. mTORi were associated with higher glomerular filtration rate (GFR), but also with increased risk of bone marrow suppression and dyslipidaemia [81, 86].

**mTORi in combination with CNIs**

The combined use of mTORi and CNIs should be avoided, because these agents potentiate nephrotoxicity, particularly when used in the early transplant period [86]. When used as long-term maintenance, mTORi have been used in two different regimens in combination with CNIs. Eight RCTs involving 1360 patients have evaluated low-dose mTORi and standard-dose CNI compared with standard dose mTORi and low-dose CNI [86]. Overall, the low-dose, CNI-standard dose mTORi regimen is associated with a 30% increased risk of rejection with no difference in graft survival. An additional 10 RCTs involving 3175 patients have evaluated the effects of high- vs. low-dose mTORi in combination with fixed-dose CNI, showing less rejection but lower GFR with higher-dose therapy, but no improvement in patient outcomes. Moderate-quality evidence for sirolimus finds net harm without improved graft or patient survival; CNI toxicity is potentiated when used in combination with sirolimus (refer to Evidence Profile and accompanying evidence in Supporting Tables 22–24 of the KDIGO guidelines).

**SUMMARY OF EVIDENCE**

RCTs that have evaluated early versus delayed use of CNI’s have shown no reason for delaying the initiation of the use of CNI to minimise DGF. However, the available evidence relates only to CsA and there is a lack of studies of tacrolimus based regimens.

There is moderate-quality evidence for a net benefit of tacrolimus versus CsA. There is no clear evidence of differences in terms of patient mortality, incidence of malignancy, infection, DGF or blood pressure. There is evidence that cholesterol, LDL-C (but not HDL-C), acute rejection and graft loss are higher with CsA versus tacrolimus. However, there is also evidence that NODAT is more common with tacrolimus than CsA, so that there is a trade-off in the different patient-relevant outcomes with CsA and tacrolimus. There is a paucity of evidence in relation to the occurrence of adverse events and incidence of acute rejection for low versus high doses of CNI’s.
There is moderate-quality evidence of a net benefit of MMF over placebo to prevent acute rejection, but low-quality evidence for all graft and patient outcomes overall. High-quality evidence indicates a net benefit of MMF over azathioprine to prevent acute rejection, with moderate-quality evidence for patient-level outcomes. There is currently no evidence from RCTs to suggest EC-MPS is associated with a lower incidence of adverse gastrointestinal events compared to MMF.

There is moderate-quality evidence indicating a higher rate of steroid sensitive acute rejections and a lower rate of steroid related adverse events for steroid avoidance or withdrawal compared to steroid maintenance. Whether or not low doses (e.g. 5 mg prednisone per day) used for long term immunosuppression are associated with major adverse effects is not clear.

The mTORi’s have a number of adverse effects that limit their use, including dyslipidaemia and bone marrow suppression. Although they have been compared with many other regimens in RCTs, in none of these RCTs was there an improvement in graft or patient survival (refer also Topic 7: “Treatment of Chronic Allograft Injury”.)

**WHAT DO THE OTHER GUIDELINES SAY?**

**Kidney Disease Outcomes Quality Initiative:** None

**UK Renal Association:** None

**Canadian Society of Nephrology:** None

**European Best Practice Guidelines:** [87]

A. The use of daily maintenance immunosuppression (IS) is mandatory in renal transplantation in order to reduce the incidence of acute rejection episodes during the first 6 months after transplantation and to improve graft survival in the short- (1 year), medium- (5 years) and long term (>10 years). (Evidence level A)

B. Maintenance immunosuppression could lead to over immunosuppression characterized by an increased incidence of infective complications (mainly viral diseases) and of de novo malignancies, which both carry a greater risk of morbidity and mortality for the recipients. Therefore the choice of the initial maintenance IS should be a balance between efficacy and tolerance of the IS drugs used in association and targeted to the need of the recipient (immunized vs. non-immunized). (Evidence level B)

C. Initial maintenance IS should be administered before transplantation (for living-related graft), or at time of transplantation but before vascular anastomosis (for cadaver graft). IS must be continued daily forever. However, the need for IS decreases overtime and it should be tailored accordingly: greater IS during the first weeks or months in order to improve acceptance to the graft and lower IS after months or a few years. (Evidence level C)

D. Non-compliance with immunosuppressive drugs and its consequences (deterioration and loss of kidney function) have been clearly overlooked and its frequency is currently estimated at ~25% of the recipients. It could be one of the major causes of late graft failure. Therefore, every measure should be implemented and then carefully evaluated in order to reduce non-compliance. (Evidence level B)

E. The most widely used initial and maintenance IS treatment during the last decade was the combination of cyclosporine A, azathioprine and prednisone/prednisolone, and the long term good results obtained with this initial triple IS therapy serve as a reference for the evaluation of newer agents. (Evidence level A)
F. The newly licenced immunosuppressive drugs such as mycophenolate mofetil (MMF) and tacrolimus may be used in maintenance immunosuppressive regimens as they have demonstrated a significant reduction in the incidence and severity of acute rejection episodes during the first year compared with previous regimens. Improvements in graft and/or patient survival have not yet been demonstrated as studies were not powered for these variables. (Evidence level A)

International Guidelines:
Basiliximab or daclizumab used as part of a calcineurin-inhibitor-based immunosuppressive regimen are recommended as options for induction therapy in the prophylaxis of acute organ rejection in adults undergoing renal transplantation. The induction therapy (basiliximab or daclizumab) with the lowest acquisition cost should be used.

Tacrolimus is an alternative to ciclosporin when a calcineurin inhibitor is indicated as part of an initial or a maintenance immunosuppressive regimen in renal transplantation for adults. The initial choice of tacrolimus or ciclosporin should be based on the relative importance of their side-effect profiles for individual people.

Mycophenolate mofetil is recommended for adults as an option as part of an immunosuppressive regimen only:
- Where there is proven intolerance to calcineurin inhibitors particularly nephrotoxicity leading to risk of chronic allograft dysfunction or
- In situations where there is a very high risk of nephrotoxicity necessitating minimisation or avoidance of a calcineurin inhibitor.

Sirolimus is recommended for adults as an option as part of an immunosuppressive regimen only in cases of proven intolerance to calcineurin inhibitors (including nephrotoxicity) necessitating complete withdrawal of these treatments.

These recommendations contain advice that may result in some medicines being prescribed outside the terms of their marketing authorisation. Clinicians prescribing these drugs should ensure that patients are aware of this and that they consent to their use in such circumstances.

The type of evidence supporting the recommendations is not specifically stated.

SUGGESTIONS FOR FUTURE RESEARCH
1. Early versus delayed initiation of tacrolimus to minimise DGF.
2. The incidence of adverse events and acute rejection for low versus high doses of CNI's.
3. The occurrence of major adverse events associated with early minimisation or withdrawal of corticosteroids.

CONFLICT OF INTEREST
Kate Wyburn has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by KHA-CARI.

Josette Eris has a Level II conflict of interest according to the conflict of interest statement set down by KHA-CARI.
Topic 3. Long-Term Maintenance Immunosuppressive Medications

Author: Natasha M. Rogers, Graeme R. Russ, P. Toby Coates

GUIDELINES

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 to 2 g daily and prednisone 5 mg daily [88]) for patients who have not experienced acute rejection. (1B)

b. We suggest that CNIs 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)

UNGRADED SUGGESTIONS FOR CLINICAL CARE

None made.

IMPLEMENTATION AND AUDIT

The use of maintenance immunosuppression is captured at defined time-points post-transplant by the ANZDATA registry and is available at the web site and in each annual report. Audit of maintenance immunosuppression and consequences for patient and graft outcomes could be undertaken at a registry level or within individual units, however proof of any relationship between maintenance immunosuppression and outcomes would require testing in an RCT.

BACKGROUND

The following background has been based on that provided in the KDIGO guideline and edited to reflect review conducted for the adaptation.

Both steroids and CNI (cyclosporin and tacrolimus) are now the mainstay of current immunosuppressive protocols for kidney transplantation. However, multiple studies have revealed appreciable kidney dysfunction in the presence of CNI. Based on RCTs, the prevalence of biopsy-proven CNI-induced nephrotoxicity is comparable regardless of the agent used. The most common phenotype of progressive graft dysfunction is the development of interstitial fibrosis and tubular atrophy, an additional hallmark finding of chronic allograft nephropathy. Emerging evidence from other non-kidney organ transplants suggests that long-term calcineurin inhibitor nephrotoxicity contributes to 5-9% of these patients developing end-stage kidney disease in association with long-term use of calcineurin inhibitors [88].

Significant morbidity, particularly adverse metabolic and cardiovascular events, is associated with long-term steroid use and has also prompted consideration for steroid withdrawal from standard immunosuppressive regimens. A number of strategies to minimize exposure to CNI have been attempted, with an emerging role for mTOR inhibition in selected patients (see Table 4).
SEARCH STRATEGY

Date of searches: Date of search: 17 October 2010, updated August 2011.

Databases searched: Medline (1966 to October Week 3, 2010). MeSH terms and text words for kidney transplantation were combined with MeSH terms and text words for CNI and steroid withdrawal. The results were then combined with the Cochrane search strategy for randomized controlled trials (RCT) and MeSH terms and text words for identifying meta-analyses and systematic reviews. The Cochrane Renal Group Specialized Register of RCT and DARE (Database of abstracts of Reviews of the Effectiveness of health care) were also searched for relevant trials not indexed in Medline.

ADEQUACY OF KDIGO SEARCH STRATEGY

The KDIGO search strategy was considered to be appropriate for the topic.

APPLICABILITY OF KDIGO RECOMMENDATIONS AND SUGGESTIONS

The KDIGO recommendations and suggestions are applicable to the Australian and New Zealand setting. Changes have been made to reflect KHA-CARI evaluation of the evidence to better define low level maintenance immunosuppression.

OVERVIEW OF THE EVIDENCE

The following provides an overview of the evidence as identified in the update searches conducted by KHA-CARI as part of the adaptation process. Reference should be made to the KDIGO guidelines for the entire evidence base.

CNI minimization or withdrawal

Systematic Reviews

A recent systematic review of 12 RCTs (n=635) [89] was conducted to assess various immunosuppressive regimens in patients with transplant duration >6 months and evidence of chronic allograft nephropathy (with or without biopsy). Medication substitutes for CNI included MMF or sirolimus, or the addition of an agent to minimize CsA dosing. Kidney function was the predominant outcomes measure and allograft histopathology was assessed in only 1 out of 12 studies. CNI withdrawal was considered safe by most studies following substitution with MMF or sirolimus, although a consensus regarding management of CAN was not reached.

An additional meta-analysis [90] analysed the benefit of MMF substitution to allow CNI elimination or minimization (19 studies, n=3312). Calculated GFR was improved (mean difference 4.4ml/min) with a trend towards improved graft survival (OR 0.72, p=0.06), although acute rejection rates were increased (OR 2.23, p<0.001) over a median follow-up period of 12 months.

An earlier meta-analysis [91] also assessed the benefit of CNI withdrawal from sirolimus-based therapy from only 6 studies (n=1047), demonstrating an increase in acute rejection rates but overall improved creatinine clearance (mean difference 7.49ml/min, 95%CI 5.08-9.89, p<0.0001) and hypertension (systolic and diastolic blood pressure) at 12 months. No difference in graft loss or patient survival was seen.
Randomised Control Trials (individual trials)

There are several additional RCTs assessing the safety of CNI withdrawal, with or without replacement by other immunosuppressive agents, particularly sirolimus (Rapamycin). Many of these trials have assessed CNI withdrawal at earlier time-points, typically 3 months following transplantation and initial immunosuppression with standard triple therapy (steroid + CNI + MMF + induction antibody). Results are similar between studies, demonstrating improved kidney function (calculated GFR) with no effect on patient or allograft survival. The mechanism is presumably related to attenuation of progression of CNI-induced nephrotoxicity, although few studies include biopsy data and the duration of follow-up is relatively short (<2 years). Several studies have demonstrated an increased risk of BPAR associated with CNI withdrawal, in addition to unsuccessful conversion due to adverse effects associated with mTOR inhibitors.

There may also be a distinction between mycophenolate mofetil- and mTOR-based regimens, with higher rejection rates seen in the former cohort [57, 92]. However, this may have been related to a lack of concentration-controlled approach for MMF dosing (requiring a target AUC of 75μg/hr/ml) following CsA withdrawal.

The significant trials (n>100) are listed in Table 4.

The CONVERT study [93] assessed the effects of CNI withdrawal after a longer post-transplant period (6 months – 10 years), and addressed outcomes at 24 months. Superior function was demonstrated in a subgroup of patients (baseline GFR >40ml/min and urinary protein/creatinine ratio <0.11). Both an increase in urinary protein excretion and a lower malignancy rate have been identified in sirolimus conversion trials, and the latter is a significant beneficial effect when considering CNI withdrawal. Similar results have been corroborated by 4 year follow-up of the CONCEPT study, with comparable trends in terms of patient and graft survival, but improved kidney function in the sirolimus arm (LeBranchu et al, AJT 2011).

Steroid withdrawal

Systematic Reviews

Despite significant study heterogeneity, an initial meta-analysis reported increasing rejection rates associated with steroid withdrawal [94]. This was confirmed by Kasiske et al. [95] who also demonstrated increased graft loss following prednisolone withdrawal. However, the majority of the studies assessed did not include MMF within the treatment regimen. Subsequent meta-analyses have reported variable results: three recent studies by Pascual et al. [96-98] have assessed steroid withdrawal in kidney transplant recipients. The largest meta-analysis [98] incorporated 30 randomised control trials (n=5949). Steroid withdrawal typically 3-6 months post-transplantation (15 studies) was distinguished from steroid avoidance or early elimination within 2 weeks post-transplant in the presence of antibody induction therapy (12 studies). Neither regimen was associated with increased mortality or graft loss; acute rejection was more frequent in steroid-sparing strategies compared to conventional use, but did not impact upon allograft survival. In addition, this increase was more likely in studies of steroid avoidance and associated with cyclosporin but not tacrolimus. Steroid sparing and withdrawal strategies showed benefits in anti-hypertensive and anti-hyperlipidaemic drug requirements and onset of post-transplant diabetes mellitus.

These findings were corroborated by Knight et al. [99] who analysed 34 studies (n=5637) assessing steroid avoidance or withdrawal, although the authors did not distinguish between these two treatment options. The absence of steroid therapy improved cardiovascular risk factors (lipid profile, incidence of diabetes, hypertension), with no difference in patient or allograft survival. However, an increased risk of acute rejection (RR 1.56, p<0.0001) was observed, in conjunction
with increased creatinine clearance. Steroid withdrawal (or abstinence) can only be recommended in low-risk recipients.

Sufficient evidence regarding paediatric recipients is not available.

**Randomised Control Trials (individual trials)**

Successful steroid withdrawal follow kidney transplantation has been less frequently studied and the most significant RCTs pertain to the paediatric population. Steroid withdrawal improves the cardiovascular risk factor profile in all patients and linear growth profiles in children, without impacting upon allograft or patient survival rates in the short-term. Table 5 outlines the significant steroid withdrawal trials. The SPIESSER trial [79] in an adult kidney transplant population (n=145) assessed both steroid withdrawal and CNI avoidance in the context of immunosuppression with anti-thymocyte globulin and mycophenolate mofetil, plus either sirolimus or CNI. Steroids were withdrawn at 6 months with a low incidence (14.3% and 8.2% for SRL and CNI arms respectively) of acute rejection within 12 months. Three year follow-up demonstrated successful steroid withdrawal in approximately 70% of patients in both groups with better kidney function in the sirolimus treated group.

**SUMMARY OF EVIDENCE**

Considering the long-term consequences of CNI exposure, the notion of complete withdrawal remains an attractive option post-transplantation. Long-term steroid exposure may lead to multiple side effects that impact upon allograft survival. The elimination of either CNI from triple therapy regimens has resulted in improved kidney function as assessed by surrogate end points (calculated glomerular filtration rate). However, kidney allograft biopsy was frequently not performed. The lack of kidney transplant biopsy studies, including protocol biopsy-driven comparison of allograft pathology following variations in treatment regimens, longer-term (>3 years) outcome studies, and few head-to-head randomized controlled trials limits current recommendations, in particular, the ability to assess whether the increase in rejection rates will impact upon longer term allograft survival. Toxicity may be minimized by administering low-dose CNI, while ensuring sufficient immunosuppression in the early (<3months) post-transplant period. The elimination of steroids from routine immunosuppression has not demonstrated increased acute rejection rates and improves cardiovascular risk profile. However, RCTs with longer duration follow-up are required.

**WHAT DO THE OTHER GUIDELINES SAY?**

**Kidney Disease Outcomes Quality Initiative:** None

**UK Renal Association:** None

**Canadian Society of Nephrology:** None

**European Best Practice Guidelines:** [87]

A. The use of daily maintenance immunosuppression (IS) is mandatory in renal transplantation in order to reduce the incidence of acute rejection episodes during the first 6 months after transplantation and to improve graft survival in the short- (1 year), medium- (5 years) and long term (>10 years).

(Evidence level A)
B. Maintenance immunosuppression could lead to over immunosuppression characterized by an increased incidence of infective complications (mainly viral diseases) and of de novo malignancies, which both carry a greater risk of morbidity and mortality for the recipients. Therefore the choice of the initial maintenance IS should be a balance between efficacy and tolerance of the IS drugs used in association and targeted to the need of the recipient (immunized vs. non-immunized).

(Evidence level B)

C. Initial maintenance IS should be administered before transplantation (for living-related graft), or at time of transplantation but before vascular anastomosis (for cadaver graft). IS must be continued daily forever. However, the need for IS decreases overtime and it should be tailored accordingly: greater IS during the first weeks or months in order to improve acceptance to the graft and lower IS after months or a few years.

(Evidence level C)

D. Non-compliance with immunosuppressive drugs and its consequences (deterioration and loss of kidney function) have been clearly overlooked and its frequency is currently estimated at ~25% of the recipients. It could be one of the major causes of late graft failure. Therefore, every measure should be implemented and then carefully evaluated in order to reduce non-compliance.

(Evidence level B)

E. The most widely used initial and maintenance IS treatment during the last decade was the combination of cyclosporine A, azathioprine and prednisone/prednisolone, and the long term good results obtained with this initial triple IS therapy serve as a reference for the evaluation of newer agents.

(Evidence level A)

F. The newly licenced immunosuppressive drugs such as mycophenolate mofetil (MMF) and tacrolimus may be used in maintenance immunosuppressive regimens as they have demonstrated a significant reduction in the incidence and severity of acute rejection episodes during the first year compared with previous regimens. Improvements in graft and/or patient survival have not yet been demonstrated as studies were not powered for these variables.

(Evidence level A)

**International Guidelines:** None

**SUGGESTIONS FOR FUTURE RESEARCH**

1. The optimal timing for CNI withdrawal could be determined.

2. The role of protocol biopsies in determining the most appropriate time for CNI withdrawal has not been studied.

3. The impact of CNI withdrawal in terms of histological benefit has not been extensively studied.

**CONFlict OF INTEREST**

G Russ and PT Coates have a Level II conflict of interest according to the conflict of interest statement set down by KHA-CARI.

