CST/CSN COMMENTARY

Canadian Society of Transplantation and Canadian Society of Nephrology Commentary on the 2009 KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients

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INTRODUCTION

KDIGO (Kidney Disease: Improving Global Outcomes) is an international initiative to develop and implement clinical practice guidelines. In November 2009, KDIGO published its guideline for the management of kidney transplant recipients.[1] This guideline was extremely comprehensive and spanned more than 150 pages. The Canadian Society of Transplantation (CST) and the Canadian Society of Nephrology (CSN) congratulate KDIGO, members of the guideline work group, and the evidence review team for producing such a thorough and exhaustive document. This guideline will be of great value to health professionals involved in the management of kidney transplant recipients.

KDIGO is an international organization and thus its guidelines have international scope. To have practical applicability, the various recommendations and suggestions will need adaptation to suit individual countries or jurisdictions. As such, the CST and CSN formed a joint work group to review the KDIGO guideline and make suggestions about its applicability and relevance in a Canadian context. This commentary was written acknowledging the unique nature of our transplant population with its ethnic diversity, our health care system that has variable funding and access to different medications and services, and our geography, which has transplant care focused in larger urban areas, requiring many patients to travel considerable distances. Our commentary provides supplementary information regarding the care of kidney transplant recipients in a Canadian context and should be viewed in conjunction with the full KDIGO document when making clinical decisions.

REVIEW AND APPROVAL PROCESS FOR THIS COMMENTARY

The development of this commentary was a joint effort between the CST and CSN. A Chair was selected and approved by both societies to direct and oversee the project. Individual members were selected based on their clinical expertise and interest in the guidelines process. Teleconferences took place in the later part of 2009 and early 2010 to determine areas of focus for our commentary. Specific sections were drafted initially by one of the coauthors based on a detailed review of the particular KDIGO chapter

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0272-6386/10/5602-0003$36.00/0

doi:10.1053/j.ajkd.2010.05.004

Box 1. KDIGO Recommendations Concerning Induction Therapy

1.1: We recommend starting a combination of immunosuppressive medications before, or at the time of, kidney transplantation (1A). *[CST/CSN workgroup concurs]*

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

1.2.1: We recommend that an IL2-RA be the first line induction therapy (1B). *[CST/CSN workgroup concurs]*

1.2.2: We suggest using a lymphocyte-depleting agent, rather than an IL2-RA, for KTRs at high immunologic risk (2B). *[CST/CSN workgroup concurs]*

Abbreviations: IL2-RA, interleukin 2 receptor antagonist; KTR, kidney transplant recipient.

supplemented by additional literature searching if needed. Because this was a commentary, no specific voting occurred, but rather consensus among coauthors was achieved on the points we raised. The commentary was reviewed by the CST executive and sent for peer review by the CSN guidelines committee. Reviews and comments were noted and the document was revised as appropriate. The final manuscript was reviewed and approved by executives of the CST and CSN.

REVIEW OF KDIGO RECOMMENDATIONS

Commentary on Chapter 1: Induction Therapy

Chapter 1 has 3 level-1 recommendations (Box 1). Although our work group generally agreed with these recommendations, we believed that the statement about induction with a biologic agent deserved further comment. Randomized trials and meta-analyses support the use of biologic induction agents for most patient populations; however, not all patients receive these agents in practice. Patients who receive a zero-HLA–mismatched donor organ have the best overall graft survival and may not receive additional benefit from induction therapy. Similarly, patients who are Epstein-Barr virus (EBV) seronegative and receive a seropositive donor kidney are at increased risk of posttransplant lymphoproliferative disorder (PTLD), and induction immunosuppression may further increase the risk of this complication. Avoiding induction agents in this clinical situation should be considered unless the patient is also at high immunologic risk for acute rejection.

Implications Within Canadian Health Care

1. The CST/CSN work group agrees with the KDIGO guideline suggesting that induction therapy be used in kidney transplantation. However, there may be certain clinical situations (eg, zero-HLA–mismatched donor) in which induction therapy may not be beneficial and should be individualized to the patient's clinical situation.

Commentary on Chapter 2: Initial Maintenance Immunosuppressive Medications

Our work group concurred with the 2 level-1 recommendations in this chapter (Box 2). The other recommendations were graded level 2 and deserved further comment. Statement 2.2 states that "We suggest that tacrolimus be the first-line CNI used." Although the term "suggest" (level 2 grade) is used rather than "recommend," we believe that this statement remains too strong based on recent evidence. The meta-analysis[2] referred to does not include the 2 randomized trials that used currently recommended (in this guideline) immunosuppressive protocols (ie, induction with a biologic agent and mycophenolic acid–based antiproliferative therapy).[3,4] Neither of these trials showed a significant difference in the rate of acute rejection or graft survival in

Box 2. KDIGO Recommendations Concerning Initial Maintenance Immunosuppressive Medications

2.1: We recommend using a combination of immunosuppressive medications as maintenance therapy including a CNI and an antiproliferative agent, with or without corticosteroids (1B). *[CST/CSN workgroup concurs]*

2.2: We suggest that tacrolimus be the first-line CNI used (2A). *[see comments]*

2.2.1: We suggest that tacrolimus or CsA be started before or at the time of transplantation, rather than delayed until the onset of graft function. (2D tacrolimus; 2B CsA) *[see comments]*

2.3: We suggest that mycophenolate be the first-line antiproliferative agent. (2B) *[CST/CSN workgroup concurs]*

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

2.5: We recommend that if mTORi are used, they should not be started until graft function is established and surgical wounds are healed. (1B). *[CST/CSN workgroup concurs]*

Abbreviations: CNI, calcineurin inhibitor; CsA, cyclosporine; mTORi, mammalian target of rapamycin inhibitor.

patients treated with tacrolimus versus cyclosporine microemulsion.[3,4] The Symphony Study also is used in the KDIGO guideline to support the superiority of tacrolimus therapy.[5] However, in this study, induction was not used in the cyclosporine arm, but was used in the tacrolimus arm. In the cyclosporine group, standard deviations for trough levels are at or less than the limit of the target range, whereas in tacrolimus-treated patients, trough levels in all cases were significantly greater than the lower target range.[5]

Whereas all medications have side effects, new-onset diabetes is particularly important because unlike other complications, such as hyperlipidemia or hypertension, the consequences of diabetes are not eliminated by treatment and its impact on graft survival is similar to that of acute rejection.[6] The meta-analysis of tacrolimus versus cyclosporine trials, as well as the DIRECT (Diabetes Incidence after REnal transplantation: Neoral C2 monitoring versus Tacrolimus) study, which was specifically designed to test the difference in glucose intolerance and measured blood glucose levels, suggests that tacrolimus is more diabetogenic.[2,4] It also is noteworthy that in the Symphony Study,[5] the incidence of new-onset diabetes was highest in the tacrolimus group, even at relatively low target levels.