N Rogers, has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by KHA-CARI.
Table 4. CNI sparing trials

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Drug regimen</th>
<th>Selected outcome</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ekberg et al. [57]</td>
<td>N=1645</td>
<td>CsA + MMF + steroid versus Daclizumab + MMF + steroids + either (a) low dose CsA (b) low dose Tac (c) low dose Rapa</td>
<td>At 1 yr, low dose Tac regimen provided - best calculated GFR - lowest BPAR incidence - best 1 yr graft survival</td>
<td>Daclizumab + MMF (2g/d) + steroids + Tac (target trough 4-8ng/ml) gives best balance of safety and efficacy</td>
</tr>
<tr>
<td>Johnson et al. [100]</td>
<td>N=430</td>
<td>Rapa +CsA + steroid initially; at 3mo randomised to (a) triple therapy (b) withdrawal CsA and increased Rapa level</td>
<td>At 1yr post-randomisation - no difference in patient or graft survival - higher acute rejection rates in CsA withdrawal group - higher mean calculated GFR in CsA withdrawal group</td>
<td>Withdrawal of CsA is safe and effective alternative therapy; may results in better renal function and BP</td>
</tr>
<tr>
<td>Oberbauer et al. [101]</td>
<td>N=430</td>
<td>As above, 48mo assessment</td>
<td>At 4yrs post-randomisation withdrawal of CsA provided - better graft survival - better calculated GFR - no difference in BPAR or mortality</td>
<td>Withdrawal of CsA attenuates progression of histologic damage and results in better graft survival</td>
</tr>
<tr>
<td>Baboolal et al. [102]</td>
<td>N=133</td>
<td>Rapa + CsA + steroid initially; at 3mo randomised to (a) CsA withdrawal (b) CsA minimisation</td>
<td>At 6mo post- randomization - better calculated GFR in CsA withdrawal group</td>
<td>Withdrawal CsA from maintenance regimen is safe and associated with improved renal function</td>
</tr>
<tr>
<td>Dudley et al. [103]</td>
<td>N=122, CsA-treated patients (serum cr creep, no rejection on biopsy), at least 6mo post- transplant randomised to (a) maintenance CsA (b) additional MMF and withdrawal CsA</td>
<td>CsA withdrawal improved rate of creatinine stabilisation or improvement. No rejection demonstrated with MMF conversion</td>
<td>Replacement of CsA with MMF is associated with better graft function and does not increase the risk of acute rejection</td>
<td></td>
</tr>
<tr>
<td>Ekberg et al. [88]</td>
<td>N=536</td>
<td>CsA + MMF + steroid versus daclizumab + MMF + steroid and</td>
<td>At 1yr post-randomisation - BPAR higher in the CsA withdrawal group</td>
<td>Low dose CsA as effective as standard dose in preventing BPAR Early (&lt;6mo) withdrawal CsA</td>
</tr>
<tr>
<td>Study</td>
<td>No. of patients</td>
<td>Drug regimen</td>
<td>Selected outcome</td>
<td>Conclusion</td>
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<tr>
<td>Hazzan et al. [92]</td>
<td>N=108</td>
<td>CsA + MMF + steroid initially; at 3mo post-transplant randomized to (a) withdrawal CsA (b) withdrawal MMF</td>
<td>At 1yr post-randomisation - no difference in patient or graft survival - BPAR higher in CsA withdrawal group - calculated GFR better in CsA withdrawal group</td>
<td>CsA withdrawal under MMF increases the risk of BPAR but leads to improved renal function at 1yr</td>
</tr>
<tr>
<td>Abramowicz et al. [104]</td>
<td>N=170</td>
<td>Patients on CsA + steroids, 3-12mo post-transplantation randomized to (a) CsA withdrawal (b) CsA continuation</td>
<td>CsA withdrawal resulted in - higher calculated creatinine clearance - higher rate of reversible acute rejection</td>
<td>CsA withdrawal modestly improves renal function at the expense of higher rates of BPAR</td>
</tr>
<tr>
<td>Abramowicz et al. [105]</td>
<td>N=151</td>
<td>5-year follow-up of above study</td>
<td>Findings as above</td>
<td>Improved calculated creatinine clearance maintained at 5yr follow-up</td>
</tr>
<tr>
<td>Guba et al. [106]</td>
<td>N=141</td>
<td>ATG induction + steroid + MMF initially; at 10-24d post-transplant (a) CsA replaced with Rapa (b) CsA continuation</td>
<td>At 1yr post- randomization CsA withdrawal associated with - better creatinine clearance/serum creatinine - lower incidence CMV - no difference in patient survival, graft survival, or BPAR</td>
<td>CsA withdrawal improves renal function. Rapa is associated with a high rate of dropout due to adverse effects</td>
</tr>
<tr>
<td>Bemelman et al. [107]</td>
<td>N=113</td>
<td>CsA + MMF + steroid initially; patients at least 3mo post-transplant randomised to steroid and (a) CsA (b) MMF (c) everolimus</td>
<td>Mean follow-up period 8mo - negligible BPAR in mTORi and CsA groups - better renal function in mTORi group</td>
<td>Replacement of CsA with mTORi safe and results in improved renal function</td>
</tr>
<tr>
<td>Bakker et al. [108]</td>
<td>N=128</td>
<td>Patients 3mo post-transplant randomised to (a) Aza (and CsA withdrawal)</td>
<td>Maximum follow-up 15 years - No difference in patient survival CsA withdrawal led to</td>
<td>Conversion to CNI-free regimen early post-transplant improved allograft function, reduced incidence</td>
</tr>
<tr>
<td>Study</td>
<td>No. of patients</td>
<td>Drug regimen</td>
<td>Selected outcome</td>
<td>Conclusion</td>
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<tr>
<td>Servais et al. [109]</td>
<td>N=193</td>
<td>Standard triple immunosuppression, at 3mo randomised to (a) Rapa (and CsA withdrawal), (b) CsA continuation</td>
<td>At 12mo post-randomisation, CsA withdrawal group showed - better calculated GFR - but no difference in biopsy-related interstitial fibrosis</td>
<td>CNI withdrawal improves allograft function, but does not improve biopsy appearance after 12mo</td>
</tr>
<tr>
<td>Gallagher et al. [110]</td>
<td>N=489</td>
<td>3 patient groups (a) steroid + Aza (b) steroid + CsA (c) steroid + CsA, replaced with steroid + Aza at 3 mo</td>
<td>Mean follow-up 20yrs CsA withdrawal improved - graft survival (compared to both groups) - renal function (compared to CsA alone) No difference in patient survival</td>
<td>Preservation of long-term renal function using CsA withdrawal</td>
</tr>
<tr>
<td>Lebranchu et al. [93]</td>
<td>N=237 (192 enrolled)</td>
<td>Standard triple IS, at 3mo converted to (a) Rapa (and CsA withdrawal) (b) CsA continuation</td>
<td>At 12mo post-randomisation - no difference in patient or graft survival - better calculated GFR in CsA withdrawal group - trend to higher BPAR in Rapa group after steroid withdrawal</td>
<td>Withdrawal of CsA is associated with an improvement in renal function</td>
</tr>
<tr>
<td>Schena et al. [111]</td>
<td>N=830</td>
<td>Standard triple IS, at 6-120mo randomised to (a) Rapa (CsA withdrawal) (b) CsA continuation</td>
<td>At 12 and 24mo post-randomisation - similar rates of BPAR, patient and allograft survival - better calculated GFR but higher proteinuria in withdrawal group</td>
<td>Superior renal function following CsA withdrawal</td>
</tr>
<tr>
<td>Egbuna et al. [112]</td>
<td>N=278</td>
<td>ATG + MMF + steroid (withdrawn after 6d) + CNI; randomised to (a) Rapa (and CNI withdrawal) (b) CsA continuation</td>
<td>At 6mo post-randomisation, CsA withdrawal associated with - improved calculated GFR 36% patients required conversion back to CNI due to adverse effects</td>
<td>Conversion to Rapa improves renal function even in absence of steroid</td>
</tr>
<tr>
<td>Study</td>
<td>No. of patients</td>
<td>Drug regimen *</td>
<td>Selected outcome</td>
<td>Conclusion</td>
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<tr>
<td>Morales et al. [113]</td>
<td>N=525</td>
<td>CsA + Rapa + steroid initially; at 3mo randomised to (a) continue CsA (b) CsA withdrawal</td>
<td>At 5y post-randomisation, CsA withdrawal associated with - better calculated GFR - better BP control No difference in lipid profile</td>
<td>CsA withdrawal safe and leads to improved renal function</td>
</tr>
<tr>
<td>Russ et al. [114]</td>
<td>N=430</td>
<td>Steroid + Rapa + CsA initially; at 3mo randomised to (a) remain on triple therapy (b) CsA withdrawal</td>
<td>At 4yr post-randomisation, CsA withdrawal associated with - better calculated GFR</td>
<td>Early and complete CsA withdrawal is preferable, regardless of baseline renal function; most marked benefit if calculated GFR&lt; 45ml/min</td>
</tr>
</tbody>
</table>
### Table 5. Steroid sparing trials

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Drug regimen</th>
<th>Selected outcome</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benfield et al.</td>
<td>Target N=274 (paediatric) N=132 (enrolments ceased due to PTLD)</td>
<td>Daclizumab + sirolimus + CNI + steroid; at 6mo randomised to (a) steroid withdrawal (b) low dose steroid</td>
<td>At 18mo post- randomisation, - no difference in BPAR - better growth velocity in steroid withdrawal group At 3yr post transplantation - higher allograft survival</td>
<td>Withdrawal of steroids with this protocol did not increase risk or allograft rejection. Complications of this protocol too high for routine use.</td>
</tr>
<tr>
<td>Höcker et al.</td>
<td>N=42 (paediatric)</td>
<td>Standard triple IS (steroid + MMF + CsA) randomised to (a) continue steroid (b) withdraw steroid</td>
<td>At 2y post- randomisation, steroid withdrawal associated with - superior growth - lower prevalence of metabolic syndrome - less HT and lower antiHT drug requirement - lower rate of hyperlipidaemia No difference in patient or allograft survival, or BPAR</td>
<td>Steroid withdrawal in paediatric patients improves cardiovascular risk factor profile, growth and metabolic syndrome at no increased risk to graft</td>
</tr>
<tr>
<td>Grenda et al.</td>
<td>N=186 (paediatric)</td>
<td>Daclizumab + MMF + Tac + steroid for 4d versus MMF + Tac + steroid continuation</td>
<td>At 6mo post- randomisation, steroid absence associated with - improved growth - reduced serum cholesterol and triglycerides. Patient and graft survival, renal function similar</td>
<td>Early steroid withdrawal aided growth at 6mo (prepubertal &gt;pubertal children)</td>
</tr>
<tr>
<td>Kumar et al.</td>
<td>N=300</td>
<td>Basiliximab induction + MMF or Rapa + CNI and (a) steroids withdrawn at d2 (b) standard steroid therapy</td>
<td>At 3y post- randomisation, steroid withdrawal associated with - lower rate new-onset DM No difference in patient or graft survival, BPAR, incidence of CAN, or graft function</td>
<td>Two day steroid withdrawal is safe and beneficial</td>
</tr>
</tbody>
</table>
### The KHA-CARI Guidelines – Caring for Australasians with Renal Impairment

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Drug regimen</th>
<th>Selected outcome</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Büchler et al. [79]</td>
<td>N=145</td>
<td>All patients received ATG + MMF + Rapa or CsA + steroids. Steroid withdrawn at 6mo</td>
<td>At 12mo post-randomisation, no difference in patient or graft survival, no difference in BPAR</td>
<td>Early steroid withdrawal is possible, even in context of mTORi</td>
</tr>
</tbody>
</table>
**GUIDELINES**

**General**

a. We suggest that the target concentration range for immunosuppressants be individualised 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 (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**

c. We recommend that cyclosporine and tacrolimus concentrations in blood should be measured (1C):

   i. frequently in the immediate post-operative 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-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)

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

**Mycophenolate mofetil (MMF) monitoring**

f. Whilst routine monitoring cannot be recommended, we suggest consideration be given to MMF 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 MMF be monitored using a multiple regression derived LSS or Bayesian estimators 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)
h. We suggest a mycophenolic acid (MPA) 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 MPA AUC0-12 target in patients more than 12 months post-transplant. (2C)

**Mammalian target of rapamycin inhibitor (mTORi) 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 mTOR inhibitor monitoring, however we note that mTORi target concentrations may vary by drug, perceived risk of rejection, and time post-transplant. (2C)

**UNGRADED SUGGESTIONS FOR CLINICAL CARE**

None

**IMPLEMENTATION AND AUDIT**

Given the recommendations that exposures be individualised according to risk profiles, meaningful audit is difficult. ANZDATA captures drug dosages, though not concentrations, which serve as a surrogate marker for impact of TDM only. Audit of use of therapeutic drug monitoring and its consequences for patient and graft outcomes could be undertaken at individual sites.

**BACKGROUND**

In almost all cases, immunosuppression for the prevention of allograft rejection is a pre-requisite for successful transplantation. However, acute and chronic immunosuppressant drug-induced toxicities are common, as is evidence of acute and chronic under- and over-immunosuppression. Immunosuppressive complications reduce drug tolerability, contribute to post-transplant morbidity, and have a substantial impact on patient and graft survival. As propensity to both rejection and drug side-effects may vary from individual to individual, drug therapy is best tailored to the requirements of each individual patient.

Therapeutic drug monitoring (TDM) involves measuring the concentration of drug in the body. Drug dosing is then adjusted to achieve target concentrations. Through allowing for individualisation of a patient's drug therapy, TDM provides the clinician with a means of maximising drug efficacy while minimising toxicity.

However, for a drug to be a suitable candidate for TDM, a number of criteria must be met. Specifically, the drug must have a narrow therapeutic window, display large between subject pharmacokinetic variability, and there must be a proven relationship between drug exposure and outcomes [119, 120]. Additionally, there must be a reliable and feasible method of measurement and a target concentration range to guide dosing.

Full dose interval area under the concentration time curve (AUC0-12) is generally considered the best marker of drug exposure [121]. However, the requirement for collection of multiple samples over a 12-hour period makes this parameter impractical for routine use. In contrast, single time
point measures [e.g. trough (C0) concentrations] are convenient, but may not reliably estimate drug exposure. An alternative is use of a limited sampling strategy (LSS), in which a limited number of samples are collected over the early part of the dosing interval. AUC0-12 is then estimated with the use of an equation derived from multiple regression analysis. LSSs offer a compromise between accuracy and practicality. However, timing of samples is critical, and LSSs are only applicable to populations very similar to the one from which they were derived [122]. The predictive power of a LSS is not assured in different patient subpopulations or where different drug regimens are applied [122-124]. LSSs must be properly validated to ensure reliable predictions [124]. Another alternative is Maximum A Posteriori (MAP) Bayesian forecasting. This uses a LSS, but also utilizes information from a population pharmacokinetic model for the drug of interest. AUC0-12 can be estimated for each individual by combining concentration measurements for that individual with available population data [122]. A major advantage of this methodology is more flexible timing of blood samples. Disadvantages include a more complex calculation [although web-based services are available to assist (http://pharmaco.chu-limoges.fr)], and reliance on the existence of an appropriate pharmacokinetic model [125, 126]. As with multiple regression-derived LSSs, MAP Bayesian estimators can only be applied to populations with characteristics similar to those of the derivation population [127].

The aim of this guideline is to review the evidence for therapeutic drug monitoring of the immunosuppressant medications in kidney transplantation, and to provide suggestions for clinical care regarding appropriate TDM schedules, methodologies and target ranges.

SEARCH STRATEGY

The search strategy was an update of that used by KDIGO (refer to Table 32 in the Appendix of the KDIGO guideline).

Databases searched: Medline, Central, Cochrane database of systematic reviews.

Date of searches: November 2010.

ADEQUACY OF KDIGO SEARCH STRATEGY

The KDIGO search strategy was considered appropriate for the topic.

APPLICABILITY OF KDIGO RECOMMENDATIONS AND SUGGESTIONS

The KDIGO guidelines and suggestions are considered to be generally applicable to Australia and New Zealand. However, in adapting the guidelines KHA-CARI have provided additional details in relation to monitoring of MMF and mTORi and provided two additional guidelines relevant to individualisation of monitoring and immunooassay methods.

OVERVIEW OF THE EVIDENCE

The following provides an overview of the evidence as identified in the KDIGO guidelines and the update searches conducted by KHA-CARI as part of the adaptation process.

Cyclosporine monitoring

There is no randomised controlled trial (RCT) evidence of a benefit of cyclosporine TDM compared to no TDM. However, it is widely accepted that cyclosporine monitoring is appropriate. Cyclosporine is a critical dose drug, having the desired therapeutic effect without major toxicity within a narrow range of blood concentrations. Cyclosporine also displays wide variation between individuals in the concentration achieved with a given dose. Multiple factors have been reported to influence cyclosporine pharmacokinetics. These include patient age and race, albumin and
haematocrit, liver function, gastrointestinal motility, time from transplantation, diurnal rhythm, food administration, concomitant medication usage, and genetic polymorphisms in enzymes and proteins responsible for drug metabolism and transport [128]. Also in support of cyclosporine TDM, cyclosporine exposure, as measured by area under the concentration time curve, has been shown to correlate well with clinical outcomes [129, 130].

Variable and generally poor correlation of cyclosporine C0 with AUC0-12 has been reported ($r^2 = 0.3-0.88$) [131, 132], and a number of studies have shown an inability of C0 concentrations to differentiate patients at risk of acute rejection [133, 134]. Pharmacokinetic studies have shown C2 to be a better predictor of AUC0-12 and AUC0-4 than C0 or other single time point measures [135]. However, two RCTs [135, 136] have shown no difference in the incidence of acute rejection, graft survival or adverse events irrespective of whether C0 or C2 were used (see Table 6). Similar to C2, multiple regression derived LSSs have superior ability to predict cyclosporine exposure compared with C0 monitoring. However, again, RCT data has shown no improvement in outcomes with use of this monitoring parameter over C0 [135]. A single study has shown highly accurate estimation of AUC0-12 with MAP Bayesian estimation ($r^2=0.985$; bias and precision -0.49% and 2% respectively) [137], but no study has compared this method with C0 monitoring, or examined its ability to influence outcomes. Overall, there is lack of evidence to suggest a benefit of any one monitoring strategy over another. Given RCT data demonstrating equivalence of C0, C2 and LSS TDM, all are acceptable monitoring strategies. However, given that measurement of C0 is the least time-consuming and labour intensive, this parameter may be preferable.

Even with the microemulsion formulation, cyclosporine absorption is incomplete and unpredictable, with large inter- and intra-individual variability. This is particularly the case in the early post-transplant period. Other pharmacokinetic determinants such as albumin and haematocrit also vary substantially in this early phase. Consequently, it has been shown that dose normalized peak concentrations and AUC increase significantly between week 2 and weeks 4 to 6, then remain stable thereafter [138]. There are no studies comparing monitoring schedules for cyclosporine. However, a reasonable approach would be frequent monitoring early when pharmacokinetic variability is greatest, with subsequent monitoring performed with a significant change in clinical parameters, concomitant immunosuppression, suspected drug interactions or where there is concern regarding over- or under-immunosuppression (e.g. rejection or opportunistic infection).

There is no validated reference range for cyclosporine C0, C2 or AUC0-12. Generally, the target concentration will vary according to recipient immunological and toxicity risk status and co-therapy administered, and thus should be patient specific.

HPLC and various immunoassay methodologies are used for cyclosporine concentration measurement. Because immunoassays can be biased by cross-reactivity with cyclosporine metabolites, they typically provide an overestimate of drug concentration [139-141]. There is not a consistent multiplier that can be applied to correct an immunoassay result. Subsequently, when interpreting results, clinicians should be aware the type and characteristics of the assay used by their particular laboratory. It should be noted that the majority of data pertaining to cyclosporine TDM is based on immunoassay measurement.

**Tacrolimus monitoring**

Because the therapeutic index and within- and between-subject pharmacokinetic variability of tacrolimus is similar to that of cyclosporine [142], tacrolimus TDM is routine in most transplant centres. However, tacrolimus TDM is less well studied than cyclosporine TDM, and the relationship between tacrolimus concentrations and clinical outcomes remains poorly defined. In a multicentre, concentration-ranging trial of tacrolimus and cyclosporine, Laskow et al [143] found a significant trend for increasing toxicity with increasing maximum trough tacrolimus concentrations ($P=0.01$). Decreasing rates of rejection were seen with increasing minimum trough tacrolimus concentrations ($P=0.021$). In contrast, Undre et al [144] found an association between low tacrolimus AUC0-12 on day 2 post-transplant and acute rejection, but no such correlation at 2 weeks or 3 months. Ekberg
et al [88] showed no relationship between C0 concentrations and diarrhoea or post-transplant diabetes mellitus [145].

C0 concentrations are usually used to guide tacrolimus dosing. However, evidence regarding the correlation of C0 with AUC0-12 is conflicting ($r^2 = 0.04-0.91$) [146-156], with some studies suggesting a better relationship in the early post-transplant period than later on [121, 157]. There is some data to suggest superior correlation of C3 or C4 concentrations with AUC0-12. Similarly, a number of multiple regression derived LSSs for tacrolimus have been proposed, the majority of which have shown improved correlation with AUC0-12 ($r^2 > 0.90$ in most instances) compared with C0 concentrations [124, 158]. A single study has tested Bayesian estimation of tacrolimus exposure in kidney transplant recipients [159]. Accurate correlations with AUC0-12 were demonstrated ($r^2$=0.94-0.99 when using > 1 sampling time point), as was improved prediction of AUC0-12 over C0 measurement. However, there has been no multi-centre validation of these monitoring strategies, so applicability to alternative populations cannot be assured. Additionally, there is no data associating these measures with clinical outcomes, so that they cannot be currently recommended over C0 monitoring.

Similar to cyclosporine, tacrolimus pharmacokinetic variability is highest in the early post-transplant period. Hence, as for cyclosporine, frequent initial monitoring seems appropriate, with concentration measurement in the later post-transplant period occurring according to clinical indication.

Historically, evidence suggested that tacrolimus C0 concentrations ≥ 10 ng/mL were required for avoidance of acute rejection [160, 161]. More recently, a large RCT showed that targeting a C0 concentration of 3-7 ng/mL yielded adequate immunosuppression [88], with the difference likely to be related to modern day use of more potent co-therapy. However, there has been no validation of this or any other C0 concentration target range. Similarly, there is no validated reference range for tacrolimus AUC0-12. Thus, as for cyclosporine, individualisation of target range is appropriate.

The issues discussed above for cyclosporine in relation to use of variable assay methodologies for drug concentration measurement also apply to tacrolimus. Immunoassays have been shown to overestimate tacrolimus concentrations by 20-60% [121, 131]. Also similarly to cyclosporine, the majority of data pertaining to tacrolimus TDM are based on immunoassay measurement.

**Mycophenolate mofetil (MMF) monitoring**

Although MMF has typically been prescribed as a fixed-dose medication for adult kidney transplant recipients, multiple characteristics of the drug suggest a role for TDM. While the therapeutic index of mycophenolic acid (MPA; the active drug moiety) is wider than that of the calcineurin inhibitors (CNIs), toxicity is often seen at the doses required for efficacy. MPA also displays considerable between-subject variability, with studies showing a ≥10-fold range in dose-normalized MPA AUC0-12 [162]. Patient differences in albumin and haemoglobin levels, kidney and liver function, body weight, concomitant medication exposure, genetic polymorphisms in enzymes responsible for drug metabolism and transport, and time from transplantation have been identified as contributors to pharmacokinetic variability [163]. Additionally, the relationship between MPA exposure and efficacy is well defined, with multiple studies (including five RCTs [28, 125, 164-166] linking low drug concentrations with acute rejection. Most studies have shown no correlation between MPA exposure and toxicity.

However, the pharmacokinetic profile of MPA is more complicated than that of the CNIs, in part because of late concentrations rises that occur as a result of enterohepatic recirculation. Subsequently, it has been shown that single time point measures are unable to adequately reflect MPA exposure [122]. Specifically, poor correlation exists between MPA C0 and AUC0-12 ($r^2 = 0.003-0.7$) [167]. MPA C0 also correlates less well with acute rejection and displays greater within-subject variability than AUC0-12 [120, 168, 169]. Studies have suggested that multiple regression-derived LSSs and Bayesian procedures allow improved prediction of MPA AUC0-12 [120, 127,
unological risk recipients, with a marked probability of concentration. Multiple regression derived LSSs has not been established. Additionally, this relationship was supported by findings that an AUC of ≤ 30 correctly identified 79% of patients rejecting within 3 months. However, AUC > 60 mg·h/L was associated with a 30% risk of rejection. A more recent RCT [125] confirmed the appropriateness of the lower limit, finding that an AUC of ≤ 30 correctly identified 79% of patients rejecting within 3 months. However, this reference range was derived from data obtained from cyclosporine co-treated recipients. Applicability to tacrolimus co-treated recipients has not been established. Additionally, this reference range is for the early post-transplant period. There is no data available regarding an appropriate MPA AUC0-12 target in patients a distance post-transplant.

Both immunoassay HPLC-based methods can be used. However, the EMIT assay overestimates MPA concentration by as much as 50% due to cross reactivity with some MPA metabolites [127]. This should be kept in mind by clinicians when interpreting MPA concentration measurements.

Enteric-coated mycophenolate sodium (EC-MPS) is the sodium salt of MPA (Myfortic®, Novartis Pharma, Basel, Switzerland) [174]. This alternative MPA formulation was designed to improve gastrointestinal tolerability. Limited sampling strategies and population models developed for MMF cannot be applied to TDM of EC-MPS because of its different and more variable pharmacokinetics. There is currently no reliable means of estimating MPA exposure in the context of EC-MPS therapy, apart from measurement of a full 12 hour AUC profile.

Mammalian target of rapamycin (mTOR) inhibitors monitoring

No RCTs have compared TDM of the mTOR inhibitors with no TDM. However, because both sirolimus and everolimus display a narrow therapeutic window and high between- and within-subject pharmacokinetic variability [175, 176], it is widely accepted that TDM is appropriate. Factors affecting pharmacokinetic variability of these drugs include liver function, concomitant medication usage or food intake, time from transplantation, paediatric age group and genetic polymorphisms in enzymes in proteins responsible for drug metabolism and transport [175, 177, 178].
High correlations exist between sirolimus and everolimus C₀ concentrations and AUC₀-12 (r² = 0.88-0.95) [175, 179, 180]. Additionally, C₀ has been correlated with both efficacy and toxicity [129, 179, 181, 182], making this parameter suitable for mTOR TDM.

No trials have compared one monitoring schedule of the mTOR inhibitors with other. Reasonable indications for TDM might include after initiation of therapy or a change in dose, with suspected drug interactions, or where there is concern regarding over- or under-immunosuppression. Additionally, given that simultaneous administration of cyclosporine with the mTOR inhibitors leads to increases in mTOR C₀ concentrations of up to 80% [177, 183], TDM should be performed with any major alteration in concomitant cyclosporine dosing. It should be noted that both everolimus and sirolimus have long half-lives (approximately 28-35 and 60 hours for the two drugs respectively) [175, 176]. Thus, steady state concentrations will not be reached until > 5 days post-dose change for everolimus and > 10 days post-dose change for sirolimus, unless a loading dose is used.

Significant increases in acute rejection have been seen with sirolimus C₀ concentrations < 5 ng/mL and everolimus C₀ concentrations <3 ng/mL, and there is limited safety data with C₀ concentrations > 12 ng/mL [182, 183]. However, there is no validated target range for the mTOR inhibitors. As for the other immunosuppressant drugs, the target concentration should be individualised based on recipient immunological and toxicity risk status and co-therapy administered.

There is an average positive bias of approximately 25% between sirolimus concentrations determined by immunoassay compared with HPLC [139]. This should be kept in mind when interpreting mTOR inhibitor concentrations.

**Prednisolone monitoring**

Prednisolone has generally been considered to have a wide therapeutic index, making TDM unnecessary. However, there is some suggestion that even when low doses are administered, prednisolone toxicities may be apparent. Additionally, marked inter-subject variability in prednisolone pharmacokinetics has been demonstrated [184], suggesting that there may be a role for prednisolone concentration monitoring. However, there is almost no published experience regarding the application of TDM to prednisolone therapy, and methods for measuring prednisolone blood concentrations are not routinely available.

**Pharmacodynamic monitoring**

There has been increasing interest in pharmacodynamic monitoring of the immunosuppressant drugs. Pharmacodynamic monitoring is appealing, as it examines the clinical effects of a drug rather than using the surrogate marker of drug concentration. It also has the ability to evaluate the effect of combination drug therapies on the immune system. However, while promising data for a number of approaches are emerging, evidence is currently insufficient to allow application of pharmacodynamic monitoring to routine clinical care.

**SUMMARY OF EVIDENCE**

There is no randomised controlled trial (RCT) evidence of a benefit of cyclosporine TDM compared to no TDM. However, it is widely accepted that cyclosporine monitoring is appropriate. Cyclosporine is a critical dose drug, having the desired therapeutic effect without major toxicity within a narrow range of blood concentrations. There is lack of evidence to suggest a benefit of any one monitoring strategy over another for CsA. Given RCT data demonstrating equivalence of C₀, C₂ and LSS TDM, all are acceptable monitoring strategies. However, given that measurement of C₀ is the least time-consuming and labour intensive, this parameter may be preferable. There
are no studies comparing monitoring schedules for cyclosporine. A reasonable approach would be frequent monitoring early when pharmacokinetic variability is greatest, with subsequent monitoring performed with a significant change in clinical parameters, concomitant immunosuppression, suspected drug interactions or where there is concern regarding over- or under-immunosuppression (e.g. rejection or opportunistic infection). There is not a consistent multiplier that can be applied to correct an immunoassay result. Subsequently, when interpreting results, clinicians should be aware the type and characteristics of the assay used by their particular laboratory.

Tacrolimus TDM is less well studied than cyclosporine, and the relationship between tacrolimus concentrations and clinical outcomes remains poorly defined. There has been no multi-centre validation of tacrolimus monitoring strategies and there is no data associating the strategies with clinical outcomes, so that they cannot be currently recommended over C₀ monitoring. As for CsA, tacrolimus is affected by variable assay methodologies.

Evidence of superiority of concentration-controlled dosing based on TDM for MMF over fixed dosing is still lacking, so that routine TDM cannot be recommended. However, there are certain subpopulations or clinical scenarios where MMF TDM may be of benefit. Examples include high immunological risk recipients, with a marked change in clinical parameters such as kidney function or serum albumin levels, concomitant immunosuppression, medications that may affect drug concentrations, or concern about over- or under-immunosuppression. Studies have suggested that multiple regression-derived LSSs and Bayesian procedures allow improved prediction of MPA AUC₀-₁₂. Additionally, two RCTs have shown a correlation of MPA AUC₀-₁₂ measured by these methods with efficacy. However, there has been minimal validation of most multiple regression derived LSSs or Bayesian estimators in alternative populations, so that their widespread applicability cannot be guaranteed. Available evidence for the proposed target MPA range of 0 to 60 mg h/L is available only for the early post-transplant period and only for transplant recipients co-treated with CsA. Applicability to recipients co-treated with tacrolimus has not been demonstrated and it is not possible to propose a target other than early post-transplant.

There is almost no published experience regarding the application of TDM to prednisolone therapy, and methods for measuring prednisolone blood concentrations are not routinely available.

Similarly due to insufficient evidence it is not currently possible to make recommendations with respect to pharmacodynamic monitoring.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: None

UK Renal Association: None

Canadian Society of Nephrology: None

European Best Practice Guidelines: [185]
Section III – The transplant recipient from initial transplant hospitalization to 1 year post-transplant.

III.5 Evaluation of renal transplant recipients and their grafts in the first post-transplant year.

A. Renal transplant patients and their grafts should be monitored frequently to diagnose complications and deterioration of function. Monitoring should start immediately after surgery and be repeated at least once daily during the initial hospital stay. After discharge, graft function should be assessed at least twice-weekly for one month and once-weekly for another month, and then at regular intervals. (Evidence Level C)
B. Minimum routine evaluation should consist of:
   - Brief medical history
   - Blood pressure, pulse rate, body weight
   - General medical examination as indicated
   - Plasma Na, K, Cl, bicarbonate, creatinine concentration, blood count
   - Urinalysis for glycosuria, proteinuria, haematuria, leukocyturia; sodium concentration; urine culture
   - Blood levels of calcineurin inhibitors and other relevant immunosuppressive drugs.
   (Evidence Level C)

SUGGESTIONS FOR FUTURE RESEARCH

1) Improving existing population models so as to enable better prediction by Bayesian methodology.

2) Assessing the general applicability, or otherwise, of multiple regression derived LSSs and Bayesian estimators in different populations.

3) Multi-centre RCTs comparing the various monitoring strategies.

4) Predictive value and clinical utility of pharmacodynamic monitoring with calcineurin, IMPDH activity or measures of T lymphocyte function.

5) Studies of the cost-effectiveness, or otherwise, of TDM.

CONFLICT OF INTEREST

S Campbell has a Level II conflict of interest according to the conflict of interest statement set down by KHA-CARI.

K Barraclough has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by KHA-CARI.
### Table 6. Randomized Controlled Trials comparing TDM methodologies for Cyclosporine.

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Ethnicity</th>
<th>Co-therapy</th>
<th>TDM Methodologies compared</th>
<th>Assay</th>
<th>Primary end-point</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Neoral Renal Transplantation Study Group 2002 [17]</td>
<td>204 adult patients randomized</td>
<td>8 countries. 96% White</td>
<td>Basiliximab induction; prednisolone. MMF and azathioprine not permitted.</td>
<td>C&lt;sub&gt;0&lt;/sub&gt; concentration versus LSS estimation of AUC&lt;sub&gt;0-12&lt;/sub&gt;</td>
<td>Immunoassay</td>
<td>Composite of death, graft loss, acute rejection.</td>
<td>30.3% vs. 32.6% in LSS group and C&lt;sub&gt;0&lt;/sub&gt; groups respectively; p=0.763</td>
</tr>
<tr>
<td>Kyllonen 2006 [18]</td>
<td>160 adult recipients</td>
<td>Not specified.</td>
<td>MMF and Prednisolone</td>
<td>C&lt;sub&gt;0&lt;/sub&gt; concentration versus C&lt;sub&gt;2&lt;/sub&gt; concentration All patients had C&lt;sub&gt;0&lt;/sub&gt; TDM after day 20 post-transplant.</td>
<td>Immunoassay (TDx, Abbott Laboratories, Abbott Park, IL)</td>
<td>Acute Rejection rate at 3 months.</td>
<td>7.5% vs. 10.8% in C&lt;sub&gt;0&lt;/sub&gt; and C&lt;sub&gt;2&lt;/sub&gt; groups respectively; p=NS</td>
</tr>
</tbody>
</table>

MMF = Mycophenolate mofetil; AUC<sub>0-12</sub> = area under the concentration time curve from 0-12 hours post-dose; C<sub>0</sub> = trough (pre-dose) concentration; C<sub>2</sub> = concentration 2 hours after the last dose; LSS = limited sampling strategy; NS = Not Significant.
### Table 7. Randomized Controlled Trials comparing TDM of MMF with no TDM.

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Ethnicity</th>
<th>Co-therapy</th>
<th>MPA PK parameter</th>
<th>Methodology</th>
<th>Assay</th>
<th>Primary end-point</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Le Meur 2007 [7]</td>
<td>137 adult recipients</td>
<td>French; specific ethnicity not specified</td>
<td>IL-2R mAb induction; CsA; prednisolone (weaning ± elimination according to centre practise)</td>
<td>AUC(_{0-12})</td>
<td>Bayesian estimation</td>
<td>HPLC</td>
<td>Composite of death, graft loss, BPAR, MMF discontinuation</td>
<td>29.2% vs. 47.7% in CC and FD groups respectively; p=0.03</td>
</tr>
<tr>
<td>Van Gelder 2008 [50]</td>
<td>901 adults and paediatric recipients</td>
<td>83.1% White; 2.9% Black; 6.2% Asian; 7.8% other</td>
<td>45% IL-2R mAb induction, 55% no IL-2R mAb induction; 54.3% CsA, 45.7% tacrolimus; prednisolone (weaning according to centre practise)</td>
<td>AUC(_{0-12})</td>
<td>4 multiple derived LSSs (for adults and paediatrics on CsA and tacrolimus respectively)</td>
<td>EMIT 53% HPLC 47%</td>
<td>Composite of death, graft loss, BPAR, MMF discontinuation</td>
<td>25.6% vs. 25.7% in CC and FD groups respectively; p=0.81</td>
</tr>
<tr>
<td>Gaston 2009 [47]</td>
<td>720 adults and paediatric recipients</td>
<td>65.8% White; 26.7% African-American; 7.4% other</td>
<td>44% antithymocyte globulin induction, 31% IL-2R mAb induction; ~ 20% CsA; ~ 80% tacrolimus*; 93.8% prednisolone in 1(^{st}) week; later use not specified</td>
<td>C(_0)</td>
<td>Not applicable</td>
<td>Not specified</td>
<td>1. Composite of death, graft loss, BPAR, loss to follow-up or withdrawal of consent 2. Change in eGFR at 12 months</td>
<td>1. 22.6% vs. 28.3% vs 29.9% for MMF(<em>{CC}/\text{CNI}</em>{RL}) vs. MMF(<em>{CC}/\text{CNI}</em>{SL}) vs. MMF(<em>{FD}/\text{CNI}</em>{SL}); p=NS for all group comparisons 2. 12.3% vs. 5.4% vs. 8.2% for MMF(<em>{CC}/\text{CNI}</em>{RL}) vs. MMF(<em>{CC}/\text{CNI}</em>{SL}) vs. MMF(<em>{FD}/\text{CNI}</em>{SL}); p=NS for all group comparisons</td>
</tr>
</tbody>
</table>

IL-2R mAb = interleukin 2 Receptor Monoclonal Antibody; CsA = cyclosporine A; AUC\(_{0-12}\) = area under the concentration time curve from 0-12 hours post-dose; C\(_0\) = trough (pre-dose) concentration; LSS = limited sampling strategy; HPLC = high performance liquid chromatography; EMIT = enzyme multiplied immunoassay technique; CC = concentration controlled; FD = fixed dose.

*Participants randomised 1:1:1 to either concentration controlled MMF with reduced dose (MMF\(_{CC}/\text{CNI}_{RL}\)), concentration controlled MMF with standard dose CNI (MMF\(_{CC}/\text{CNI}_{SL}\)), or fixed dose MMF with standard dose CNI (MMF\(_{FD}/\text{CNI}_{SL}\)).
## Topic 6. Treatment of Acute Rejection

Author: John Kanellis and William Mulley

### GUIDELINES

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 intravenous 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)

### UNGRADED SUGGESTIONS FOR CLINICAL CARE

None.

### IMPLEMENTATION AND AUDIT

Individual units should consider an audit of rates of biopsy confirmation of acute rejection episodes and a review of patient and graft outcomes following treatment.

### BACKGROUND

*The following background has been based on that provided in the KDIGO guideline and edited to reflect review conducted for the adaptation.*

The current guidelines are adapted from the KDIGO guidelines with minor alterations to account for local practice. They seek to give broad direction to Nephrologists caring for kidney transplant recipients. The suggestions for treating acute rejection are based on available evidence, current practice and consensus opinion of the KDIGO/CARI adaptation working group.
An acute rejection episode leads to allograft damage and is the consequence of an immune response by the host. It may be of cellular (lymphocyte) and/or humoral (circulating antibody) origin. Acute rejection is usually suspected in patients experiencing an increase in serum creatinine, after the exclusion of other causes of graft dysfunction (generally with a biopsy). It may also be subclinical and diagnosed on surveillance biopsy (also known as screening or protocol biopsy).

We know from the early days, that untreated acute rejection inevitably results in graft destruction. Therefore, it is strongly recommended that acute rejection episodes be treated, unless the treatment is expected to do more harm to the patient than good. Local data confirms that when rejection is successfully treated and kidney function is restored to pre-rejection levels, there is no detriment to graft survival [3]. Rejection episodes which are recurrent, have a vascular component, or which incompletely respond to therapy leaving residual graft dysfunction are associated with inferior long term graft function and survival [3].

Acute rejection is characterized by a decline in kidney function accompanied by well-established diagnostic features on kidney allograft biopsy which are defined by the Banff criteria [186]. Subclinical acute rejection is defined by the presence of histological changes specific for acute rejection on screening or protocol biopsy, without overt clinical symptoms or signs. It is important to note that although the creatinine may appear satisfactory in some of these "subclinical" cases, a lower level may be achievable following treatment of the rejection episode.