With regard to statement 2.2.1, the work group did not believe it was supported by the data. As discussed in the KDIGO guideline, results with early as opposed to delayed introduction of cyclosporine therapy were not different. Although the investigators mention that there may be theoretical reasons to obtain early therapeutic calcineurin-inhibitor (CNI) blood levels, no study has shown a definitive benefit. Accordingly, in the context of patients in the hospital who have received biologic induction agents (as recommended), we believe there is no reason to suggest early or delayed CNI introduction based on the available evidence.

Our work group acknowledges that few areas in transplantation have been more controversial than the issue of steroid therapy withdrawal, which is suggested in statement 2.4. There have been several large randomized controlled trials addressing early steroid therapy withdrawal. The earlier studies that did not show a difference in acute rejection used induction therapy in only the steroid-withdrawal arm, but not in the control group. Thus, the acute rejection rate in the control arm may have been increased because of the lack of induction therapy.[7,8] Two recent studies[9,10] that used induction therapy in all arms showed a significant increase in acute rejection in the early-steroid-withdrawal or avoidance groups. One study used tacrolimus and the other used cyclosporine; thus, the increase in acute rejection was independent of the CNI used. Although graft and patient survival were not significantly different in the 5-year blinded study,[10] there was an increased incidence of chronic allograft nephropathy in the steroid-withdrawal arm, raising the possibility of worse long-term outcomes. Furthermore, neither study showed a substantial benefit of steroid therapy withdrawal, such as a decrease in new-onset diabetes.[9,10] It is clear that the accumulated data for steroid therapy withdrawal and the addition of more effective immunosuppression have caused most centers to use much lower dosages of steroids than previously. This may have minimized the benefits of steroid therapy withdrawal on steroid-related adverse events in these recent trials.

A recent meta-analysis published after release of the KDIGO guideline has shown that steroid therapy avoidance or withdrawal was associated with an increased risk of acute rejection (relative risk [RR], 1.56 [95% confidence interval (CI), 1.31-1.87]) compared with maintenance steroid therapy.[11] Despite this effect, there was no significant difference in patient or graft survival.[11] The analysis also showed that steroid avoidance or withdrawal was associated with a decrease in hypertension (RR, 0.90 [95% CI, 0.85-0.94]), new-onset diabetes (RR, 0.64 [95% CI, 0.50-0.83]), and hypercholesterolemia (RR, 0.76 [95% CI, 0.67-0.87]).[11] It is not clear why decreases in these important cardiovascular risk factors did not translate into improved patient survival, but it may be due to the relatively short follow-up of the individual trials included in the analysis. Deciphering the effect of a decrease in cardiac risk factors from steroid therapy avoidance or withdrawal likely will require analysis of registry data with long follow-up.

Implications Within Canadian Health Care

1. Across Canada, there is variation in practice with respect to the initial CNI used. In general, most centers use tacrolimus as the standard CNI. However, many programs will use

cyclosporine in patients at increased risk of new-onset diabetes (eg, hepatitis C positive, obese, etc). The CST/CSN work group believes that no individual CNI is preferred and the decision for use should be individualized based on immunologic risk, use of concomitant immunosuppression (eg, induction and mycophenolic acid), and diabetes risk, as well as the consequences of other adverse effects (eg, hirsutism, alopecia, etc).

2. Canadian practice with regard to steroid use differs significantly from the United States. Most Canadian adult kidney transplant programs use steroids both perioperatively and during the long term. Although a few Canadian programs routinely use steroid-free regimens, most will use this in only select cases (eg, patients with osteoporosis, very high risk of diabetes, etc). The work group could not achieve complete consensus on this topic, but agreed that supporting statement 2.4 regarding the discontinuation of steroid therapy early post-transplant would not be consistent with most Canadian transplant programs. Until further long-term data emerge, the CST/CSN work group believes that for most patients, steroid therapy should be continued long term. However, in low-immunologic-risk patients who receive induction therapy, early steroid therapy elimination may be considered on an individual case basis.

Commentary on Chapter 3: Long-term Maintenance Immunosuppressive Medications

The work group noted that the 3 statements in this chapter (Box 3) were suggestions made based on moderate or low quality of evidence and that the first deserved further comment. Although we agree that the lowest possible dose of CNI be used long term, additional information should be added to the rationale. The most frequent pathologic state seen in patients with long-term graft deterioration is interstitial fibrosis/tubular atrophy (IFTA) not otherwise specified, which may be caused by multiple factors, including both immunologic and nonimmunologic. Although there is no doubt that CNIs can be nephrotoxic, the strategy of decreasing CNI dosage implies that CNIs have a major role in the development of IFTA. However, recent information suggests that other factors may have an important role in the genesis of IFTA.[12,13] Thus, caution is necessary when suggesting a long-term decrease in CNI dosage, especially in patients at higher immunologic risk.

Box 3. KDIGO Recommendations Concerning Long-term Maintenance Immunosuppressive Medications

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

3.2: We suggest that CNIs be continued rather than withdrawn. (2B) *[CST/CSN workgroup concurs]*

3.2: If prednisone is being used beyond the first week after transplantation, we suggest prednisone be continued rather than withdrawn. (2C) *[CST/CSN workgroup concurs]*

Abbreviation: CNI, calcineurin inhibitor.

Implications Within Canadian Health Care

1. Variation in long-term immunosuppression combinations and dosing exists within Canada. We recommend that decisions about long-term immunosuppression therapy be individualized based on the risk of rejection and the risk of immunosuppression-related complications. Although no data currently are available, we suggest close follow-up of patients as immunosuppression is changed or dose is reduced.

Commentary on Chapter 4: Strategies to Reduce Drug Costs

The statements in this section (Box 4) generally were based on weak evidence or not graded because they were common sense. In Canada, the cost of currently licensed immunosuppression is not an issue because provincial or regional programs are in place to assist patients without private insurance. However, it is not clear if new immunosuppressive agents that may be more costly will be covered as they currently are today. All medications in Canada, including generic compounds, need approval from Health Canada; therefore, statement 4.2 is not relevant to our practice. At the present time, generic compounds do not have a major share in the Canadian immunosuppression market. However, we agree that physicians and patients must be made aware of any medication substitutions so that appropriate monitoring can occur.

Box 4. KDIGO Recommendations Concerning Strategies to Reduce Drug Costs

4.1: If drug costs block access to transplantation, a strategy to minimize drug costs is appropriate, even if use of inferior drugs is necessary to obtain the improved survival and quality of life benefits of transplantation compared with dialysis (Not Graded). *[CST/CSN workgroup concurs]*

4.1.1: We suggest strategies that may reduce drug costs include: limiting use of a biologic agent for induction to patients who are high-risk for acute rejection (2C); using ketoconazole to minimize CNI dose (2D); using a nondihydropyridine CCB to minimize CNI dose (2C); using azathioprine rather than mycophenolate (2B); using adequately tested bioequivalent generic drugs (2C); using prednisone long-term (2C). *[CST/CSN workgroup concurs]*

4.2: Do not use generic compounds that have not been certified by an independent regulatory agency to meet each of the following criteria when compared to the reference compound (Not Graded): contains the same active ingredient; is identical in strength, dosage form, and route of administration; has the same use indications; is bioequivalent in appropriate bioavailability studies; meets the same batch requirements for identity, strength, purity and quality; is manufactured under strict standards. *[see comments]*

4.3: It is important that the patient, and the clinician responsible for the patient's care, be made aware of any change in a prescribed immunosuppressive drug, including a change to a generic drug (Not Graded). *[CST/CSN workgroup concurs]*

4.4: After switching to a generic medication that is monitored using blood levels, obtain levels and adjust the dose as often as necessary until a stable therapeutic target is achieved (Not Graded). *[CST/CSN workgroup concurs]*

Abbreviations: CCB, calcium channel blocker; CNI, calcineurin inhibitor.

Implications Within Canadian Health Care

1. In Canada, the cost of immunosuppression is covered by a mix of private insurance and government funding that differs somewhat between provinces. However, in general, the cost of immunosuppression is not a barrier to transplantation. The CST/CSN work group believes that this current level of support must be maintained by the provincial/regional governments so that medication cost does not prevent Canadians from pursuing transplantation. In addition, new immunosuppressive agents that are proved with high-quality data to improve patient outcomes and are cost-effective also should be funded.

Commentary on Chapter 5: Monitoring Immunosuppressive Medications

The work group noted that one recommendation (the need to measure CNI blood levels) was graded level 1, but the remainder of this section was graded level 2 based on low- to very low-quality data (Box 5). The work group agrees with the data presented in this section of the KDIGO guideline. Importantly, there are no high-quality trials to define optimal target levels for cyclosporine, tacrolimus, mycophenolic acid, or mammalian target of rapamycon (mTOR) inhibitors, as well as timing of levels for cyclosporine microemulsion (ie, C0 [2-hour trough level] vs C2 [2-hour postdose level]), that have been shown to prevent acute rejection while minimizing toxicity. Nonetheless, it is current Canadian practice to monitor these drug levels and adjust dosages based on locally acceptable targets. Although not evidence based, this strategy generally leads to less drug being used over time because most programs decrease target levels when patients are out of the early posttransplant phase. There have been several randomized trials examining mycophenolic acid monitoring posttransplantation.[14-16] However, results and potential benefits to the patient have been conflicting. Although the KDIGO guideline only "suggests" mycophenolic acid monitoring, the CST/CSN work group

Box 5. KDIGO Recommendations Concerning Monitoring Immunosuppressive Medications

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

5.1.1: We suggest monitoring CsA using 12-h trough (C0), 2-h post-dose (C2) or abbreviated AUC (2D). *[CST/CSN workgroup concurs]*

5.1.2: We suggest monitoring tacrolimus using 12-h trough (C0). (2C) *[CST/CSN workgroup concurs]*

5.2: We suggest monitoring MMF levels. (2D) *[see comments]*

5.3: We suggest monitoring mTORi levels. (2C) *[CST/CSN workgroup concurs]*

Abbreviations: AUC, area under the concentration-time curve; CNI, calcineurin inhibitor; CsA, cyclosporine; MMF, mycophenolate mofetil; mTORi, mammalian target of rapamycin inhibitor.

believes that routine monitoring for low-risk stable patients will only add cost with minimal benefit to the patient.

Implications Within Canadian Health Care

1. Most Canadian transplant programs do not monitor mycophenolic acid levels as part of routine clinical care. Although not based on specific data, several Canadian programs monitor mycophenolic acid levels in certain situations, such as when the dosage of another immunosuppressive agent is being decreased or withdrawn because of toxicity or a patient has experienced a recent acute rejection, to ensure adequate overall immunosuppression. Future trials of mycophenolic acid monitoring need to show some benefit along with fewer side effects and improved cost-effectiveness for this strategy to be adopted as standard practice.