Acute cellular rejections are acute T-cell–mediated rejections that usually respond to treatment with corticosteroids. Severe rejection, particular those with a vascular component, are unlikely to respond to corticosteroids. Borderline acute rejection is defined by histopathological changes that are only ‘suspicious for acute rejection’ according to the Banff classification schema [186]. A rejection episode is said to be resistant to treatment when graft function does not return to baseline after the last dose of treatment, or when a repeat biopsy continues to show significant features of rejection despite treatment. The presence of either steroid resistant acute rejection, or vascular acute rejection (Banff 2A or greater) is an indication to consider T-lymphocyte depleting antibody.

Antibody-mediated rejection is defined by histological changes caused by a circulating, anti-HLA, donor-specific antibody. The following criteria are generally used to determine whether an acute rejection is caused by a donor-specific antibody:

i) staining of peritubular capillaries with C4d (fourth complement fraction);
ii) the presence of a circulating, anti-HLA, donor-specific antibody; and
iii) histological changes consistent with an antibody-mediated rejection including the presence of mononuclear and/or polymorphonuclear cells in peritubular and glomerular capillaries, thrombosis, vascular rejection and in some cases acute tubular necrosis.

SEARCH STRATEGY

The search strategy was an update of that used by KDIGO (refer to Table 32 in the Appendix of the KDIGO guideline).

Databases searched: Medline, Central, Cochrane database of systematic reviews.

Date of searches: November 2010.

ADEQUACY OF KDIGO SEARCH STRATEGY

The search strategy and evidence provided seems adequate for this topic. There are several publications which give some insight into this topic although there are few high quality RCTs.
APPLICABILITY OF KDIGO RECOMMENDATIONS AND SUGGESTIONS

Because of the lack of high quality evidence and the difficulty in subjecting some of the accepted practices to an RCT, many of the KDIGO suggestions for the treatment of acute rejection are opinion-based rather than evidence-based. They are however, generally in keeping with local practice. They provide appropriate guidance to Nephrologists in Australia and New Zealand and make practical and sensible suggestions.

There was little discussion regarding the options for altering maintenance immunosuppression and a suggestion regarding this has been added. There were also relatively strong suggestions regarding the use of anti-T cell therapies in treating rejection. In Australia our approach with these agents has generally been more conservative.

OVERVIEW OF THE EVIDENCE

The following provides an overview of the evidence as identified in the KDIGO guidelines and the update searches conducted by KHA-CARI as part of the adaptation process.

Biopsy

As there are several possible causes of decreased kidney function, it is recommended that the diagnosis and treatment of acute rejection, be based on a biopsy. In addition, the treatment of decreased kidney allograft function that is not caused by acute rejection with additional immunosuppressive medication may be harmful, leading to unwanted side effects and an increased risk of infections.

A recent systematic review by Wu et al 2009 [187] examined acute rejection and its effect on graft function and survival. Thirty-one observational studies were included and the definition of acute rejection varied. Additionally there was large heterogeneity between the studies. Nevertheless, the relative risk of graft loss was greater in subjects that had suffered biopsy proven acute rejection (Banff I or greater; RR: 1.2-10.5).

Although there are no RCTs to establish that obtaining a biopsy improves outcomes of suspected acute rejection, there are alternative diagnoses that might mimic an acute rejection episode. CNI toxicity or BK polyomavirus (BKV) nephropathy would generally be treated differently than acute rejection, for example with a reduction in immunosuppressive medication. Therefore, logic dictates that, whenever possible, biopsy confirmation should be obtained to avoid inappropriate treatment.

Treating subclinical and borderline cellular rejection.

Some centers use protocol biopsies to detect subclinical acute rejection. Treating acute rejection discovered in this way, may help improve graft survival although there is still some controversy regarding this. In a RCT, the detection and treatment of subclinical acute rejection in patients (N = 72) on CsA, MMF and corticosteroids resulted in better graft function [188, 189]. However, in a larger (N = 218) multicenter RCT in patients on tacrolimus, MMF and corticosteroids, protocol biopsies and treatment of subclinical acute rejection were not beneficial [190]. Finally, in a single-center RCT of 102 recipients of living-donor kidneys (treated with CsA [N=96] or tacrolimus [N=6],MMF [N=55] or azathioprine [N = 47] and corticosteroids) protocol biopsies and treatment of subclinical acute rejection resulted in improved graft function [191]. Uncontrolled data suggest that, when the incidence of clinical acute rejection is low, the number of patients with subclinical acute rejection may be too small to warrant the inconvenience and cost of protocol biopsies [192].
Whether or not to treat borderline acute rejection remains controversial. There are no RCTs addressing whether treatment of borderline acute rejection prolongs graft survival, and whether overall benefits outweigh harm.

**Corticosteroids**

Corticosteroid therapy is the most commonly used, first-line treatment for acute cellular rejection episodes. Although most patients respond to corticosteroids, the dose and duration of treatment has not been well defined by RCTs. Treatment starting with intravenous methylprednisolone 250–1000 mg daily for 3 days is a common practice.

If function does not return to baseline, or if there is a new decline in function after successful treatment of an acute rejection, a biopsy should be considered to rule out resistant rejection, BKV nephropathy and other causes of graft dysfunction.

**Lymphocyte-depleting antibodies**

A large systematic review by Webster et al, concluded that treatment of acute cellular rejection with an anti–T-cell antibody (OKT3, ATG or ALG) was more effective in restoring kidney function and preventing graft loss than treatment with corticosteroids [193]. Treatment with an antibody was also associated with more adverse effects, but whether the overall benefits of antibody treatment vs. corticosteroids outweigh harm was uncertain [193]. The review also concluded that antibody therapy was more effective than corticosteroids for treating first rejection episodes, the relative risk of treatment failure being significantly lower in the antibody group (RR: 0.57. 95% CI: 0.38-0.87). Caveats include variable definitions for steroid resistance and heterogeneity amongst the rejections, with the diagnosis of antibody-mediated rejection not clearly assessed in many of these studies. Additionally, many of the studies were based on immunosuppressive regimens that did not include MMF and tacrolimus.

There are no RCTs examining whether anti–T-cell antibodies vs. corticosteroids should be the initial treatment of Banff IIA or IIB (vascular) rejection. A low strength of evidence suggests no net benefits or harm between antibodies or steroids alone (refer to Evidence Profile in Supporting Table 39 in the KDIGO guidelines).

Studies suggest that steroid-resistant or recurrent T-cell–mediated rejection responds to treatment with polyclonal or monoclonal anti–T-cell antibodies [193].

Anti–T-cell antibodies (Thymoglobulin, ATG, ALG) can be used when corticosteroids have failed to reverse rejection or for treatment of a recurrent rejection. OKT3 was previously used for similar indications but is no longer available in Australia. In such circumstances, benefits generally outweigh harm. However, there is inadequate evidence from RCTs to conclusively establish the best treatment for steroid-resistant or recurrent acute cellular rejection (see Evidence Profile in Supporting Table 38 of KDIGO guidelines). Most studies comparing various anti-T cell strategies did not have adequate statistical power to show a difference in efficacy. However, in one RCT, ATG was better tolerated than OKT3 [194].

**Antibody-mediated rejection**

A number of measures may be effective in treating antibody-mediated rejections, including plasma exchange, intravenous immunoglobulin, anti-CD20 antibody and anti–T-cell antibodies.

Therapeutic strategies that include combinations of plasma exchange to remove donor-specific antibody, and/or intravenous immunoglobulins and anti-CD20+ monoclonal antibody (rituximab) to suppress donor-specific antibody production have been used to successfully treat acute humoral rejection. However, the optimal protocol to treat acute humoral rejection remains to be determined. Indeed, there are no RCTs with adequate statistical power to compare the safety and efficacy of
these different therapeutic strategies. In a RCT in 20 children, rituximab was associated with better function and improved post rejection biopsy scores compared to treatment with anti–T-cell antibody and/or corticosteroids [195]. Clearly, additional studies to define the optimal treatment of acute humoral rejection are needed. A typical protocol may include IV steroids and plasma exchange, 1-3 cycles, combined with IVIG to a total dose of 1-2g/kg. As IVIG is effectively removed by plasma exchange, at least part of the IVIG dose should be given after the last plasma exchange.

Rejection Episodes

It is possible that the addition of MMF to the post-rejection maintenance immunosuppressive medication regimen, or replacement of azathioprine with MMF, will help to prevent subsequent acute rejection. A RCT (N = 221) compared MMF to azathioprine in the treatment of first acute rejection [196]. Patients receiving MMF had fewer subsequent rejections, and among the 130 who completed the trial, at 3 years graft survival was better in the MMF group [196]. A summary of the RCTs on replacement of azathioprine by MMF in the setting of rejection is provided in Supporting Tables 40–41 of the KDIGO guidelines.

There is a paucity of good quality studies analysing the relative merits of switching immunosuppressive regimens or increasing the overall immunosuppression following a rejection episode. As well as the potential benefit to the graft, one must consider the potential harm (e.g. infections, cancer and other side effects). Despite this lack of evidence, it is standard practice to switch between regimens or increase overall immunosuppression following rejection episodes, in an attempt to improve overall outcomes. Further studies are required in this area.

SUMMARY OF EVIDENCE

Although there are no RCTs to establish that obtaining a biopsy improves outcomes of suspected acute rejection, there are alternative diagnoses that might mimic an acute rejection episode. CNI toxicity or BK polyomavirus (BKV) nephropathy would generally be treated differently than acute rejection, for example with a reduction in immunosuppressive medication. Observational studies have established an association between biopsy proven graft acute rejection and graft loss. On this basis, biopsy confirmation should be obtained to avoid inappropriate treatment.

Evidence regarding the treatment of subclinical and borderline cellular rejection is currently limited and indicates either no benefit or improved graft function associated with protocol biopsies and treatment of subclinical rejection. There are no RCTs addressing whether treatment of borderline acute rejection prolongs graft survival, and whether overall benefits outweigh harm.

Corticosteroid therapy is the most commonly used, first-line treatment for acute cellular rejection episodes. Although most patients respond to corticosteroids, the dose and duration of treatment has not been well defined by RCTs.

Treatment of acute cellular rejection with an anti-T-cell antibody maybe more effective in restoring kidney function and preventing graft loss and for treating first rejection episodes compared to treatment with a corticosteroid. However whether the overall benefits outweigh the harm has not been established. There are no RCTs examining whether anti–T-cell antibodies vs. corticosteroids should be the initial treatment of Banff IIA or IIB (vascular) rejection. A low strength of evidence suggests no net benefits or harm between antibodies or steroids alone.

The optimal protocol to treat acute humoral rejection remains to be determined as there are no RCTs with adequate statistical power to compare the safety and efficacy of the different therapeutic strategies.

There is a paucity of studies analysing the relative merits of switching immunosuppressive regimens or increasing the overall immunosuppression following a rejection episode. As well as the potential benefit to the graft, it is necessary to consider the potential harm (e.g. infections, cancer
and other side effects). Despite this lack of evidence, it is standard practice to switch between regimens or increase overall immunosuppression following rejection episodes, in an attempt to improve overall outcomes.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: None

UK Renal Association: None

Canadian Society of Nephrology: None

European Best Practice Guidelines: [197]
Guideline III.9.2
A. For the treatment of the first cellular rejection episode, high doses of intravenous methylprednisolone are recommended. This treatment is expected to reverse most acute rejection episodes. Although the use of polyclonal (ATG/ALG) or monoclonal (OKT3) antibodies as first-line therapy is effective, their adverse event profile and cost mean that the use of corticosteroids as first-line therapy is preferred. (Evidence level C).

B. ATG/ALG or OKT3 are recommended for the treatment of severe acute rejection episodes (Banff grade III), recurrent acute rejection episodes, corticosteroid resistant rejection episodes or in patients with contraindications to corticosteroids. (Evidence level C).

C. In patients with recurrent rejection after ant-T lymphocyte antibody treatment, it is recommended to modify baseline immunosuppression. (Evidence level B).

D. ALG/ATG is preferable to OKT3 for the treatment of acute rejection episodes. Although both preparations are effective in reversing such episodes, OKT3 has a slightly poorer adverse event profile because of the first-dose effect. (Evidence level B).

E. Rabbit anti-T lymphocyte antisera are preferable to horse anti-T lymphocyte antisera. (Evidence level A).

British Transplant Society

The clinical effectiveness and cost effectiveness of immunosuppressive therapy for renal transplantation (2002).

The mainstay of treatment for early acute cellular rejection has been augmented immunosuppression with intravenous high dose steroids. Frequently, baseline immunosuppression is adjusted either temporarily or permanently following acute rejection especially if multiple episodes occur. Treatment of early acute humoral rejection and steroid resistant (or partially resistant) acute cellular rejection is more problematic with a variety of strategies including intravenous immunoglobulin, plasma exchange and anti-lymphocyte antibodies being employed. Even in large programmes these are rare events and it is very difficult to acquire enough case experience to make recruitment to a randomised trial to test efficacy realistic.

International Guidelines: None

SUGGESTIONS FOR FUTURE RESEARCH

Further RCTs to:
1. Determine whether treating borderline acute rejection improves outcomes.
2. Assess whether protocol biopsies and the treatment of subclinical acute rejection are cost-effective.
3. Examine the optimal treatment for antibody-mediated acute rejection.
4. Compare outcomes between various strategies for altering baseline immunosuppressive therapy following a rejection episode.

CONFLICT OF INTEREST

J Kanellis and W Mulley have no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by KHA-CARI.
Topic 7. Treatment of Chronic Allograft Injury

Author: Germaine Wong, Phil O’Connell

GUIDELINES

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)

   a. For patients with CAI, 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 mTORi. For patients with CAI and an eGFR < 40 ml/min/1.73m², a switch to mTORi is not recommended. (2D)

UNGRADED SUGGESTIONS FOR CLINICAL CARE

None

IMPLEMENTATION AND AUDIT

Individual units should consider an audit of biopsy use in patients with declining kidney function and a review of patient and graft outcomes following changes to drug regimens in response to CNI toxicity.

BACKGROUND

The following background has been based on that provided in the KDIGO guideline and edited to reflect review conducted for the adaptation.

CAI is a diagnosis of exclusion characterized by the progressive reduction in graft function not due to recurrence of disease or other recognized causes. Histologically, CAI is defined by IF/TA. Other features may include subclinical rejection, transplant glomerulopathy or transplant vasculopathy.

It is important that patients suspected of having CAI undergo biopsy to rule out other possible reversible causes of the decline in kidney function.

The role of CNI toxicity, chronic antibody-mediated rejection and other immune and non-immune mechanisms of injury are unclear. The treatment of CAI has been controversial.

SEARCH STRATEGY

The search strategy was an update of that used by KDIGO (refer to Table 32 in the Appendix of the KDIGO guideline). Additional key papers have been identified the authors that were published after the KHA-CARI update search.
Databases searched: Medline, Central, Cochrane database of systematic reviews.

Date of searches: November 2010.

ADEQUACY OF KDIGO SEARCH STRATEGY

The KDIGO search strategy is considered adequate for the topic.

APPLICABILITY OF KDIGO RECOMMENDATIONS AND SUGGESTIONS

The KDIGO recommendations and suggestions are considered appropriate for use in Australia and New Zealand. However, changes to suggestions relating to replacing the CNI with a mTORi have been made to reflect more recent evidence.

OVERVIEW OF THE EVIDENCE

The following provides an overview of the evidence as identified in the KDIGO guidelines and the update searches conducted by KHA-CARI as part of the adaptation process.

CNI withdrawal and replacement

There are only 2 RCTs in people with established CAI:

1. Creeping Creatinine study – MMF substituted with CyA – no differences in outcomes at 12 months. [103]

2. Chronic allograft renal failure study – CyA was replaced with Tacrolimus – increase in serum creatinine by 60 µmol/L, but no differences in other outcomes and side effects profiles. [198]

Overall the quality of evidence evaluating the effects of replacing a CNI in patients with CAI is low and there is uncertainty regarding benefit-harm trade-offs (refer to Supporting Tables 42-44 of the KDIGO guidelines).

CNI replacement with mTOR

No RCTs have examined whether switching KTRs with established CAI from a CNI to an mTORi is beneficial. However, the CONVERT trial enrolled over 800 participants with estimated glomerular filtration rate (eGFR) ≥20 mL/min/1.73 m2 to continuation of CNI (n = 275) vs. converting to sirolimus (n = 555) [111]. Patients were stratified into two groups based on eGFR 20–40 mL/min/1.73 m2 (N = 87) and eGFR >40 mL/min/1.73 m2 (N = 743). The Data Monitoring and Safety Board stopped the trial for patients with eGFR 20–40 mL/min/1.73 m2 when the primary safety end point (acute rejection, graft failure or death at 12 months) occurred in 8 of 48 of sirolimus vs. 0 of 25 CNI patients (p = 0.045). In the stratum eGFR >40 mL/min/1.73 m2, the primary end point (change in eGFR baseline to 12 months) was not different in the two groups, but there was more proteinuria in the sirolimus group. This post hoc subgroup analysis suggested that converting patients with eGFR 20–40 mL/min/1.73 m2 from CNI to sirolimus may be harmful, and that converting patients with eGFR >40 mL/min/1.73 m2 may not be beneficial [111].

Similar to the CONVERT study, the SPARE the NEPHRON study had shown that kidney transplant recipients who were maintained on MMF/CNI for a period of 6 months from the time of transplantation and then converted to maintenance immunosuppression with MMF/SRL had
greater improvement in measured GFR than those who were maintained on MMF/ CNI at 12 and 24 months [199]. These findings are comparable to that of the CONCEPT study [93], which showed significant improvement in graft function 12 months after conversion to mTORi-based regimen from CNI based therapy 3 months after transplantation. In the recently published post CONCEPT study, participants randomised to the mTORi-based treatment arms showed continued benefits in kidney function at four years, but no demonstrated significant improvement in graft function and cancer outcomes at the end of the 4-year follow-up [200].

Among recipients with established kidney impairment, the benefits of CNI elimination and minimisation are less certain. In the recently published ASCERTAIN trial, whereby 394 kidney transplant recipients on maintenance immunosuppression with reduced kidney function, were randomised to undergo CNI elimination, minimisation or standard CNI treatment-based regimens, showed no overall benefits in terms of kidney function and biopsy proven rejection rates in the CNI elimination and minimisation arms compared to the controls at 12 and 24 months. Some additional benefits in the overall kidney function were observed in the post-hoc analyses among recipients with a baseline eGFR greater than 50ml/min who received conversion to mTORi compared to CNI maintenance between baseline and 24 months [201]. However, a significantly greater number of participants in the conversion arm had experienced proteinuria and adverse side effects than the controls, and in part, responsible for the high rates of discontinuation and drop outs in all of these trials.

The outcomes of these trials should be interpreted with caution. The quality of the included studies is low and the majority of these trials are limited by the design, the high number of patient withdrawals and the methodology of analyses. It is also unclear whether the improvement in kidney function observed in the short term translates into better longer term graft function, graft and patient survival and improved overall quality of life. It is imperative that researchers and clinicians consider these fundamental and important elements when designing and conducting future prospective studies. Replacement of the standard CNI-based treatment with mTORi will undoubtedly result in poorer tolerability among a large number of transplant recipients. Long term judicious monitoring for side effects and careful consideration of the balance between the harms against the benefits of cancer and potential improved kidney function is crucial.

Other novel immunosuppressants such as belatacept, sotrastaurin and JAK3 inhibitors offer potential for CNI-free immunosuppression, however their efficacy and safety, particular in the setting of CAI remains to be proven [202].

SUMMARY OF EVIDENCE

Overall the quality of evidence evaluating the effects of replacing a CNI in patients with CAI is low and there is uncertainty regarding benefit-harm trade-offs.

No RCTs have examined whether switching kidney transplant recipients with established CAI from a CNI to an mTORi is beneficial. Post hoc subgroup analyses of trials of CNI replacement with mTORi have shown improved graft function associated with conversion to mTORi. However, mTORi is also associated with adverse side effects and proteinuria. It is unclear whether the improvement in kidney function observed in the short term translates into better longer term graft function, graft and patient survival and improved overall quality of life.