Commentary on Chapter 6: Treatment of Acute Rejection

The work group noted that all recommendations in this chapter (Box 6) were based on low or very low quality of evidence. The lack of quality data is remarkable given that acute rejection has been the predominant complication that patients and physicians have focused on since transplantation began. The statement regarding treatment of subclinical and borderline rejection deserves further comment. Early work by Rush et al[17] showed improved graft function when subclinical rejection, diagnosed using protocol biopsy, was treated. However, this was in the era of cyclosporine and azathioprine.[17] These findings were confirmed by another single-center study in which most recipients were on cyclosporine and azathioprine immunosuppression therapy.[18] A Canadian multicenter randomized trial failed to show a benefit of protocol biopsies (followed by treatment of subclinical rejection if present) for adult patients on tacrolimus and mycophenolate-based immunosuppression therapy.[19] It should be noted that most studies included patients at relatively low immunologic risk and the utility of protocol biopsies (and treatment of subclinical rejection) in high-risk populations is not known (see commentary on chapter 9 for further discussion). Borderline acute rejection is a separate issue. If found on a biopsy performed for cause (eg, allograft dysfunction), it would seem reasonable to treat as acute rejection. In centers in which protocol biopsies are performed, treatment of borderline rejection would depend on the clinical situation. For example, treatment may be indicated if borderline rejection was found on a protocol biopsy specimen of someone who had experienced a previous acute rejection episode or received pretransplant desensitization.

The optimal treatment of acute antibody-mediated rejection is not established. The potential therapies listed in the KDIGO guideline generally are used in combination with optimization of baseline immunosuppression. The diagnosis of antibody-mediated rejection includes the presence of circulating donor-specific antibody (DSA).[20] Therefore, many programs test for HLA antibodies either at the time of a biopsy performed for cause or if the biopsy specimen shows features consistent with antibody-mediated rejection.

Box 6. KDIGO Recommendations Concerning Treatment of Acute Rejection

6.1: We recommend biopsy before treating acute rejection, unless the biopsy will substantially delay treatment (1C) *[CST/CSN workgroup concurs]*

6.2: We suggest treating subclinical and borderline acute rejection. (2D) *[see comments]*

6.3: We recommend corticosteroids for the initial treatment of acute cellular rejection. (1D) *[CST/CSN workgroup concurs]*

6.3.1: We suggest adding or restoring maintenance prednisone in patients not on steroids who have a rejection episode. (2D) *[CST/CSN workgroup concurs]*

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

6.4: We suggest treating antibody-mediated acute rejection with one or more of the following alternatives, with or without corticosteroids (2C): plasma exchange; intravenous immunoglobulin; anti-CD20 antibody; lymphocyte-depleting antibody. *[see comments]*

6.5: For patients who have a rejection episode, we suggest adding mycophenolate if the patient is not receiving mycophenolate or azathioprine, or switching azathioprine to mycophenolate. (2D) *[CST/CSN workgroup concurs]*

Implications Within Canadian Health Care

1. Lymphocyte-depleting antibodies are used routinely to treat steroid-resistant acute rejection in Canada. OKT3 is no longer available in Canada and therefore the CST/CSN work group

recommends that polyclonal antithymocyte agents be the drug of choice.

2. The CST/CSN work group agrees that the optimal therapy for antibody-mediated acute rejection is not known. Although there are recent Canadian guidelines for the use of intravenous (IV) immunoglobulin (IVIG) in solid-organ transplants,[21] the evidence base for these guidelines is low. Access to the various therapies, such as rituximab, plasma exchange, and IVIG, vary from province to province and even between centers within the same province. Until high-quality data are published showing significant benefit of one therapeutic strategy, it seems reasonable for Canadian centers to use the agent or combination of agents that is readily available and approved in their jurisdiction.

3. For patients at high immunologic risk who may undergo routine protocol biopsies (see commentary on chapter 9), treatment of subclinical and borderline rejection may be indicated and will need to be based on clinical judgment given the lack of evidence in this population.

Commentary on Chapter 7: Treatment of Chronic Allograft Injury

Aside from the recommendation to perform biopsy on patients with decreasing function, the statements in this section are based on low or very low quality of evidence (Box 7). The second statement suggests dose reduction, withdrawal, or replacement of the CNI in the presence of CNI toxicity. Data supporting this suggestion are weak. One randomized trial (Creeping Creatinine Study) showed improvement in short-term glomerular filtration rates (GFRs) when the CNI was replaced with mycophenolate mofetil.[22] However, there are no controlled data supporting dose reduction or outright CNI therapy withdrawal in this setting. The third statement suggests that the CNI be replaced with an mTOR inhibitor for GFR >40 mL/min and minimal proteinuria. This recommendation was based on a subgroup analysis of CONVERT (Sirolimus Renal Conversion Trial), which failed to show an overall benefit in recipients who were switched from a CNI to an mTOR inhibitor.[23] In this trial, patients were not entered specifically because they had chronic allograft injury; it is unknown whether patients with this biopsy finding, preserved function, and minimal proteinuria will benefit from a switch to an mTOR inhibitor. This issue needs confirmation in a prospective trial before it can be recommended in routine clinical practice. In the CONCEPT trial, patients were randomly assigned at 12 weeks to remain on cyclosporine therapy or be converted to sirolimus therapy.[24] The sirolimus-treated groups showed improvement in GFR, but quantification of interstitial fibrosis on 1-year biopsy specimens was not different between groups.[24] Although there are data showing that short-term GFR is increased in those successfully converted to sirolimus therapy, there is no evidence that this GFR improvement leads to better long-term outcomes.

Box 7. KDIGO Recommendations Concerning Treatment of Chronic Allograft Injury

7.1: We recommend kidney allograft biopsy for all patients with declining kidney function of unclear cause, to detect potentially reversible causes. (1C) *[CST/CSN workgroup concurs]*

7.2: For patients with CAI and histological evidence of CNI toxicity, we suggest reducing, withdrawing, or replacing the CNI. (2C) *[see comments]*

7.2.1: For patients with CAI, eGFR >40 mL/min/1.73 m^2, and urine total protein excretion <500 mg/g creatinine (or equivalent proteinuria by other measures), we suggest replacing the CNI with a mTORi (2D). *[see comments]*

Abbreviations: CAI, chronic allograft injury; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; mTORi, mammalian target of rapamycin inhibitor.

Implications Within Canadian Health Care

1. The evidence base for the management of chronic allograft injury unfortunately is very weak. Most Canadian patients who have undergone transplant in the past decade are already receiving mycophenolate and thus the Creeping Creatinine trial would apply to very few of our patients. The CST/CSN work group did not believe the data were sufficient to suggest replacing the CNI with sirolimus therapy for patients with chronic allograft injury, minimal proteinuria, and preserved GFR.

Commentary on Chapter 8: Monitoring Kidney Allograft Function

Except for the recommendation to measure serum creatinine, all statements in this chapter were graded level 2 and based on low or very low quality of evidence (Box 8). None are contro-

Box 8. KDIGO Recommendations Concerning Monitoring Kidney Allograft Function

8.1: We suggest measuring urine volume (2C): every 1-2 hours for at least 24 hours after transplantation (2D); daily until graft function is stable. (2D) *[CST/CSN workgroup concurs]*

8.2: We suggest measuring urine protein excretion, (2C) at least: once in the first month to determine a baseline (2D); every 3 months during the first year (2D); annually, thereafter. (2D) *[CST/CSN workgroup concurs]*

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

8.3.1: We suggest estimating GFR whenever serum creatinine is measured, (2D) using: one of several formulas validated for adults (2C); or the Schwartz formula for children and adolescents. (2C) *[CST/CSN workgroup concurs]*

8.4: We suggest including a kidney allograft ultrasound examination as part of the assessment of kidney allograft dysfunction. (2C) *[CST/CSN workgroup concurs]*

Abbreviation: GFR, glomerular filtration rate.

versial and all are representative of standard clinical practice in Canada.

Commentary on Chapter 9: Kidney Allograft Biopsy

Although statements in this chapter are based on low or very low quality of evidence (Box 9), they represent monitoring practices used at most Canadian transplant centers. The issue of protocol biopsies is reviewed in detail in the background section, yet no statement about their use is made in the KDIGO guideline. The CST/CSN work group agrees with the data summary in this section, which generally states that protocol biopsies may not be worthwhile with current immunosuppression given the low rates of subclinical rejection (see commentary on Chapter 6). However, our work group believed that the following populations at increased immunologic risk may benefit from routine protocol biopsies: pediatric patients, those with preformed DSA or receiving blood group ABO-incompatible transplants, and those in minimization or steroid-avoidance protocols.

Pediatric kidney transplant recipients receiving modern immunosuppression continue to experience higher rates of rejection than adults.[25] Recent studies have reported rates of subclinical rejection detected on protocol biopsy ranging from 12%-44% in pediatric recipients despite therapy with basiliximab, CNIs, mycophenolate mofetil, and corticosteroids.[26-28] Although there is a paucity of data, subclinical rejection has been linked to chronic allograft injury in children and treatment may be associated with better preservation of long-term function.[28,29] Patients with DSA at the time of transplant have an increased rate of subclinical antibody-mediated rejection, and this is associated with subsequent chronic allograft injury.[30,31] These patients also may be at higher risk of cell-mediated subclinical rejection, perhaps owing to the presence of accompanying T-cell immunologic memory.[31,32] Similar observations of both antibody- and cell-mediated subclinical rejection, despite increased baseline immunosuppression, have been made in recipients of blood group ABO-incompatible transplants.[33,34] Finally, immunosuppressive drug therapy minimization strategies continue to be tested and data exist that these recipients may be at higher risk of subclinical rejection, although this has not been a universal finding.[35-37]

Implications Within Canadian Health Care

1. Most standard kidney transplant recipients in Canada receiving modern immunosuppression do not need routine protocol biopsies. However, the CST/CSN work group suggests that certain populations at increased immunologic risk (as noted) be considered for protocol biopsy surveil-

Box 9. KDIGO Recommendations Concerning Kidney Allograft Biopsy

9.1: We recommend kidney allograft biopsy when there is a persistent, unexplained increase in serum creatinine. (1C) *[CST/CSN workgroup concurs]*

9.2: We suggest kidney allograft biopsy when serum creatinine has not returned to baseline after treatment of acute rejection. (2D) *[CST/CSN workgroup concurs]*

9.3: We suggest kidney allograft biopsy every 7-10 days during delayed function. (2C) *[CST/CSN workgroup concurs]*

9.4: We suggest kidney allograft biopsy if expected kidney function is not achieved within the first 1-2 months after transplantation. (2D) *[CST/CSN workgroup concurs]*

9.5: We suggest kidney allograft biopsy when there is: new onset of proteinuria (2C); unexplained proteinuria ≥3.0 g/g creatinine or ≥3.0 g per 24 hours. (2C) *[CST/CSN workgroup concurs]*

lance given the increased risk of subclinical rejection. This decision needs to incorporate patient preferences, local availability of biopsy services, and the additional costs incurred. For pediatrics, this recommendation will be consistent with current practice because more than half the Canadian pediatric transplant programs perform protocol biopsies as part of standard care.

Commentary on Chapter 10: Recurrent Kidney Disease

There were no recommendations in this chapter based on high-quality evidence (Box 10). The work group noted that the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers will decrease protein excretion in patients with recurrent glomerulonephritis, but it is not known whether these agents will improve their long-term prognosis. The work group also noted that idiopathic membranous nephropathy, an important cause of recurrent disease, was not specifically mentioned in the guidelines. Results of intensifying maintenance immunosuppression and/or using cytotoxic agents, such as chlorambucil or cyclophosphamide, to treat recurrent membranous nephropathy generally have been disappointing. More recently, rituximab has emerged as a potentially promising therapy.[38] A recent study suggested that complete or partial remission can be achieved in most patients.[39] A single dose of rituximab with subsequent CD19 or CD20 monitoring to determine response has been proposed as an alternate strategy to maintain efficacy while decreasing both toxicity and cost.[40] These promising preliminary reports need to be strengthened with randomized trials.

Commentary on Chapter 11: Preventing, Detecting and Treating Nonadherence

The guidelines in this chapter (Box 11) are not graded and represent common sense suggestions. The work group did not believe that further comment was warranted.