Other novel immunosuppressants such as belatacept, sotrastaurin and JAK3 inhibitors offer potential for CNI-free immunosuppression, however their efficacy and safety, particular in the setting of CAI remains to be established.
WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative:

UK Renal Association:

Canadian Society of Nephrology:

European Best Practice Guidelines:

[203] Guideline IV.2.1
A. Any significant deterioration in graft function should be investigated using the appropriate diagnostic tools and, if possible, therapeutic interventions should be initiated. The usual causes of a decline in GFR after the first year include transplant specific causes such as chronic allograft nephropathy, acute rejection episodes, chronic CNI nephrotoxicity, transplant renal artery stenosis and ureteric obstruction, as well as immunodeficiency related causes and non-transplanted-related causes, such as recurrent or de novo renal diseases and bacterial infections. (Evidence level B).
B. Any new onset and persistent proteinuria of >0.5g/24h should be investigated and therapeutic interventions should; be initiated. The usual causes include chronic allograft nephropathy and transplant glomerulopathy, and recurrent or de novo glomerulonephritis.

International Guidelines:

SUGGESTIONS FOR FUTURE RESEARCH

1. RCT examination of novel immunosuppressants (belatacept, sotrastaurin and JAK-3 inhibitors) as potential alternatives to CNI-based therapy in patients with CAI.

CONFLICT OF INTEREST

G Wong and P O’Connell have no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by KHA-CARI.
GUIDELINES

a. We suggest monitoring urine protein:creatinine ratio or albumin:creatinine ratio 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; and (2D)
   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)

UNGRADED SUGGESTIONS FOR CLINICAL CARE

IMPLEMENTATION AND AUDIT

Individual units should consider an audit of procedures used to monitor allograft function and review against patient and graft outcomes.

BACKGROUND

The following background has been based on that provided in the KDIGO guideline and edited to reflect review conducted for the adaptation.

Post-transplant complications may affect graft function before symptoms or signs develop. Monitoring graft function may therefore allow early detection of important clinical entities such as acute rejection, calcineurin inhibitor toxicity and recurrent glomerular disease before they are apparent symptomatically. Early detection leading to early intervention is likely to lead to best possible outcomes. Therefore monitoring graft function should be expected to improve outcomes for patients with kidney transplants, compared to no monitoring.

Graft monitoring is universally practiced after kidney transplantation but there is little evidence available to guide selection of monitoring tests, frequency of testing, thresholds for diagnosis and treatment for detected conditions. Serum creatinine is usually chosen for graft function monitoring.
due to universal availability and familiarity. Recommendations are based on opinion and monitoring theory.

SEARCH STRATEGY

The search strategy was an update of that used by KDIGO (refer to Table 32 in the Appendix of the KDIGO guideline).

Databases searched: Medline, Central, Cochrane database of systematic reviews.

Date of searches: November 2010.

ADEQUACY OF KDIGO SEARCH STRATEGY

The KDIGO search strategy was generally considered to be adequate for the topic.

APPLICABILITY OF KDIGO RECOMMENDATIONS AND SUGGESTIONS

The KDIGO recommendations are applicable to the Australian and New Zealand setting.

OVERVIEW OF THE EVIDENCE

The following provides an overview of the evidence as identified in the KDIGO guidelines and the update searches conducted by KHA-CARI as part of the adaptation process.

Graft function monitoring

Common causes of kidney transplant dysfunction (e.g. acute rejection, acute calcineurin inhibitor toxicity, recurrent or de novo glomerulonephritis, ureteric obstruction) are likely to respond best to the earliest possible intervention. These conditions will often cause asymptomatic graft dysfunction early in the course of the illness, progressing over days to weeks. There is therefore a period of time where they might be detected using graft function monitoring before symptoms develop.

There is no evidence to support any particular method of monitoring kidney function over any other. Serum creatinine is favoured because it is widely available and highly reproducible, with low intra-individual and analytic variability [204, 205].

There is no evidence to support any particular monitoring frequency. Frequency of testing should be greatest in the first post-transplant month when risk of common causes of asymptomatic graft dysfunction is the greatest.

Serum creatinine varies between individuals after kidney transplantation. Results should be interpreted in light of an individual's prior measurements, but there is no evidence to support further investigation of any particular relative or absolute rise in creatinine.

There is no evidence to support use of estimated glomerular filtration rate (eGFR) equations over serum creatinine alone. In the short term, monitoring using glomerular filtration rate estimating equations (eGFR) based on serum creatinine offer no advantages over serum creatinine alone as other determinants (e.g. age, race, sex in the case of the Modification of Diet in Renal Disease (MDRD) equation) are constant. In long-term follow up, eGFR might be expected to improve detection of changes in underlying graft function masked by constant serum creatinine in the aging recipient. However, in an observational study, eGFR using the MDRD or Cockcroft and Gault equations did not improve the performance of serum creatinine alone for detecting histological allograft changes at six months post-transplant [206].
**Additional Blood Testing**

Further investigation of an unexplained rise in creatinine should include assessment of calcineurin inhibitor concentration and BK virus in blood by PCR. Other testing would vary based on the clinical circumstances.

**Allograft ultrasound**

Kidney transplant dysfunction that is not explained should be investigated in the first instance by an allograft ultrasound to exclude urinary obstruction, collections and vascular compromise.

**Proteinuria**

Proteinuria after transplant may be indicative of recurrent or de novo glomerular disease or interstitial fibrosis and tubular atrophy, and is associated with poorer transplant and patient outcomes. Early detection of these lesions could improve outcomes by allowing early intervention, although there are no randomised controlled trials of treatment of proteinuria of any cause in this patient group.

**SUMMARY OF EVIDENCE**

There is little evidence available to guide selection of monitoring tests, frequency of testing, thresholds for diagnosis and treatment for detected conditions. Recommendations and suggestions are therefore based on opinion and monitoring theory and the assumption that monitoring graft function should allow for timely diagnosis and treatment that may improve outcomes.

There is no evidence to support any particular method of monitoring kidney function over any other. Serum creatinine is favoured because it is widely available and highly reproducible, with low intra-individual and analytic variability.

There is no evidence to support any particular monitoring frequency. Frequency of testing should be greatest in the first post-transplant month when risk of common causes of asymptomatic graft dysfunction is the greatest.

There is no evidence to support use of estimated glomerular filtration rate (eGFR) equations over serum creatinine alone.

**WHAT DO THE OTHER GUIDELINES SAY?**

**Kidney Disease Outcomes Quality Initiative:** None

**UK Renal Association:**

Draft guidelines suggest that patients should be reviewed in 2-3 times weekly for the first month after transplantation, 1-2 times weekly for months 2-3, every 1-2 weeks for months 4-6, every 4-6 weeks for months 6-12 and 3-6 monthly thereafter. There is no specific recommendation for tests to be performed at these reviews.

**Canadian Society of Nephrology:** None

**European Best Practice Guidelines:**
Guidelines published in 2000 suggest that kidney transplant recipients are reviewed at least daily following transplantation until discharge, then twice weekly for one month, then once weekly for another month and the at regular intervals. Plasma creatinine concentration and urinalysis for proteinuria are recommended at each review, along with plasma sodium, potassium, chloride, bicarbonate, a blood count and immunosuppressive drug concentrations.

SUGGESTIONS FOR FUTURE RESEARCH

1. Frequency of monitoring of serum creatinine. Frequency of monitoring could be addressed with a trial randomising recipients to more or less frequent monitoring.

2. Threshold of rise for further interventions. Diagnostic test studies could address the test performance of different rises in serum creatinine and different definitions of “baseline creatinine” for detection of clinically relevant conditions (e.g. acute rejection).

3. Treatment of proteinuria. Treatment of proteinuric renal disease with angiotensin converting enzyme (ACE) inhibitors or angiotensin-2 receptor blockers in non-transplant patients slows progression of disease. Randomised controlled trials of these interventions in kidney transplant recipients with proteinuria are need.

CONFLICT OF INTEREST

N Cross has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by KHA-CARI.

Author: William Mulley and John Kanellis

GUIDELINES

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 protein to creatinine ratio or ≥1.0 g per 24 hours.) (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)

UNGRADED SUGGESTIONS FOR CLINICAL CARE

None

IMPLEMENTATION AND AUDIT

Individual units should consider an audit of biopsy practices in responses to allograft dysfunction and a review of surveillance biopsy practices.

BACKGROUND

Allograft biopsies may be used for a variety of purposes, ranging from the need for determination of acutely abnormal allograft function to planning biopsies for clinically stable allografts. “Indication biopsies” are those biopsies conducted to determine the cause of unexpected kidney dysfunction generally prompted by unexplained elevated serum creatinine or proteinuria. Protocolised “surveillance biopsies” are those biopsies performed at predetermined time points post transplantation in the absence of such an indication. Surveillance biopsies are performed to detect subclinical changes such as rejection as well as guiding potential immunosuppressive changes.

The optimal studies to determine the relative merit of performing an allograft biopsy in each situation are randomised controlled trials (RCTs). Unfortunately these have not been and are unlikely ever to be performed for indication biopsies. Despite a lack of evidence to suggest performing a biopsy in a patient with acute allograft dysfunction is in any way superior to not
performing a biopsy it would seem unethical to conduct a RCT to rectify this evidence gap. Therefore indirect evidence is the best available to support such a policy. The situation is somewhat different for surveillance biopsies in which there have been 4 RCTs (discussed below) even here however, the evidence provided is not directly generalisable to all subgroups of kidney transplant recipients meaning that for both indication and surveillance biopsies clinical judgement remains key.

SEARCH STRATEGY

The search strategy was an update of that used by KDIGO (refer to Table 32 in the Appendix of the KDIGO guideline).

Databases searched: Medline, Central, Cochrane database of systematic reviews.

Date of searches: November 2010.

ADEQUACY OF KDIGO SEARCH STRATEGY

The search for the surveillance biopsy section is considered to be adequate, however the search strategy for the indication biopsy section has not been stated.

APPLICABILITY OF KDIGO RECOMMENDATIONS AND SUGGESTIONS

The KDIGO guidelines have been adapted with minor alterations to account for local practice. They seek to give broad direction to Nephrologists caring for renal transplant recipients. The additional suggestions for surveillance biopsies have been added based on available evidence, current practice and consensus opinion of the KHA-CARI adaptation working group.

The KDIGO suggestions for indication biopsies are generally opinion rather than evidence based but are relevant to practice in Australia and New Zealand. They provide appropriate guidance to Australian and New Zealand Nephrologists and make no radical or controversial suggestions. No suggestions were provided for surveillance biopsies despite a somewhat better evidence base and as such these have been added.

The suggestions as stated represent a reasonable guide but should be interpreted in the light of the limitations of the available data. Biopsies will quite justifiably continue to be performed outside of these suggested parameters, tailored to the individual patient situation, as determined by the clinical judgement of the treating physician.

OVERVIEW OF THE EVIDENCE

The following provides an overview of the evidence as identified in the KDIGO guidelines and the update searches conducted by KHA-CARI as part of the adaptation process.

**Indication Biopsies**

Despite its known limitations in accurately detecting changes in the glomerular filtration rate (GFR) serum creatinine levels are routinely used for this purpose. The degree of elevation which best predicts the need for an allograft biopsy is not known but a rise of ≥30% has been shown to correlate with an increased risk of graft loss [207]. Prior to performing an allograft biopsy pre and post renal causes such as intravascular volume depletion, infection, drug toxicity (including excessive CNI levels) and renal obstruction should be excluded. The elevation in serum creatinine should be confirmed with a repeat sample to exclude laboratory error.
As mentioned, there are no published studies to support performing versus not performing a renal allograft biopsy in the setting of an unexplained sustained elevation in serum creatinine. This action is however routinely taken given that the elevated creatinine itself does not discriminate between the various possible causes of dysfunction whilst histological assessment can. Possible diagnoses include, but are not limited to, acute or chronic rejection, calcineurin inhibitor (CNI) toxicity, infection, post-transplant lymphoproliferative disease or recurrent or de novo glomerulonephritis. Each diagnosis may be met with a different treatment strategy. Whilst the evidence supporting the efficacy of the treatments to yield an improvement in outcomes is debatable for some diagnoses such as CNI toxicity and polyoma virus nephropathy it is somewhat more robust for acute rejection [188, 191, 193]. Subtypes of rejection can also be determined [208] which is of use given that different treatment options are generally employed for cell-mediated and antibody-mediated rejection [209-213].

When serum creatinine has not returned to baseline after acute rejection, steroid resistant rejection may be identified which may be amenable to treatment with second line agents such as anti-lymphocyte antibodies [193]. Alternatively persistent or new antibody-mediated rejection may be seen prompting a different response. A third possibility is the discovery of a new diagnosis such as a polyoma virus nephropathy or PTLD. The timing of the repeat biopsy is subjective however if renal function has not improved or has deteriorated 5-7 days after pulse corticosteroid therapy, the rejection may be considered steroid resistant and repeat biopsy is indicated [214].

Renal transplant recipients are frequently screened for allograft pathology by estimation of urinary protein (refer to “Monitoring Kidney Allograft Function”). Possible causes are manifold and include glomerulonephritis, transplant glomerulopathy and diabetic nephropathy. Glomerulonephritis (recurrent and de novo) are not uncommon and represent an important cause of renal allograft failure [215, 216] (refer to “Recurrent Kidney Disease”). Proteinuria may be the first indication of glomerulonephritis and is associated with worse graft and patient survival such that new onset proteinuria or nephrotic range proteinuria should be investigated by a biopsy [217]. Whilst evidence supporting successful therapy for glomerulonephritis in the renal allograft is limited, achieving the diagnosis allows therapies to be entertained and prognostic information to be given to the patient (refer to “Recurrent Kidney Disease”). In addition alternative, potentially treatable diagnoses may be identified. Proteinuria exceeding 1 g/day provides an arbitrary threshold for biopsy, consistent with local practice though not defined by trial data.

**Surveillance Biopsies**

Observational studies have shown that the incidence of acute rejection during DGF is higher than in patients without DGF [218-220]. Kidney function cannot be used as an indication for biopsy to diagnose superimposed acute rejection while the patients are already being treated with dialysis due to DGF, or when the serum creatinine does not fall from pre-transplant values. It is therefore prudent to obtain periodic biopsies of the kidney during DGF to diagnose acute rejection. There are few data to determine when and how often biopsies during DGF should be obtained. However, studies in which biopsies have been obtained every 7–10 days, while patients are receiving dialysis for DGF, have shown that acute rejection can be present for the first time on the second, third or even fourth biopsy [219].

In centres that have a very low overall incidence of acute rejection, the incidence of acute rejection during DGF could also be low enough to obviate the need for biopsies during DGF. A biopsy may no longer be needed when there are signs that DGF is resolving, for example when urine output is increasing rapidly or serum creatinine is declining.

The suggestion that allograft biopsy be performed if expected kidney function is not achieved within the first 1-2 months after transplantation falls between the indication and surveillance biopsy demarcation. It refers to that group of patients who have a level of renal function which is below that which would be anticipated for the donor/recipient pairing. For example a slight 60 year old
female recipient of a 25 year old healthy male kidney would be expected to achieve a serum creatinine below 100µmol/L. If her serum creatinine at 1 month remained above this level without any other explanation it would be prudent to biopsy to eliminate renal pathology. This type of situation is commonly encountered but requires a high level of clinical acumen particularly where the level of kidney function is reasonable but potentially suboptimal. There are no direct data to support this strategy and the suggestion is based on consensus opinion.

Acute rejection, chronic allograft injury and CNI toxicity can occur in the absence of a measurable decline in kidney function. Several studies have shown that surveillance biopsies can detect clinically unapparent (subclinical) acute rejection, CAI and CNI nephrotoxicity. The reported prevalence of subclinical rejection (Banff grade 1A or higher) varies from 13% to 25% at 1–2 weeks, 11–43% at 1–2 months, 3–31% at 2–3 months and 4–50% at 1 year [221-227]. Data from observational studies indirectly suggest that detecting and treating subclinical acute rejection with surveillance biopsies may be beneficial. Subclinical rejection is associated with CAI [221, 222, 228, 229] and reduced graft survival [228-231].

In another study, subclinical acute rejection in 14-day surveillance biopsies was associated with poorer 10-year graft survival [231]. Graft survival rates with subclinical rejection, borderline subclinical rejection or no rejection were 88%, 99% and 98% at 1 year (p < 0.05), and 62%, 94% and 96% at 10 years (p < 0.05), respectively. In a paediatric study, subclinical rejection was associated with progressive CAI, reduced creatinine clearance and shorter graft survival [229].

Treatment of subclinical rejection may improve outcomes. In a RCT, 72 patients were randomly allocated to undergo surveillance biopsies and treatment of subclinical rejection at 1, 2, 3, 6 and 12 months (biopsy group), or surveillance biopsies without treatment at 6 and 12 months only (control group) [188]. Patients in the biopsy arm of the study had a significant decrease in acute rejection episodes, a reduced 6-month chronic tubulointerstitial score and a lower 2-year serum creatinine. Interstitial fibrosis was less in those treated for subclinical rejection [188]. In another trial, 52 living-donor KTRs were randomized to undergo surveillance biopsies and 50 controls had only indication biopsies [191]. At 1 and 3 months, surveillance biopsies revealed borderline changes in 11.5% and 14% patients, acute rejection in 17% and 12% and CAI in 4% and 10%, respectively. The incidence of clinically evident acute rejection episodes was similar in the two groups, but the biopsy group had lower serum creatinine at 6 months (p = 0.0003) and 1 year (p < 0.0001). Therefore, based on low-quality evidence, the benefit of performing surveillance biopsies in CsA/azathioprine-treated patients without induction therapy appears indicated. The RCTs performed implemented surveillance biopsies within the first 3 months.

Baseline immunosuppression appears important in determining the incidence of subclinical rejection and thereby the benefit of surveillance biopsies. Tacrolimus- and MMF treated patients generally have a lower rate of acute rejection than patients treated with CsA and azathioprine, and tacrolimus is associated with a reduced incidence of subclinical rejection [192, 228, 232-234], lower acute Banff scores [235, 236] and 1-year serum creatinine [234].

In a RCT, 121 patients were randomly allocated to biopsies at 0, 1, 2, 3 and 6 months, and 119 to biopsies at 0 and 6 months [190]. At 6 months, 35% of the biopsy arm and 20.5% of the control arm patients had interstitial fibrosis and tubular atrophy (ci + ct) scores ≥2 (p = 0.07). Of note, the frequency of clinical acute rejection episodes was only 10% in the biopsy arm and 7% in the control arm (p >0.05). The prevalence of subclinical rejection in the biopsy arm was 4.6%. Creatinine clearance at 6 months was not different (p > 0.05) in the two groups. Use of surveillance biopsies, therefore, for diagnosis of subclinical rejection may not be appropriate in all tacrolimus- and MMF-treated patients. The short duration of follow-up however does not allow determination of the longer term implications of treating subclinical rejection in these patients.

Whilst, it is unclear whether the detection of these conditions by surveillance biopsy improves outcomes, other conditions besides subclinical rejection can be detected; including CNI toxicity, recurrent disease, transplant glomerulopathy, CAI and polyoma virus nephropathy. In addition, in
the absence of published studies examining the utility of surveillance biopsies in recipients predicted to be at higher risk of subclinical rejection, (PRA >50%, ABO incompatible) surveillance biopsies provide more definitive guidance than can be obtained from non-invasive measures. Even in low immunologic risk recipients surveillance biopsies may inform decision making in tailoring immunosuppression to minimise side-effects whilst balancing rejection risks.

The safety of biopsies has been documented in several series [236, 237]. The reported risk of major complications from surveillance biopsy, including substantial bleeding, macroscopic haematuria with ureteric obstruction, peritonitis or graft loss, is approximately 1% [238-240]. The reported incidence of graft loss from surveillance biopsy is 0.03%. Surveillance biopsies can be done safely as an outpatient procedure. Data collected on 1705 surveillance kidney transplant biopsies at one centre showed that all of the complications became evident in the first 4 h after the biopsy [241].

Surveillance biopsies, however, may be expensive. The Mayo Clinic reported that surveillance biopsies cost US$3000 per biopsy, and it cost US$114 000 to detect one case of acute subclinical rejection [192]. Therefore, decisions on whether or not to perform surveillance biopsies should take these and other factors, including patient preferences, into account.