Commentary on Chapter 12: Vaccination

There were 2 level-1 recommendations, with the remainder being level-2 recommendations in this section (Box 12). The work group believed that 2 recommendations deserved further comment. The recommendation (graded 1D in the KDIGO guideline) to provide approved inactivated vaccines to all kidney transplant recipients according to recommended schedules for the general population seemed reasonable. The exception to this recommendation was hepatitis

Box 10. KDIGO Recommendations Concerning Recurrent Kidney Disease

10.1: We suggest screening KTRs with primary kidney disease caused by FSGS for proteinuria (2C) at least: daily for 1 week (2D); weekly for 4 weeks (2D); every 3 months, for the first year (2D); every year, thereafter. (2D) *[CST/CSN workgroup concurs]*

10.2: We suggest screening KTRs with potentially treatable recurrence of primary kidney disease from IgA nephropathy, MPGN, anti-GBM disease, or ANCA-associated vasculitis for microhematuria, (2C) at least: once in the first month to determine a baseline (2D); every 3 months during the first year (2D); annually, thereafter. (2D) *[CST/CSN workgroup concurs]*

10.3: During episodes of graft dysfunction in patients with primary HUS, we suggest screening for thrombotic microangiopathy (e.g. with platelet count, peripheral smear for blood cell morphology, plasma haptoglobin, and serum lactate dehydrogenase). (2D) *[CST/CSN workgroup concurs]*

10.4: When screening suggests possible treatable recurrent disease, we suggest obtaining an allograft biopsy. (2C) *[CST/CSN workgroup concurs]*

10.5: Treatment of recurrent kidney disease:

10.5.1: We suggest plasma exchange if a biopsy shows minimal change disease or FSGS in those with primary FSGS as their primary kidney disease. (2D) *[CST/CSN workgroup concurs]*

10.5.2: We suggest high-dose corticosteroids and cyclophosphamide in patients with recurrent ANCA-associated vasculitis or anti-GBM disease. (2D) *[CST/CSN workgroup concurs]*

10.5.3: We suggest using an ACE-I or an ARB for patients with recurrent glomerulonephritis and proteinuria. (2C) *[see comments]*

10.5.4: For KTRs with primary hyperoxaluria, we suggest appropriate measures to prevent oxalate deposition until plasma and urine oxalate levels are normal (2C), including: pyridoxine (2C); high calcium and low oxalate diet (2C); increased oral fluid intake to enhance urinary dilution of oxalate (2C); potassium or sodium citrate to alkalinize the urine (2C); orthophosphate (2C); magnesium oxide (2C); intensive hemodialysis to remove oxalate. (2C) *[CST/CSN workgroup concurs]*

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ANCA, antineutrophil cytoplasmic antibody; ARB, angiotensin II receptor blocker; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; HUS, hemolytic uremic syndrome; IgA, immunoglobulin A; KTR, kidney transplant recipient; MPGN, membranoproliferative glomerulonephritis.

Box 11. KDIGO Recommendations Concerning Preventing, Detecting, and Treating Nonadherence

11.1: Consider providing all KTRs and family members with education, prevention, and treatment measures to minimize nonadherence to immunosuppressive medications. (Not Graded) *[CST/CSN workgroup concurs]*

11.2: Consider providing KTRs at increased risk for nonadherence with increased levels of screening for nonadherence. (Not Graded) *[CST/CSN workgroup concurs]*

Abbreviation: KTR, kidney transplant recipient.

B vaccine, for which responsiveness is decreased in patients with end-stage renal disease and kidney transplant recipients. The work group agreed with the suggestion to assess postvaccination titers to document a response and the need for additional booster. However, the suggestion to continue with indefinite annual testing in all transplant recipients in the absence of supportive data seemed excessive and it may be more appropriate to tailor the testing to the risk profile. In addition, it should be noted that the vaccinations mentioned in this first statement are likely to have the best response if given before transplantation.

The work group also agreed with the recommendation to avoid live vaccines in kidney transplant recipients. However, we believed that more emphasis should be placed on the appropriate use of live vaccines before transplantation to avoid risks in the immunocompromised host later on. For example, in the pediatric population, there are good data to indicate that in seronegative patients, varicella-zoster virus vaccine before transplantation can prevent disseminated disease after transplantation. Although there are limited data, a comment about the human papillomavirus (HPV) vaccine should have been included in the guideline because of the known association between HPV and anogenital warts and cervical neoplasia, both of which are common in the kidney transplant population.

Implications Within Canadian Health Care

1. Although national guidelines exist for vaccination in Canada, health care provision and costs are borne by each individual province, and there are regional differences in payment for certain vaccines. Likewise, regional disparities exist in ready access to travel clinics or specialists in infectious diseases.

2. The CST/CSN work group recommends that seronegative patients be given the varicella-zoster virus vaccine before transplantation.[41] As noted, coverage for this vaccine will vary across the country.

3. The CST/CSN work group suggests that all male and female transplant candidates aged 9-26 years be considered for the HPV vaccine pretransplant (3-dose series; Gardasil; Merck, www.merck.com).[41] This vaccine also should be

Box 12. KDIGO Recommendations Concerning Vaccination

12.1: We recommend giving all KTRs approved, inactivated vaccines, according to recommended schedules for the general population, except for HBV vaccination. (1D) *[CST/CSN workgroup concurs]*

12.1.1: We suggest HBV vaccination (ideally prior to transplantation) and HBsAb titers 6-12 weeks after completing the vaccination series. (2D) *[CST/CSN workgroup concurs]*

12.1.1.1: We suggest annual HBsAb titers.(2D) *[see comments]*

12.1.1.2: We suggest revaccination if the antibody titer falls below 10 mIU/mL. (2D) *[CST/CSN workgroup concurs]*

12.2: We suggest avoiding live vaccines in KTRs. (2C) *[see comments]*

12.3: We suggest avoiding vaccinations, except influenza vaccination, in the first 6 months following kidney transplantation. (2C) *[CST/CSN workgroup concurs]*

12.3.1: We suggest resuming immunizations once patients are receiving minimal maintenance doses of immunosuppressive medications. (2C) *[CST/CSN workgroup concurs]*

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

12.4: We suggest giving the following vaccines to KTRs who, due to age, direct exposure, residence or travel to endemic areas, or other epidemiological risk factors are at increased risk for the specific diseases: rabies, (2D); tick-borne meningoencephalitis, (2D); Japanese B encephalitis—inactivated, (2D); Meningococcus, (2D); Pneumococcus, (2D); Salmonella typhi—inactivated. (2D); *[CST/CSN workgroup concurs]*

12.4.1: Consult an infectious disease specialist, a travel clinic or public health official for guidance on whether specific cases warrant these vaccinations. (Not Graded) *[CST/CSN workgroup concurs]*

Abbreviations: HBsAb, antibody to hepatitis B surface antigen; HBV, hepatitis B virus; KTR, kidney transplant recipient.

considered for kidney transplant recipients ages 9-26 years if they did not receive it pretransplant.[41] As with other vaccines, response may be suboptimal in the transplant population. As noted, coverage for this vaccine will vary across the country.

Commentary on Chapter 13: Viral Disease

BK Polyoma Virus

All recommendations in this section were level 2 and based on very low- or low-quality evidence (Box 13). The work group believed that given the low quality of evidence, suggestions for screening also should have included other potential modalities, such as urine decoy cells or urine nucleic acid testing with supplementary plasma testing as needed. In addition, the recommendation regarding reduction of immunosuppression based on a particular BK virus load is inappropriate given that the BK assays lack standardization and the number of copies that may signal the need for intervention likely varies significantly depending on the assay used.

Implications Within Canadian Health Care

1. Nucleic acid testing for BK virus is not available in many Canadian transplant centers. Until high-quality data regarding optimal screening strategies become available, the CST/CSN work group believes that there are several reasonable options for screening in the first year post-transplant. These may include urine decoy cells, urine nucleic acid testing, plasma nucleic acid testing, or a combination of these modalities based on local availability, cost, and logistical issues regarding follow-up of patients (eg, use of urine decoy cells may be difficult for patients residing far from the transplant centre).

Cytomegalovirus

The section on cytomegalovirus (CMV) has many evidence-based recommendations and sound suggestions based on lesser strength of evidence. In general, the work group supported most of the recommendations and suggestions. However, the recommendation to provide CMV prophylaxis for all seropositive recipients regardless of whether they had received T-cell–depleting antibodies is not based on solid evidence. Seropositive recipients who do not receive T-cell–depleting antibodies are at a much lower risk of CMV viremia, and a pre-emptive strategy using routine laboratory monitoring with treatment of early viremia is an acceptable option. The text of the guideline acknowledges that a study of 3 versus 6 months of prophylaxis in high-risk kidney transplant recipients (donor CMV positive, recipient negative) was underway. This study (IMPACT [Improved Protection Against Cytomegalovirus in Transplant]) has now been published and found a significant decrease in CMV disease (36.8% vs 16.1%) at 1 year in those who received 200 versus 100 days of prophylaxis.[42] The guideline made no reference to prevention of disease recurrence in patients who have been treated for their first episode of CMV disease. Alternatives may include close clinical observation, regular virologic monitoring, or use of a 1- to 3-month course of secondary antiviral prophylaxis.

Implications Within Canadian Health Care

1. The costs of CMV prophylaxis are significant, with a 3-month course cost of Can $4,000-$5,000 per patient. In Canada, those without private insurance get assistance from provincial drug formularies to cover these medication costs. Guidelines for patient and antiviral coverage vary from province to province. The current KDIGO guideline will provide strong rationale for establishing uniform access to CMV prophylaxis across all regions in Canada.
2. The CST/CSN work group believes that CMV-seropositive recipients who do not receive T-cell–depleting agents could be managed with either a prophylaxis or a pre-emptive strategy to prevent CMV disease. The choice of strategy may depend on center-specific immunosuppression protocols, as well as the local availability and cost of each alternative.
3. The CST/CSN work group believes that high-risk patients (donor CMV positive, recipient negative) would benefit from prolongation of valganciclovir prophylaxis to 6 months based on recently available data.[42]

EBV and PTLD

This section had one level-1 recommendation about immunosuppression therapy reduction/withdrawal for those with EBV disease or PTLD, which the work group agreed with. The other

Box 13. KDIGO Recommendations Concerning Viral Diseases

13.1: BK POLYOMA VIRUS

13.1.1: We suggest screening all KTRs for BKV with quantitative plasma NAT (2C) at least: monthly for the first 3-6 months after transplantation (2D); then every 3 months until the end of the first post-transplant year (2D); whenever there is an unexplained rise in serum creatinine (2D); and after treatment for acute rejection. (2D) *[see comments]*

13.1.2: We suggest reducing immunosuppressive medications when BKV plasma NAT is persistently greater than 10 000 copies/mL (10^7 copies/L). (2D) *[see comments]*

13.2: CYTOMEGALOVIRUS

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

13.2.2: In patients with CMV disease, we suggest weekly monitoring of CMV by NAT or pp65 antigenemia. (2D) *[CST/CSN workgroup concurs]*

13.2.3: CMV treatment:

13.2.3.1: We recommend that all patients with serious (including most patients with tissue invasive) CMV disease be treated with intravenous ganciclovir. (1D) *[CST/CSN workgroup concurs]*

13.2.3.2: We recommend that CMV disease in adult KTRs that is not serious (e.g. episodes that are associated with mild clinical symptoms) be treated with either intravenous ganciclovir or oral valganciclovir. (1D) *[CST/CSN workgroup concurs]*

13.2.3.3: We recommend that all CMV disease in pediatric KTRs be treated with intravenous ganciclovir. (1D) *[CST/CSN workgroup concurs]*

13.2.3.4: We suggest continuing therapy until CMV is no longer detectable by plasma NAT or pp65 antigenemia. (2D) *[CST/CSN workgroup concurs]*

13.2.4: We suggest reducing immunosuppressive medication in life-threatening CMV disease, and CMV disease that persists in the face of treatment, until CMV disease has resolved. (2D) *[CST/CSN workgroup concurs]*

13.2.4.1: We suggest monitoring graft function closely during CMV disease. (2D) *[CST/CSN workgroup concurs]*