(refer to Evidence Profile and accompanying evidence in Supporting Tables 45–47 of the KDIGO guidelines).

SUMMARY OF EVIDENCE

Whilst the optimal study for the merits of performing indication biopsies would be an RCT, these have not been and are unlikely to be performed and thus recommendations and suggestions are based on observational studies. Whilst evidence from RCTs is available for surveillance biopsies, it is not able to be generalised to all subgroups.

The degree of elevation of serum creatinine that best predicts the need for an allograft biopsy is not known, however a rise of ≥30% has been associated with increased risk of graft loss. There are no published studies to support performing versus not performing a renal allograft biopsy in the setting of an unexplained sustained elevation in serum creatinine. Whilst the evidence supporting the efficacy of the treatments to yield an improvement in outcomes is debatable for some diagnoses such as CNI toxicity and polyoma virus nephropathy it is somewhat more robust for acute rejection. The timing of the repeat biopsy is subjective however if renal function has not improved or has deteriorated 5-7 days after pulse corticosteroid therapy, the rejection may be considered steroid resistant and repeat biopsy is indicated.

Whilst evidence supporting successful therapy for glomerulonephritis in the renal allograft is limited, achieving the diagnosis allows therapies to be entertained and prognostic information to be given to the patient (refer to Topic 10 “Recurrent Kidney Disease”). In addition alternative, potentially treatable diagnoses may be identified.

Observational studies have shown that the incidence of acute rejection during DGF is higher than in patients without DGF. Surveillance biopsies may therefore be indicated as kidney function cannot be used an indication for biopsy while the kidney transplant recipient is on dialysis or when serum creatinine does not fall from pre-transplant values.

There is no evidence to support the use of biopsy for kidney transplant recipients whose expected kidney function is not achieved within 1 to 2 months following transplant. Rather, the suggestion is made on the basis of consensus opinion.

Several studies have shown that surveillance biopsies can detect subclinical rejection of Banff grade 1A or higher. Observational studies suggest such detection may be beneficial as subclinical rejection has been associated with CAI and reduced graft survival. Low quality evidence from
RCTs of kidney transplant recipients receiving CsA/azathioprine without indication therapy provide an indication of the benefit of surveillance biopsy.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: None

UK Renal Association: None

Canadian Society of Nephrology: None

European Best Practice Guidelines:

There is no topic specific to allograft biopsy in the EBPG, however Section III.9 on acute rejection [197] provides the following recommendations

B It is recommended to exclude other causes of graft dysfunction and to take a biopsy to confirm the clinical diagnosis of acute rejection. The biopsy result can be used to guide the intensity of anti-rejection therapy or to assess the long-term prognosis. (Evidence level B)

C Reporting of biopsies should be standardised according to an internationally agreed scheme to reflect the histopathological pattern and severity of the rejection episode. (Evidence level B).

D In patients with prolonged delayed graft function, surveillance biopsies should be considered to detect or exclude acute rejection episodes. (Evidence level B).

International Guidelines: None

SUGGESTIONS FOR FUTURE RESEARCH

1. Further RCTs comparing surveillance biopsies vs. not at specified time points e.g.1 and/or 3 months for patients on maintenance Tacrolimus, MMF and steroids.

2. RCTs of surveillance biopsies vs. not in specific recipient subgroups such as HLA-sensitised or ABO incompatible recipients.

CONFLICT OF INTEREST

W Mulley and J Kanellis have no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by KHA-CARI.
GUIDELINES

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 albumin creatinine ratio (ACR) or protein creatinine ratio (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 (IgA) nephropathy, membranoproliferative glomerulonephritis (MPGN), anti-glomerular basement membrane (anti-GBM) disease, or antineutrophil cytoplasmic autoantibody (ANCA) associated vasculitis for microhaematuria 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 (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)

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 primary FSGS as their primary kidney disease (2D).
   ii. We suggest high-dose corticosteroids and cyclophosphamide, with or without plasmapheresis, in patients with recurrent ANCA-associated vasculitis or anti-GBM 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).
   iv. 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).
UNGRADED SUGGESTIONS FOR CLINICAL CARE

None

IMPLEMENTATION AND AUDIT

Units may consider auditing completeness of screening for proteinuria and/or haematuria post transplant among patients with a form of primary glomerular disease which is known to recur post-transplant

BACKGROUND

The following background has been based on that provided in the KDIGO guideline and edited to reflect review conducted for the adaptation.

Recurrence of the primary kidney disease is usually established when there is biopsy-documented involvement of the kidney allograft with the primary kidney disease. The following points are of note:
- Some recurrent kidney diseases cause allograft failure.
- Treatment of some recurrent kidney diseases may prevent, or delay, the onset of graft failure.
- Recurrence affects prognosis for both the current graft and potential future grafts.
- Screening for recurrent kidney disease may result in early diagnosis and treatment that may be beneficial, and may provide important prognostic information pertinent to the current and subsequent grafts.

SEARCH STRATEGY

The search strategy was an update of that used by KDIGO (refer to Table 32 in the Appendix of the KDIGO guideline).

Databases searched: Medline, Central, Cochrane database of systematic reviews.

Date of searches: November 2010.

ADEQUACY OF KDIGO SEARCH STRATEGY

In general the KDIGO search strategy is considered appropriate for identifying evidence related to the recurrent kidney disease in kidney transplant recipients.

APPLICABILITY OF KDIGO RECOMMENDATIONS AND SUGGESTIONS

The KDIGO recommendations and suggestions are considered to be generally applicable to practice in Australia and New Zealand.

OVERVIEW OF THE EVIDENCE

The following provides an overview of the evidence as identified in the KDIGO guidelines and the update searches conducted by KHA-CARI as part of the adaptation process.

A review of the KDIGO summary has been undertaken and the text amended to reflect the review of the search strategy and studies identified by the search update.
Recurrence of primary kidney diseases is an important cause of morbidity and graft loss following kidney trans-plantation, in both adults and children. In a study of 1505 cases with both native kidney and kidney allograft biopsies documenting recurrent glomerular disease, graft loss due to recurrent glomerulonephritis was the third most frequent cause for graft failure 10 years after kidney transplantation [216]. Recurrence may present as increased serum creatinine (reduced GFR), new-onset or increased proteinuria and/or haematuria. The impact of recurrence varies according to the primary kidney disease. Not all diseases recur with equal frequency. The risk of recurrence is particularly increased in FSGS, immunoglobulin A (IgA) nephropathy, membranoproliferative glomerulonephritis (MPGN), haemolyticuremic syndrome (HUS), oxalosis and Fabry’s disease and, to a lesser extent, with lupus nephritis, anti-glomerular basement membrane (GBM) disease, vasculitis and diabetes [242]. Also, the timing of recurrence and manner of presentation vary for different diseases. FSGS, HUS and oxalosis may recur in the first few days to weeks after transplantation, whereas the timing is variable in the others [243].

In a majority of instances, proteinuria and/or reduced GFR provide the initial basis for suspecting disease recurrence. Since these parameters are periodically assessed in KTRs as part of their routine monitoring, a separate strategy for detection of disease recurrence is not warranted.

The modality of screening for some of these diseases, however, may vary from the usual posttransplant monitoring if timely detection is not achieved by the routine posttransplant monitoring strategies (refer to Table 8 adapted from KDIGO).

There is also weak evidence (uncontrolled case studies and case reports) that disease-specific treatment may be beneficial for some recurrent diseases.

**Idiopathic FSGS**

Idiopathic FSGS recurs in 20–50% of KTRs (up to 80% if it has recurred in a prior kidney transplant) [244]. It is important to distinguish idiopathic from secondary causes of FSGS that generally do not recur. Putative risk factors for recurrence include age of onset of FSGS in native kidneys between 6 and 15 years [245], rapid course of the original disease (e.g. less than 3 years from diagnosis to CKD stage 5), diffuse mesangial proliferation on histology and non-African American ethnicity. The strongest risk factor is recurrence in a previous transplant.

Idiopathic FSGS can recur at any time after transplantation, but recurrence is more common early after transplantation. Recurrent disease presents with proteinuria, which is usually heavy. About 80% of cases recur in the first 4 weeks [246]. Interpretation of proteinuria, especially in the early posttransplant period, requires knowledge of pre- transplant proteinuria. Although proteinuria from the native kidneys declines after transplantation [247], the time taken for its disappearance is variable. Posttransplant proteinuria therefore should be interpreted in light of the pretransplant values.

There have been no RCTs of therapy for recurrent idiopathic FSGS. However, uncontrolled series suggest that patients with recurrent idiopathic FSGS may have a substantial reduction in urine protein excretion after plasma exchange [248, 249]. Typically, 8-10 exchanges have been required [248]. Remission is likely due to removal of circulating factors that alter glomerular permeability to proteins. Predictors of response to plasma exchange include early initiation of treatment after recurrence, and possibly an early recurrence of disease [249]. Proteinuria may recur after treatment, and may require additional plasma exchange, or even periodic, ongoing treatments. The presumption is that reducing protein excretion with plasma exchange will help preserve allograft function, but no studies have examined this. There is no good evidence to suggest that prophylactic plasma exchange is protective against recurrent FSGS [250, 251].
For patients who do not respond to plasma exchange, or for patients who have non-nephrotic proteinuria, general anti-progression strategies including blood pressure control and anti-proteinuric strategies using an angiotensin-converting enzyme inhibitor (ACE-I) and/or an angiotensin II receptor blocker (ARB) appear reasonable.

**IgA nephropathy**

IgA nephropathy is the most common type of glomerulonephritis worldwide and is a common cause of CKD stage 5 treated with transplantation. Recurrent IgA nephropathy is common after transplantation, affecting from 13% to 53% according to differences in duration of follow-up and biopsy policy [252]. In the ANZDATA Registry analysis, the estimated 10-year incidence of graft loss due to recurrence was 9.7% (CI = 4.7–19.5%) [216]. Recurrence risk in retransplants is increased if the first graft was lost due to recurrent IgA nephropathy in less than 10 years [253]. There is no proven therapy for preventing recurrent IgA nephropathy, although preliminary reports suggest induction therapy with Thymoglobulin may be protective [254]. ACE-I and ARBs have been shown to reduce proteinuria and possibly preserve kidney function in recurrent IgA nephropathy [255].

**Membranoproliferative glomerulonephritis**

Secondary causes of MPGN, such as hepatitis C, should be ruled out. The histological recurrence rate in idiopathic type I MPGN is 20–30% and exceeds 80% in type 2 disease. Manifestations include microhaematuria, proteinuria and deterioration of kidney function. Risk factors for recurrence include severity of histological lesions in native kidneys, HLA-B8DR3, living related donors and previous graft loss from recurrence [256, 257]. There are no controlled trials but reports of response to long-term cyclophosphamide [258], plasma pheresis [259-261] and CsA [262].

**Hemolytic-uremic syndrome**

Hemolytic-uremic syndrome recurs commonly in adults and in children in whom the original kidney disease was D− variant. The overall recurrence risk is less than 10% in the paediatric population; D+ HUS usually does not recur, while idiopathic D− or familial HUS may recur in 21–28% of children [263]. Recurrence occurs in about 80–100% of patients with factor H or factor I mutation, while patients with a mutation in membrane cofactor protein do not have recurrence [264, 265]. The risk is higher in adults, with 33–56% [266-268] showing clinical manifestations and an additional 16–20% of patients demonstrating clinically silent recurrence. Recurrence is particularly frequent in adults with autosomal recessive or dominant HUS [263]. Recurrence develops within 4 weeks in most cases. Most patients show microangiopathic anaemia, thrombocytopenia and kidney dysfunction, whereas others present with rapidly progressive graft dysfunction without showing the classic hematologic manifestations. Platelet count should be performed during episodes of graft dysfunction in KTRs with HUS as the original cause of CKD stage 5. In those with falling counts, additional tests such as examination of peripheral blood smear to look for fragmented cells (schistocytes), haptoglobin and lactate dehydrogenase estimation to document haemolysis are warranted. Long-term graft survival is lower in those with recurrence.

Treatment strategies have included plasmapheresis, intra-venous immunoglobulin and rituximab. Aggressive plasma-pheresis using fresh frozen plasma (40–80 mL/kg per session) increases the levels of deficient factors and has provided encouraging results, even in those with factors H and I mutations [269-271]. As factor H is synthesized in the liver, combined liver and kidney transplantation (together with preoperative and intraoperative plasmapheresis using fresh frozen plasma and low-molecular-weight heparin) could reduce the risk of recurrence [270, 272-274]. Intravenous immunoglobulin and rituximab have been reported to rescue recurrent HUS resistant
to multiple courses of plasma exchanges [275, 276]. There is no evidence that avoidance of CNI, mTORi and OKT3 (that may themselves cause thrombotic microangiopathy) will reduce the recurrence risk.

**ANCA-associated vasculitis and anti-GBM disease**

Both antineutrophil cytoplasmic antibody (ANCA) associated vasculitis and anti-GBM disease may present with rapidly progressive CKD and crescentic glomerulonephritis. Recurrence rates are low if the disease is quiescent at the time of transplant. In an analysis of pooled data from 127 patients with ANCA-associated vasculitis, 17% of patients had recurrence, with kidney manifestation in 57.1%. Kidney dysfunction occurred in 33% of those with recurrence [277]. More recent studies [278] report lower (7%) recurrence rates, most beyond the first posttransplant year with no direct or indirect impact on allograft function. ANCA-associated vasculitis relapses in the kidney allograft usually manifest as pauci-immune necrotizing glomerulonephritis, but graft function can also be affected by acute arteritis, ureteral stenosis and obstructive uropathy due to granulomatous vasculitis.

Pretransplantation disease course, disease subtype, ANCA type or titre, time of transplantation or donor type does not predict recurrence. Kidney ANCA-associated vasculitis generally responds well to high-dose prednisolone and cyclophosphamide [279-281]. Other treatment modalities that have been tried include MMF, plasmapheresis with or without intravenous immunoglobulin and rituximab [282-288].

Histological evidence of anti-GBM disease can be found in biopsies in 15–50% of cases. Clinical recurrence is rare, described in isolated case reports only [252, 289] and graft failure due to recurrence is rare [216]. The incidence of recurrence may be higher in those with circulating anti-GBM antibody at the time of transplantation. Treatment of clinically active anti-GBM disease may include pulse steroids, cyclophosphamide and plasma exchange.

**Primary hyperoxaluria**

Primary hyperoxaluria is caused by deficiency of hepatic peroxisomal alanine:glyoxylate aminotransferase, leading to increased synthesis and urinary excretion of oxalate, recurrent calcium oxalate urolithiasis, irreversible nephrocalcinosis and eventually CKD. Because the enzyme defect in primary hyperoxaluria is not corrected by isolated kidney transplantation, oxalate overproduction persists, leading to recurrence of calcium oxalate deposits in over 90% of transplanted kidneys, and eventually leading to graft loss [290], unless the enzyme is replaced through a simultaneous liver trans-plant [291]. The total body oxalate burden is very high in CKD stage 5 patients, and the urinary oxalate excretion increases greatly as soon as graft function is established. Plasma and urine oxalate levels may remain high for some period of time even in patients undergoing simultaneous kidney and liver transplantation. High urinary oxalate concentration promotes precipitation of calcium oxalate crystals first in the distal tubules, leading to graft dysfunction. This secondarily results in deposition in the parenchyma of the graft, leading to allograft failure. This risk is obviously increased further in those with primary nonfunction of the graft. Transplant protocols designed to minimize complications of recurrent disease include early posttransplant urinary dilution through aggressive fluid administration, and early and frequent dialysis in those with DGF.

Isolated kidney transplantation is not recommended in primary hyperoxaluria as the disease invariably recurs and leads to graft loss. The disease is sometimes diagnosed for the first time after kidney transplantation when oxalate deposits are detected on biopsy in patients with graft dysfunction. Whenever possible, these patients should be referred to specialized centres for liver transplantation. In the immediate postoperative phase, extra dialysis sessions may be necessary.
Specific measures designed to increase oxalate excretion and reduce production help in minimization of recurrence, and should be in place for all patients during the first months or years after kidney or combined liver–kidney transplantation [293]. These include maintenance of urine output >3.0–3.5 L/day, and the use of alkaline citrate, neutral phosphate and magnesium oxide. Severe dietary oxalate restriction is of limited benefit [294], but intake of nutrients extremely rich in oxalate and ascorbic acid, a precursor of oxalate, should be discouraged. Pharmacological doses of pyridoxine may reduce hyperoxaluria in some patients, especially in those with a Gly170Arg mutation [295]. Pyridoxine responsiveness can be assessed by observation of >30% reduction in urinary oxalate excretion to 10 mg/kg/day dose of pyridoxine [296] in patient’s sibs with less severe kidney disease if it was not done at the predialysis stage. Urinary alkalinisation with citrate reduces the risk of urinary calcium oxalate supersaturation by forming a soluble complex with calcium, which reduces the likelihood of binding and precipitation with other substances, such as oxalate [297]. The dosage is 0.1–0.15 g/kg body weight of a sodium or sodium/potassium citrate preparation. The adequacy of therapy and patient compliance can be verified by measuring urinary pH and citrate excretion. Orthophosphate (20–60 mg/day), along with pyridoxine, has also been shown to reduce urinary calcium oxalate crystallization [298].

**Fabry disease**

Fabry disease is a rare, X-linked inherited disease characterized by a deficiency of alpha-galactosidase A (alpha-Gal- A), resulting in progressive systemic accumulation of glycosphingolipids. Transplantation is the treatment of choice for most patients with CKD stage 5 due to Fabry disease [299]. Although patients with Fabry disease may have histological recurrence of the disease in the allograft, how often recurrence causes graft failure is not clear. In a re- cent US Organ Procurement and Transplantation Network registry study, 197 KTRs with Fabry disease had 74% 5- year graft survival, compared to 64% in KTRs with other kidney diseases [300]. Two formulations of recombinant human alpha-Gal A are currently available: agalsidase alpha (Replagal, Transkaryotic Therapies, Cambridge, MA) and agalsidase (Fabrazyme, Genzyme, Cambridge, MA). In non-KTRs, treatment with recombinant human alpha-Gal A has been shown to reduce the rate of decline in kidney function. However, it is unclear whether treatment improves graft survival, or reduces other complications of Fabry disease in KTRs. Treatment appears to be safe in KTRs [301, 302]; however it is very expensive, and whether it is cost-effective for improving KTR outcomes is not known.

**SUMMARY OF EVIDENCE**

The risk of recurrence is particularly increased in FSGS, immunoglobulin A (IgA) nephropathy, membranoproliferative glomerulonephritis (MPGN), hemolyticuremic syndrome (HUS), oxalosis and Fabry’s disease and, to a lesser extent, with lupus nephritis, anti-glomerular basement membrane (GBM) disease, vasculitis and diabetes. FSGS, HUS and oxalosis may recur in the first few days to weeks after transplantation, whereas the timing is variable in the others.

The modality of screening for some of these diseases, may vary from the usual post-transplant monitoring if timely detection is not achieved by the routine post-transplant monitoring strategies (refer to Table 8 adapted from KDIGO). There is also weak evidence that disease-specific treatment may be beneficial for some recurrent diseases.

Idiopathic FSGS recurs in 20–50% of KTRs (up to 80% if it has recurred in a prior kidney transplant). Recurrent disease presents with proteinuria, which is usually heavy. About 80% of cases recur in the first 4 weeks. There have been no RCTs of therapy for recurrent idiopathic
FSGS. However, uncontrolled series suggest that patients with recurrent idiopathic FSGS may have a substantial reduction in urine protein excretion after plasma exchange.

Recurrent IgA nephropathy is common after transplantation, affecting from 13% to 53% according to differences in duration of follow-up and biopsy policy. There is no proven therapy for preventing recurrent IgA nephropathy.

The histological recurrence rate in idiopathic type I MPGN is 20–30% and exceeds 80% in type 2 disease. There are no controlled therapy trials however, case reports indicate response to long-term cyclophosphamide, plasmapheresis and CsA.

Hemolytic-uremic syndrome recurs commonly in adults and in children in whom the original kidney disease was D− variant. Recurrence occurs in about 80–100% of patients with factor H or factor I mutation, while patients with a mutation in membrane cofactor protein do not have recurrence. Treatment strategies have included plasmapheresis, intravenous immunoglobulin and rituximab. There is no evidence that avoidance of CNI, mTORi and OKT3 (that may themselves cause thrombotic microangiopathy) will reduce the recurrence risk.

Recurrent rates of antineutrophil cytoplasmic antibody (ANCA) associated vasculitis and anti-GBM disease are low if the disease is quiescent at the time of transplant. More recent studies report recurrence rates of 7%, most of which occur beyond the first posttransplant year with no direct or indirect impact on allograft function. Kidney ANCA-associated vasculitis generally responds well to high-dose prednisolone and cyclophosphamide. Treatment of clinically active anti-GBM disease may include pulse steroids, cyclophosphamide and plasma exchange.

The enzyme defect in primary hyperoxaluria is not corrected by isolated kidney transplantation, and oxalate overproduction persists leading to recurrence of calcium oxalate deposits in over 90% of transplanted kidneys, and eventually leading to graft loss, unless the enzyme is replaced through a simultaneous liver transplant. Isolated kidney transplantation is not recommended in primary hyperoxaluria as the disease invariably recurs and leads to graft loss. Specific measures designed to increase oxalate excretion and reduce production help in minimization of recurrence, and should be in place for all patients during the first months or years after kidney or combined liver–kidney transplantation.

Although patients with Fabry disease may have histological recurrence of the disease in the allograft, how often recurrence causes graft failure is not clear. In non-KTRs, treatment with recombinant human alpha- Gal A has been shown to reduce the rate of decline in kidney function. However, it is unclear whether treatment improves graft survival, or reduces other complications of Fabry disease in KTRs.

**WHAT DO THE OTHER GUIDELINES SAY?**

**Kidney Disease Outcomes Quality Initiative:** None

**UK Renal Association:** None

**Canadian Society of Nephrology:** None

**European Best Practice Guidelines:** [303]

A. In the case of recurrent focal and segmental glomerulosclerosis (FSGS), aggressive treatment with high-dose cyclosporine in children, ACE inhibitors and/or Angiotensin II antagonists, plasma exchange or immunoadsorption may result in remission in some patients. (Evidence level B)
B. In the case of recurrent membranous nephropathy (MN), there is no specific treatment. However, control of risk factors, such as hypertension, heavy proteinuria and hyperlipidaemia, and prevention of thrombotic complications are recommended. (Evidence level C)

C. In the case of recurrent membranoproliferative glomerulonephritis (MPGN), there is no specific treatment. However, control of risk factors, such as hypertension, heavy proteinuria and hyperlipidaemia, and prevention of thrombotic complications are recommended. (Evidence level C)

D. In the case of recurrent IgA glomerulonephritis, use of additional steroids is not yet a validated treatment. The control of risk factors, such as hypertension, heavy proteinuria and hyperlipidaemia, is recommended. (Evidence level C)

E. In the rare case of recurrent anti-glomerular basement membrane (anti-GBM) glomerulonephritis with reappearance of anti-GBM antibodies, it is recommended to initiate plasma exchange and to treat with appropriate immunosuppressive agents (e.g. cyclophosphamide). (Evidence level C)

International Guidelines: None

SUGGESTIONS FOR FUTURE RESEARCH

Given the rarity of recurrent disease, two strategies may be considered: (1) ANZDATA registry based studies of impact of recurrence on graft survival have been undertaken and should be periodically updated to inform practice and to provide prognostic information for patients and carers; (2) multi-centre, prospective studies of specific interventions should be considered for specific entities, such as impact of induction and/or maintenance immunosuppression on recurrence rates and consequences of recurrence

CONFLICT OF INTEREST

S Chadban has a Level II conflict of interest according to the conflict of interest statement set down by KHA-CARI.

S Kotwal has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by KHA-CARI.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Screening (in addition to serum creatinine)</th>
<th>Minimum screening frequency</th>
<th>Diagnostic tests (in addition to kidney biopsy)</th>
<th>Potential Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSGS</td>
<td>Proteinuria</td>
<td>Weekly for 4 weeks, every 3 months for 1 year, then annually.</td>
<td>Dipstick, ACR, PCR</td>
<td>Plasmapheresis</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>Proteinuria, microhaematuria</td>
<td></td>
<td>Dipstick or ACR plus urine microscopy</td>
<td></td>
</tr>
<tr>
<td>MPGN</td>
<td>Proteinuria, microhaematuria</td>
<td>Every 3 months in the first year and then annually.</td>
<td>Serum complement levels</td>
<td></td>
</tr>
<tr>
<td>Anti-GBM disease</td>
<td>Proteinuria, microhaematuria</td>
<td></td>
<td>Anti-GBM antibodies</td>
<td>Plasmapheresis</td>
</tr>
<tr>
<td>Pauci-immune vasculitis</td>
<td>Proteinuria, microhaematuria</td>
<td></td>
<td>Anti-GBM antibodies</td>
<td>Plasmapheresis</td>
</tr>
<tr>
<td>HUS</td>
<td>Proteinuria, platelet count</td>
<td>During episodes of graft dysfunction</td>
<td>Platelet count, peripheral blood smear, LDH</td>
<td>Cyclophosphamide and corticosteroids</td>
</tr>
</tbody>
</table>
Topic 11. Preventing, Detecting, and Treating Non-Adherence

Author: Martin Howell, Steven Chadban

GUIDELINES

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)

UNGRADED SUGGESTIONS FOR CLINICAL CARE

None

IMPLEMENTATION AND AUDIT

Given the difficulty in detecting non-adherence and the recommendation to review and address non-adherence on an individual basis, a meaningful audit is difficult. Nonetheless individual units should consider a review of the incidence of suspected non-adherence against patient and graft outcomes.

BACKGROUND

The 2009 NCCPC Medicine Adherence guidelines [304] define adherence as ‘the extent to which the patient’s behaviour matches agreed recommendations from the prescriber’. In addition these guidelines state that ‘adherence should be considered as being multidimensional and should not be seen as the patient’s problem, rather it represents a limitation in the delivery of healthcare often due to a failure to fully agree the prescription in the first place or to identify and provide the support that patients need later on.’

In relation to immunosuppressant medication, nonadherence may take the form of:

- Missing entire doses as a one off, irregularly or for extended periods;
- Adjusting timing of doses for reasons of lifestyle, work commitments etc. occasionally or over extended periods; or
- Adjusting doses to minimise side effects or for personal beliefs for example regarding the efficacy of the medication.

Nonadherence may be either intentional or unintentional. The majority of incidences of nonadherence are likely to be unintentional (e.g. as a result of forgetfulness, lack of planning for holidays etc.). However, individual decisions to change the timing of doses to suit lifestyle or work commitments or to change the doses as a consequence of side effects are examples of intentional nonadherence. There may be a reluctance to discuss intentional nonadherence with medical carers.
Adherence has been estimated using a variety of direct and indirect methods including self report, clinician report, prescription refills, electronic monitoring devices and blood monitoring. Self report is the most commonly used method for assessment of nonadherence and, while likely to underestimate the extent of nonadherence compared to that measured using electronic monitoring devices, provides a moderately reliable basis for assessing the extent of nonadherence.

The definition of what level of deviation from prescribed medication constitutes a nonadherent patient in studies of immunosuppressant medication is highly varied and there is no level of deviation that can currently be considered acceptable. Most studies identify adherence as a dichotomous outcome (i.e. adherent/nonadherent), however terms such as partial adherence have also been used. Some electronic monitoring devices allow estimation of deviation from prescribed timing of doses and have been used to calculate a continuous adherence score.

KDIGO have suggested an alternate definition of nonadherence as “deviation from the prescribed medication regimen sufficient to adversely influence the regimen’s intended effect”. Whilst nonadherence has been associated with adverse clinical outcomes, it is not currently possible to correlate outcomes with the extent of non adherence (e.g. minor deviations versus missing doses for extended periods). Furthermore, there is currently no evidence to suggest that nonadherence is more likely to occur with specific immunosuppressants for example as suggested by KDIGO for regimens that include steroids.

SEARCH STRATEGY

The search strategy was an update of that used by KDIGO (refer to Table 32 in the Appendix of the KDIGO guideline).

Databases searched: Medline, Central, Cochrane database of systematic reviews.

Date of searches: November 2010.

ADEQUACY OF KDIGO SEARCH STRATEGY

In general the KDIGO search strategy is considered appropriate for identifying evidence related to the prevention, detection and treatment of nonadherence, however, the update conducted by KHA-CARI has identified a number of additional studies not included in the KDIGO guidelines.

APPLICABILITY OF KDIGO RECOMMENDATIONS AND SUGGESTIONS

The KDIGO guidelines have provided two ungraded points for consideration rather than evidenced based suggestions or recommendations. KHA-CARI consider that on the basis of the evidence, the two ungraded points are not supported and have provided two graded suggestions that reflect the evidence to date. Current evidence would suggest that at risk individuals cannot be reliably identified and that the possible occurrence and reason for nonadherence should be considered on an individual basis, recognising that most nonadherence is unintentional. Furthermore there is no evidence that identifies any measures (education, prevention or treatment) that have been shown to minimise nonadherence to immunosuppressants. Rather the evidence points to nonadherence being multi factorial and furthermore, non-patient related factors may be as important or more important as patient related factors.

OVERVIEW OF THE EVIDENCE

The following provides an overview of the evidence as identified by the update searches conducted by KHA-CARI as part of the adaptation process.
The KHA-CARI Guidelines – Caring for Australasians with Renal Impairment

The KHA-CARI search identified systematic reviews and meta-analyses as well as observational studies additional to those identified by KDIGO relevant to prevention, detection and treatment of nonadherence and these are described below. These studies provide additional evidence in relation to the extent of nonadherence, clinical consequences, risk factors and interventions to address nonadherence.

**Summary of Studies not included in KDIGO**

### Systematic Reviews – Clinical Consequences, Risk Factors and Barriers

Dew et al (2009) [305] conducted a systematic review and meta analysis of the annual event rate and risk factors of non adherence in paediatric solid organ transplant patients. The review identified a total of 61 studies of which 30 (1,313 patients) included kidney transplant patients of which 18 addressed immunosuppression non adherence. Non adherence outcomes included multiple components of medical adherence in addition to immunosuppression medication (e.g. clinic appointments, diet, smoking etc.). The overall non adherence rate to immunosuppression was 12.5 cases per 100 persons per year (95% CI 7.6 to 18.2) with no significant difference between organ type. The assessment of risk factors for non adherence was limited by the small number of studies that examined potential risk factors. As a consequence immunosuppression, clinic appointments, test and global non adherence were combined. Whilst a number of significant correlations were found, the effect sizes were generally small to modest with the most robust associations found for lower family cohesion/support and greater child psychological distress. As a consequence Dew et al (2009) considered that other factors such as provider-related and healthcare systems-related factors may prove to be stronger risk factors for nonadherence in both adults and children [305].

The objective of the systematic review and meta analysis by Dew et al (2007) [306] was to estimate the annual event rate of nonadherence to multiple components of medical regimens for adult solid organ transplant recipients to determine whether nonadherence was associated with patient psychosocial risk factors. The review identified a total of 147 studies of which 72 (20,787 patients) included kidney transplant recipients and of these 32 addressed immunosuppression nonadherence. The average rate of immunosuppressant medication nonadherence amongst the kidney transplant recipient studies was 35.6 cases per 100 ppy (95% CI 31.1 to 40.1). Among organ types the highest nonadherence rate occurred for kidney transplants and the lowest for heart transplants. The nonadherence rates for immunosuppressant medication in studies conducted in North America was significantly higher than studies conducted elsewhere (predominantly Europe). Of the psychosocial variables assessed only non-white ethnicity, poorer social support and poorer perceived health were significantly associated with greater immunosuppressant nonadherence, however the effect sizes were small. The authors suggest this indicates that there should be a shift of focus to provider-related and system-related factors as determinants of nonadherence [306].

### Studies – Clinical Consequences, Risk Factors and Barriers

Gordon (2009) et al [307] undertook a combined qualitative/quantitative study examining barriers to adherence amongst 82 recently transplanted kidney transplant recipients (approximately 2 months since transplant). The rate of self report non adherence was low (i.e. 12%), however a large number of barriers to taking medication were identified and described under the following four categories:

(i) Personal schedules, routines and health.
(ii) Characteristics of medicines.
(iii) Medication dosage and scheduling.
(iv) Access to medicines and pharmacies.

Strategies to aid in taking immunosuppressive medication included:

(i) Establishing systems of visual clues.
In a third of the patients, these strategies were reported as resulting in medication taking becoming automatic. This study points to the value of simple strategies and a focus on simplifying medication dosage etc.

Chisolm-Burns et al (2008) [308] undertook a retrospective assessment of non modifiable characteristics associated with adherence to cyclosporine and tacrolimus medication amongst 70 North American (US) adult kidney transplant recipients based on pharmacy prescription refill records. The mean adherence rate calculated from 3 consecutive monthly refills was 87.1% (±7.55%) i.e. a mean nonadherence rate of 12.9%. The final stepwise regression analysis showed that age and time post transplant were significant (p<0.05) predictors of adherence to either tacrolimus or cyclosporine medication accounting for approximately 23% of the variance. Secondary analysis showed that if a patient’s age was ≥60 years the rate of adherence decreased by approximately 8% and by approximately 5% if the transplant was received > 4 years ago.

A 5 year prospective cohort study of 356 Swiss adult stable (>1 year post transplant) kidney transplant recipients investigating the prevalence, risk factors and clinical consequences to non adherence to immunosuppressants was reported by Denhaerynck et al (2007) [309] and Denhaerynck et al (2009) [310]. Adherence to medication was measured electronically in 249 patients and by self report, blood assay and health care worker reports in all patients. No statistically significant relationship was found between graft loss and non adherence as measured by any of the 4 techniques. Similarly there was no statistically significant association between adherence at the start of the study and changes in serum creatinine levels. It should be noted however that adherence levels were high with a mean adherence of 98.4% (range 47 to 110%) of prescribed doses being taken when measured electronically. Significant associations were measured between electronically monitored dosing adherence and gender (females more likely to be adherent); day of the week (highest level of non adherence to dosing occurred on Saturday and Sunday); using a pill box (higher adherence) and self reported adherence. Nonetheless, self report was demonstrated as being useful in identifying non-adherent patients. The sensitivity of self report nonadherence compared to electronically monitored was 26%.

A cross sectional anonymous questionnaire survey of 507 Japanese adult kidney transplant recipients attending outpatient clinics was reported by Ichimaru et al (2008) [311]. The questionnaire addressed missing of multiple doses (i.e. morning and evening) on a daily as well as weekly frequency of non adherence to prescribed dosing time. In relation to twice daily medication (i.e. CNI’s) the adherence rate was significantly lower for the evening dose compared to the morning with 87.5% in the morning and 76.7% in the evening responding “take the drug every day”. The most commonly selected reason for non adherence in the evening was “could not take the drug for personal reason” and “missed a dose”. The frequency of adherence to both morning and afternoon dosing showed an association with time after transplant with higher non adherence occurring in those with more than 5 years after transplant.

A prospective cohort study of azathioprine adherence amongst 137 North American (US) adult kidney transplant recipients followed for up to 4 years using electronic monitoring devices was conducted by Nevins et al (2009) [312]. Cohorts defined by the relative adherence rates in the first 6 months after transplantation, maintained differences throughout the 4 year follow up. There was a trend to increasing non adherence with time with a lower rate of decline in average adherence in the more adherent cohorts. Those patients missing less than 1.5% of the azathioprine doses experienced the smallest number of acute rejections and had the best late allograft outcomes. A pattern of early decline in adherence shortly after discharge was associated with higher rates of acute rejection and graft loss and remained the strongest predictor of clinical outcomes having significantly higher rejection rates and death censored graft losses.
Pinsky et al. [313] conducted a retrospective cohort study of data from the USRDS of first time kidney transplant recipients from 1995 to 2001. Data collection was limited to recipients with maintenance immunosuppression in the first year comprising MMF, azathioprine, cyclosporine or tacrolimus. Compliance to the regimen was assessed using Medicare prescription data to calculate a Medicare possession ratio which is an unobtrusive measure of non adherence. A total of 15,525 transplant recipients met the criteria with 11,199 having compliance measures for the three years of the study, of these 23 % were identified as having overall low compliance and 6.3% having high compliance. Persistently lower compliance was more likely in the 19-24 years age group compared to the 24-44 years group (OR 1.49 95% CI 1.06 to 2.10). Poor and fair compliance was associated with increased risk of allograft loss compared to excellent compliance (HR 1.80 95% CI 1.52 to 2.13; and HR 1.63 95% OR 1.37 to 1.93 respectively).

Russell et al. [314] undertook a prospective cohort study of 50 cognitively intact North American kidney transplant recipients aged 55 years or older. Immunosuppressant medication adherence was monitored for 12 months using an electronic monitoring system with 37 completing the study. Selection criteria included a requirement for a twice daily immunosuppressant regimen. Medication adherence was scored to reflect whether medication was taken within (score 0.5) or outside (score 0.25) a 3 hour window of the prescribed time or not at all (score 0) giving a daily score range from 0 to 1. The median score for the 11 month monitoring period was 0.78 which corresponds to taking one of the twice daily immunosuppressants on time and one late or early. No significant associations were found with age, gender, ethnicity or time since transplant. Cluster analysis indicated three patterns of non adherence describing the majority of the participants (70%) as follows: 27% generally took the twice-daily medication on time evening and morning; 19% were frequently on time with the morning dose but late with the evening dose; 16 % often on time or early with the morning dose but late or missed the evening dose; and 8% were commonly late with the morning dose and early with the evening dose. There were no significant associations with graft rejection episodes or graft loss or with depression, social support, side effects or quality of life measures. Overall the study suggests that the evening dose as being the most problematic.

Schmid-Mohler et al. (2010) [315] report a cross sectional study of 114 adult Swiss kidney transplant recipients 1 to 5 years after their first kidney transplant. The study applied behavioural theory to identify predictors of non adherence. Self reported non adherence was determined using a four item instrument measuring non adherence to immunosuppressants in the past four weeks assessing omission of both single and successive doses, timing non adherence and dose reductions. Non adherence was also assessed using two collateral reports (one from a renal nurse and one from a doctor). Measures of patients norms, attitudes, self-efficacy and barriers were collected using validated instruments. A total of 24% of the participants were classified as being non adherent, 26% as partially adherent and 50% as adherent, while 15.8% reported missing at least one dose in the last month. In relation to intention to take immunosuppressants, 73% stated their intention was to always take them as prescribed. Intention was found to play only a minor role in non adherence. That is non adherence is predominantly unintentional or accidental. Only one attitude “Not all immunosuppressants are necessary to prevent rejection” was a predictor of lower adherence. The study supports the concept that forgetfulness and interruption of daily routines are the most powerful predictors for non adherence in kidney transplant recipients.

Systematic Reviews of Interventions

De Blesser et al. (2009) [316] completed a systematic review of the efficacy of adherence-enhancing interventions in adult and paediatric transplant patients. Study inclusion criteria were interventions aimed at enhancing immunosuppressive medication-adherence in organ transplantation, including a measureable medication-adherence outcome. Interventions were classified according to the following 3 groups: 1. Educational/cognitive; 2. Counseling/behavioural; 3. Psychologic/affective. A total of 12 studies were identified from a search completed up until August 2008, seven of which focused on kidney transplants and four were paediatric patients with
only five studies RCTs. Most used pill counts and blood concentrations with 3 using electronic monitoring. Varying operational definitions of non adherence were used.

The majority of the studies showed major short comings related to methodology and content. Furthermore there was a lack of definition of non adherence with only two studies using clinically meaningful cut-offs and both showing that minor deviations are sufficient to be associated with late acute rejection or graft loss which contrasts to other chronic conditions such as hypertension where partial adherence may remain beneficial. Other issues identified were a lack of baseline assessment of adherence, lack of control groups, lack of definition of the usual care before intervention, and small size and lack of power of the studies.

Of the 12 studies, only 5 had statistically significant results and no single intervention proved superior at increasing medication adherence. Only two studies were built upon theoretical models explaining behavioural change. Most studies focussed on improving only one aspect such as knowledge or cost of medication despite systematic reviews and meta analyses in other chronic illness populations indicating that interventions should be multidimensional. Overall this review indicates the evidence relating to interventions aimed at increasing adherence to immunosuppressant medication to be of poor quality, inadequate and inconclusive.

A systematic review and meta-analysis of RCTs of interventions designed to improve medication adherence among older adults was undertaken by Conn (2009) [317]. The study inclusion criteria included a mean age of at least 60 years, published between 1970 and 2007 with interventions specifically designed to increase medication adherence with 5 or more participants. A total of 33 studies (11,827 participants) were identified. The overall mean effect size for medication adherence was 0.33 (95% CI 0.22 to 0.45) with significant heterogeneity. Interventions were more effective in populations taking multiple medications compared to those taking only one or two medications. Behavioural interventions (e.g. prompts, dose modification, special pill containers) were more effective than cognitive based interventions. Similarly, interventions that include behaviour based strategies appear to be more effective than education. In summary the review suggests that interventions amongst older adults should focus on behavioural strategies for example by simplifying doses, employing specific packaging and using prompts.

A Cochrane review of unconfounded RCTs of interventions to change adherence with prescribed medications for medical disorders in which both adherence and treatment effects were measured has been undertaken by Haynes et al (2009) [318]. Whilst the review is not specific to either organ transplant recipients or immunosuppressants, it nonetheless represents a comprehensive review relevant to medication adherence. Studies with positive findings were required to have at least 6 months follow up from the time of patient entry, however shorter follow up was allowed for negative trials. In total the review (up to January 2007) identified 78 trials testing 93 unconfounded interventions. Studies relating to transplant were all excluded on the basis of the inclusion criteria. The included studies covered a narrow range of disorders – predominantly hypertension, schizophrenia, and COPD. Only 9 studies concerned short term conditions. Interventions were diverse and complex, and were grouped into 21 areas. Less than half of the interventions tested were associated with statistically significant increases in medication adherence and only 29 reported statistically significant improvement in treatment outcomes. Most studies were small with a high possibility of false-negative error.

There is a lack of theoretical underpinning and consistent features for most adherence interventions even though adherence problems are a constant feature of all medical regimens. Almost all of the interventions were complex, including combinations or more convenient care, information, reminders, self-monitoring, reinforcement, counselling, family therapy, psychological therapy, crisis intervention, manual telephone follow-up and supportive care. Even the most effective interventions did not lead to a large improvements in adherence and treatment outcomes. Haynes et al (2009) [318] conclude that there is little evidence that medical adherence can be improved consistently, within resources usually available in clinical settings, and that this will predictably lead to improvements in treatment outcomes. Also many of the interventions for long
term medications were exceedingly complex and labour intensive and difficult to see how they could be implemented in a non research environment. The review point to simple strategies such as dose adjustment as being most beneficial, however, it is not known whether this translates to improved clinical outcomes. Haynes et al (2009) [318] note in particular that “If there is a common thread to these at all, it is more frequent interaction with patients with attention to adherence.” However the complex strategies are not very effective despite the amount of effort and resources they can consume. There is little evidence that low adherence is disease or regimen-specific, with the possible exception of psychiatric disorders.

Studies – Interventions

No additional studies were found in relation to kidney transplant recipients.

SUMMARY OF EVIDENCE

In summary the available evidence indicate the following:

- The extent of nonadherence is highly variable ranging from <10% to >30%. This variation reflects the heterogeneity of the populations assessed, the varying definition of nonadherence and the varying methods used to measure nonadherence.

- The clinical consequences of nonadherence is subject to the same issues as assessing the extent of nonadherence. Whilst some studies show nonadherence to be a significant predictor of graft loss, other studies have shown no relationship. Given the variability in assessment of nonadherence, it is not possible to identify the degree of nonadherence that would be unacceptable, nonetheless some studies suggest an increased risk of graft loss with relatively minor deviations. In general the available evidence is dominated by retrospective or cross sectional studies and where there have been prospective studies these are generally of short duration. This limits the ability to identify nonadherence as a casual factor in long term graft loss.

- Risk factors – as for clinical consequences, identification of risk factors for nonadherence is largely reliant on retrospective and cross sectional studies and it is only possible to identify risk factors at a broad level with minimal ability to identify individual risk factors. Indeed the systematic reviews by Dew et al (2009) and Dew et al (2007) conclude that the focus for risk factors should be on provider related and health care system related issues given the absence of clear patient related factors. In summary, nonadherence is more likely in adolescents and the elderly and to increase with time after transplantation.

- Interventions - systematic reviews/meta-analyses provide little evidence that medical adherence can be improved consistently, within resources usually available in clinical settings, and that this will predictably lead to improvements in treatment outcomes. The most effective approaches have been those that address behavioural issues using simple personalised strategies.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: None
UK Renal Association: None

Canadian Society of Nephrology: None

European Best Practice Guidelines: [319]

A. The detection of non-compliers should be a permanent concern of the transplant team (doctors, nurses and others). (Evidence level C)

B. Because non-compliance is associated with late graft dysfunction and graft loss, it is important to reduce the proportion of non-compliers by implementing specific educational programmes addressing this problem and the importance of immunosuppressive medications. (Evidence level C)

C. Non-compliance starts during the first year and may increase thereafter. Therefore, the specific educational programme should be repeated and adapted to the need of the transplant recipient, with delivery of few but clear messages. (Evidence level C)

International Guidelines: None

SUGGESTIONS FOR FUTURE RESEARCH

1. Studies to identify features which predict which kidney transplant recipients are at highest risk of non-adherence.

2. Patient-focussed studies to determine which behaviours and beliefs contribute to adherence versus non-adherence

CONFLICT OF INTEREST

S Chadban has a Level II conflict of interest according to the conflict of interest statement set down by KHA-CARI.

M Howell has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by KHA-CARI.
**Topic 12. Vaccination**

Author: Helen Pilmore and Paul Manley

<table>
<thead>
<tr>
<th>GUIDELINES</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. We recommend giving all kidney transplant recipients approved, inactivated vaccines according to recommended schedules for the general population. (1D)</td>
</tr>
<tr>
<td>b. We recommend pre-transplant vaccination with varicella for potential transplant recipients who are non-immune. (1D)</td>
</tr>
<tr>
<td>c. We suggest hepatitis B virus (HBV) vaccination (ideally prior to transplantation) and measurement to confirm development of protective antibody to hepatitis B surface antigen (HBsAb) titres 6 – 12 weeks after completing the vaccination series. (2D)</td>
</tr>
<tr>
<td>i. We suggest annual HBsAb titres thereafter (2D); and</td>
</tr>
<tr>
<td>ii. We suggest revaccination if the antibody titres fall below 10mIU/ml. (2D)</td>
</tr>
<tr>
<td>d. We suggest avoiding live vaccines in kidney transplant recipients. (2C)</td>
</tr>
<tr>
<td>e. We suggest avoiding vaccination, except influenza vaccination, in the first 6 months after kidney transplantation. (2C)</td>
</tr>
<tr>
<td>f. 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)</td>
</tr>
</tbody>
</table>

**UNGRADED SUGGESTIONS FOR CLINICAL CARE**

None

**IMPLEMENTATION AND AUDIT**

A unit level audit of vaccination status of kidney transplant recipients should be considered.

**BACKGROUND**

The following background has been based on that provided in the KDIGO guideline and edited to reflect review conducted for the adaptation.

The risk of infections are increased in patients who are immunosuppressed. Recommended vaccinations are those approved and suggested by Australian and New Zealand Government and are documented in local vaccination policies.

This guideline outlines recommendations according to local risks of infection and vaccination policies.

- Little or no harm has been described with the use of licensed, inactivated vaccines in KTRs.
- Most vaccines produce an antibody response, albeit diminished, in immunocompromised individuals, including KTRs.
- The potential benefits outweigh the harm of immunization with inactivated vaccines in KTRs.
- Serious infection can result from live vaccines in immunocompromised patients, including KTRs.
- In the absence of adequate safety data to the contrary, it should be assumed that the harm of live vaccines outweigh their benefits in KTRs.
- Vaccinations are most likely to be effective when immunosuppression is lowest, when KTRs are receiving the lowest possible doses of immunosuppressive medication.
- Influenza vaccination needs to be provided on an annual basis in advance of the onset of the annual influenza season. Even while KTRs are receiving high levels of immunosuppression, the benefits of timely vaccination outweigh the risks of delaying vaccination.
- Human Papillomavirus infection causing cervical cancer is an important risk for transplant recipients and in the absence of other evidence HPV vaccination should be encouraged.

SEARCH STRATEGY

The search strategy was an update of that used by KDIGO (refer to Table 32 in the Appendix of the KDIGO guideline).

**Databases searched:** Medline, Central, Cochrane database of systematic reviews.

**Date of searches:** November 2010.

ADEQUACY OF KDIGO SEARCH STRATEGY

Search strategy was generally considered adequate. Additional searches have been added to relevant to HPV vaccination.

APPLICABILITY OF KDIGO RECOMMENDATIONS AND SUGGESTIONS

Most of the KDIGO recommendations are applicable to ANZ. Minor changes have been made addressing local schedules and HPV vaccination.

OVERVIEW OF THE EVIDENCE

*The following provides an overview of the evidence as identified in the KDIGO guidelines and the update searches conducted by KHA-CARI as part of the adaptation process.*

**Inactivated Vaccines**

Both Australia and New Zealand have national vaccination schedules. Recently vaccination for Human Papillomavirus has been available in both countries for females age 12 – 26.

Although only a limited number of studies evaluating the safety and efficacy of inactivated vaccines have been performed in solid-organ transplant recipients in general, and in KTRs in particular, available evidence suggests that inactivated vaccines are safe. There is no evidence that vaccinations lead to an increased risk of rejection.

Unfortunately, data on the efficacy of individual inactivated vaccines are limited. In general, existing data suggest that the response to vaccination in KTRs is diminished compared to immunization prior to transplantation. Accordingly, the optimal timing for immunizing KTRs is prior to transplantation. However, this is not always possible and, in some cases, repeated vaccinations after transplantation are necessary. A number of studies have been performed in organ transplant recipients that demonstrate immunogenicity of several inactivated vaccines after solid-organ transplantation. Influenza vaccination is among the most thoroughly evaluated in organ transplant recipients. Although response to influenza vaccination may vary among KTRs and from year to year, 30–100% of immunized KTRs will achieve protective haemagglutination-inhibiting serum antibody titres. Of note, the efficacy of influenza vaccination appears to be superior in paediatric compared to adult KTRs [320]. Data are also available supporting the use of the 23-valent polysaccharide pneumococcal vaccine for KTRs >2 years of age. In contrast, hepatitis B vaccine has significantly diminished immunogenicity in organ transplant recipients compared to organ transplant candidates [321]. Specific data regarding the immunogenicity of most of the remaining inactivated vaccinations are not available for solid-organ transplant recipients. Although data are lacking, most experts agree that the benefits outweigh the risks of immunization with inactivated vaccines [322].

The risk of cervical cancer is high after renal transplantation [323]. Vaccination for HPV has become available for all females aged 12 – 18 in Australia and New Zealand with a catch up programme for patients up until the age of 26. There is no current data on the efficacy of the HPV vaccination in the setting of renal transplantation however as the risk of cervical cancer is high, we believe that vaccination according to the national schedules should be encouraged.

There are sufficient data in KTRs indicating that the risk of vaccination with inactivated vaccines is minimal. The risk of infection, on the other hand, is higher in KTRs than in the general population. Therefore, vaccination with inactivated vaccines is warranted according to the national schedules.

**Live vaccines**

The currently licensed live vaccines use either attenuated viral strains that have been manipulated to reduce their virulence while attempting to maintain their immunogenicity, or, as in the case of Bacillus Calmette-Guérin (BCG), substitute a related bacterium that is thought to be less pathogenic, but still able to provide cross-reacting immunity to the target pathogen. While data are limited, significant concern exists for the use of live viral vaccines in immunocompromised patients. To date, only a limited number of studies have evaluated the use of live viral vaccines in organ transplant recipients [324]. The high incidence of infections in KTRs is ample cause for concern that live vaccinations may cause infection in KTRs. While limited published experience is available describing the use of some live viral vaccines in organ transplant recipients [324], the limited number and small sample sizes included in these studies raise concerns about both the safety and efficacy of these vaccines in KTRs. Accordingly, most experts agree that, in general, the risks outweigh the potential benefits of using live vaccines in KTRs [325].

A number of live vaccinations licensed for use in the general population are contraindicated in KTRs (Table 9).

Being a live-vaccine, varicella vaccination is contraindicated post-transplant. Primary infection post-transplant carries a high morbidity and mortality rate. Thus, vaccination is recommended pre-transplant for those potential allograft recipients who are non-immune (see section 13.4).
Vaccination Timing

The reduced antibody response to different vaccines in KTRs is most likely due to immunosuppressive medication. Although there are no RCTs, it is reasonable to assume that giving vaccines when the amount of immunosuppressive medications patients are receiving is lowest is most likely to maximize the response to the vaccine [322]

Immunosuppressive medication amounts are usually highest in the first few months after transplantation, when the risk of acute rejection is also the greatest. Sometime during the first 6–12 months, the amount of immunosuppressive medication is generally reduced to the lowest maintenance levels, if there is no acute rejection, and this is likely to be the best time for vaccination. This time of minimal maintenance immunosuppressive medication, and optimal time for vaccination, may be different in patients treated for acute rejection.

Influenza infection is a potentially important cause of morbidity and mortality in KTRs. The use of influenza vaccination has been demonstrated to be safe and generally effective in organ transplant recipients, including KTRs [326, 327]. In particular, it is worth noting that there is no proven association between the use of influenza vaccination in organ transplant recipients and the development of rejection. Accordingly, annual use of influenza vaccination is recommended for both KTRs and their household contacts. Because acquisition of influenza will occur during annual seasonal epidemics, it may not be possible to delay giving this vaccine until the patient is out far enough from transplant or on low levels of immunosuppression. Given that this is an inactivated viral vaccine, the major consequence of using this too early is that the immunization will not work. Given the potential benefit of providing the vaccine, it is recommended to give this vaccine prior to the onset of the annual influenza season, as long as the recipient is at least 1-month posttransplant. This timing is chosen as the vaccine is least likely to work during the first month after transplant, especially if the KTR has received induction therapy.

Hepatitis B revaccination

The need for hepatitis B vaccination booster is controversial and practice varies. Patients with impaired immune function tend to have lower peak HBsAb levels compared to immunocompetent individuals. There are few data on durability of immunologic memory in immunocompromised hosts. However, there have been reports of clinically significant infection due to hepatitis B virus (HBV) in previously immunized dialysis patients in whom production of HBsAb was no longer measurable [328].

Serial measurements of HBsAb levels to inform the use of a booster dose of hepatitis B vaccine has been recommended for dialysis patients by the US Advisory Committee on Immunization Practices [328]. In addition, the European Consensus Group on Hepatitis B immunity has expanded this recommendation to include patients with impaired immune function [329]. Immunological memory wanes faster in immunocompromised renal transplant recipients. A level above 10 mIU/mL is generally taken to be protective, but transplant recipients with titres less than 100 mIU/mL tend to lose them rapidly. The potential for low anti-HBs levels to mask significant infection (indicated by hepatitis B surface antigen (HBsAg)) and the rapid decline led a European Consensus Group to suggest booster vaccination at titres below 100 mIU/mL. Although there is no clear evidence to support this recommendation, given the relative risk–benefit ratio of hepatitis B vaccine, it seems prudent to assess annually the need for a booster dose of this immunization.
Additional Vaccines

Kidney transplant recipients may be at increased risk for vaccine-preventable pathogens through residence or travel to endemic areas, or due to inadvertent exposure. Recommendations for individuals traveling to certain geographic locations frequently include receipt of one or more immunizations against these pathogens. These recommendations would logically apply to KTRs, as long as the recommended vaccinations are inactivated, for example salmonella typhi Vi polysaccharide vaccine, or meningococcal vaccine. Consultation with an infectious disease specialist, travel clinic or public health official is recommended to clarify appropriate use of vaccinations for scenarios where travel or exposure may warrant use of these additional vaccinations.

Although efficacy data may not be available in KTRs, inactivated vaccines are generally safe. In contrast, some immunizations typically recommended for travellers are available only as live-attenuated vaccines. The use of these vaccines cannot be recommended, as neither safety nor efficacy data are available in this patient population.

SUMMARY OF EVIDENCE

There are sufficient data in KTRs indicating that the risk of vaccination with inactivated vaccines is minimal. The risk of infection, on the other hand, is higher in KTRs than in the general population. Therefore, vaccination with inactivated vaccines is warranted according to the national schedules. There is no evidence that vaccinations lead to an increased risk of rejection.

There is no data on the efficacy of HPV vaccination in kidney transplant recipients, however as the risk of cervical cancer is high, vaccination according to the national schedule is suggested.

In general, existing data suggest that the response to vaccination in KTRs is diminished compared to immunization prior to transplantation. Accordingly, the optimal timing for immunizing KTRs is prior to transplantation. However, this is not always possible and, in some cases, repeated vaccinations after transplantation are necessary.

To date, only a limited number of studies have evaluated the use of live viral vaccines in organ transplant recipients. The limited number and small sample sizes included in these studies raise concerns about both the safety and efficacy of live vaccines in KTRs. As a consequence the current consensus opinion is that the risks outweigh the potential benefits of using live vaccines in KTRs. However, vaccination with varicella, which is contraindicated post-transplant being a live-vaccine, is recommended prior to transplantation due to the high morbidity and mortality of primary varicella infection post-transplant.

In the absence of RCTs, it is reasonable to assume that giving vaccines when the amount of immunosuppressive medications patients are receiving is lowest is most likely to maximize the response to the vaccine. The use of influenza vaccination has been demonstrated to be safe and generally effective in organ transplant recipients, including KTRs. Because acquisition of influenza will occur during annual seasonal epidemics, it may not be possible to delay giving this vaccine until the patient is out far enough from transplant or on low levels of immunosuppression.

There are few data on durability of immunologic memory in immunocompromised hosts and the need for HBV vaccination booster in kidney transplant recipients is controversial. However, given the relative risk–benefit ratio of hepatitis B vaccine, it seems prudent to assess annually the need for a booster dose of this immunization.

Recommendations for individuals travelling to certain geographic locations frequently include receipt of one or more immunizations against a range of pathogens. These recommendations would logically apply to KTRs, as long as the recommended vaccinations are inactivated.
the absence of safety and efficacy data the use of live attenuated vaccines cannot be recommended.

WHAT DO THE OTHER GUIDELINES SAY? [CHECK]

Kidney Disease Outcomes Quality Initiative: None

UK Renal Association: None

Canadian Society of Nephrology: None

European Best Practice Guidelines: None

International Guidelines: None

SUGGESTIONS FOR FUTURE RESEARCH

1. Research on the efficacy of HPV vaccination.

2. Research on efficacy of influenza vaccination with different immunosuppressive regimens.

CONFLICT OF INTEREST

H Pilmore has a Level II conflict of interest according to the conflict of interest statement set down by KHA-CARI.

P Manley has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by KHA-CARI.

Table 9. Contraindicated vaccinations after transplantation (KDIGO Table 13)

<table>
<thead>
<tr>
<th>Vaccinations</th>
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<tbody>
<tr>
<td>Varicella zoster</td>
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<tr>
<td>BCG</td>
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<tr>
<td>Smallpox</td>
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<tr>
<td>Intranasal influenza</td>
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<tr>
<td>Live oral typhoid Ty21a and other newer vaccines</td>
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<tr>
<td>Measles (except during an outbreak)</td>
</tr>
<tr>
<td>Mumps</td>
</tr>
<tr>
<td>Rubella</td>
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<tr>
<td>Oral polio</td>
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<tr>
<td>Live Japanese B encephalitis vaccine</td>
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<tr>
<td>Yellow fever</td>
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<tr>
<td>BCG, Bacillus Calmette-Guérin</td>
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