13.3: EPSTEIN-BARR VIRUS AND POST-TRANSPLANT LYMPHOPROLIFERATIVE DISEASE

13.3.1: We suggest monitoring high-risk (donor EBV seropositive/recipient seronegative) KTRs for EBV by NAT (2C): once in the first week after transplantation (2D); then at least monthly for the first 3-6 months after transplantation (2D); then every 3 months until the end of the first post-transplant year (2D); and additionally after treatment for acute rejection. (2D) *[see comments]*

13.3.2: We suggest that EBV-seronegative patients with an increasing EBV load have immunosuppressive medication reduced. (2D) *[CST/CSN workgroup concurs]*

13.3.3: We recommend that patients with EBV disease, including PTLD, have a reduction or cessation of immunosuppressive medication. (1C) *[CST/CSN workgroup concurs]*

13.4: HERPES SIMPLEX VIRUS 1, 2 AND VARICELLA ZOSTER VIRUS

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

13.4.2: We recommend that KTRs with systemic HSV 1, 2 infection be treated (1B) with intravenous acyclovir and a reduction in immunosuppressive medication. (1D) *[CST/CSN workgroup concurs]*

13.4.2.1: We recommend that intravenous acyclovir continue until the patient has a clinical response, (1B) then switch to an appropriate oral antiviral agent (e.g. acyclovir, valacyclovir, or famciclovir) to complete a total treatment duration of 14-21 days. (2D) *[CST/CSN workgroup concurs]*

13.4.3: We suggest using a prophylactic antiviral agent for KTRs experiencing frequent recurrences of HSV 1, 2 infection. (2D) *[CST/CSN workgroup concurs]*

13.4.4: We recommend that primary VZV infection (chicken pox) in KTRs be treated (1C) with either intravenous or oral acyclovir or valacyclovir; and a temporary reduction in amount of immunosuppressive medication. (2D) *[CST/CSN workgroup concurs]*

13.4.4.1: We recommend that treatment be continued at least until all lesions have scabbed. (1D) *[CST/CSN workgroup concurs]*

13.4.5: We recommend that uncomplicated herpes zoster (shingles) be treated (1B) with oral acyclovir or valacyclovir (1B), at least until all lesions have scabbed. (1D) *[CST/CSN workgroup concurs]*

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

13.4.7: We recommend that prevention of primary varicella zoster be instituted in varicella-susceptible patients after exposure to individuals with active varicella zoster infection (1D): varicella zoster immunoglobulin (or intravenous immunoglobulin) within 96 hours of exposure (1D); if immunoglobulin is not available or more than 96 h have passed, a 7-day course of oral acyclovir begun 7-10 days after varicella exposure. (2D) *[CST/CSN workgroup concurs]*

(Continued)

Box 13 (Cont'd). KDIGO Recommendations Concerning Viral Diseases

13.5: HEPATITIS C VIRUS

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

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

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

13.5.4: Measure ALT in HCV-infected patients monthly for the first 6 months and every 3-6 months, thereafter. Perform imaging annually to look for cirrhosis and hepatocellular carcinoma. (Not Graded) [Based on KDIGO Hepatitis C Recommendation 4.4.1.] *[CST/CSN workgroup concurs]*

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

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

13.5.6: We suggest that patients with HCV-associated glomerulopathy not receive interferon. (2D) [Based on KDIGO Hepatitis C Recommendation 4.4.5.] *[CST/CSN workgroup concurs]*

13.6: HEPATITIS B VIRUS

13.6.1: We suggest that any currently available induction and maintenance immunosuppressive medication can be used in HBV infected KTRs. (2D) *[CST/CSN workgroup concurs]*

13.6.2: We suggest that interferon treatment should generally be avoided in HBV infected KTRs. (2C) *[CST/CSN workgroup concurs]*

13.6.3: We suggest that all HBsAg-positive KTRs receive prophylaxis with tenofovir, entecavir, or lamivudine. (2B) *[CST/CSN workgroup concurs]*

13.6.3.1: Tenofovir or entecavir are preferable to lamivudine, to minimize development of potential drug resistance, unless medication cost requires that lamivudine be used. (Not Graded) *[CST/CSN workgroup concurs]*

13.6.3.2: During therapy with antivirals, measure HBV DNA and ALT levels every 3 months to monitor efficacy and to detect drug resistance. (Not Graded) *[CST/CSN workgroup concurs]*

13.6.4: We suggest treatment with adefovir or tenofovir for KTRs with lamivudine resistance (>5 log10 copies/mL rebound of HBV-DNA). (2D) *[CST/CSN workgroup concurs]*

13.6.5: Screen HBsAg-positive patients with cirrhosis for hepatocellular carcinoma every 12 months with liver ultrasound and alpha feto-protein. (Not Graded) *[CST/CSN workgroup concurs]*

13.6.6: We suggest that patients who are negative for HBsAg and have HBsAb titer <10 mIU/mL receive booster vaccination to raise the titer to ≥ 100 mIU/mL. (2D) *[CST/CSN workgroup concurs]*

13.7: HUMAN IMMUNODEFICIENCY VIRUS

13.7.1: If not already done, screen for HIV infection. (Not Graded) *[see comments]*

13.7.2: To determine antiretroviral therapy, refer HIV-infected KTRs to an HIV specialist, who should pay special attention to drug–drug interactions and appropriate dosing of medications. (Not Graded) *[CST/CSN workgroup concurs]*

Abbreviations: ALT, alanine aminotransferase; BKV, BK polyoma virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBsAb, antibody to hepatitis B surface antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; KTR, kidney transplant recipient; NAT, nucleic acid testing; PTLD, posttransplant lymphoproliferative disease; VZV, varicella-zoster virus.

recommendations were made on lower quality data. The work group agreed that EBV-seronegative recipients who receive seropositive kidneys are at greatest risk of PTLD, but those who receive seronegative organs also are at risk of EBV viremia caused by exogenous infection.[43] Hence, the work group believed that centers could consider extending surveillance to all seronegative recipients regardless of donor serostatus. Although the KDIGO recommendations do not mention antivirals, there are observational data suggesting that prophylaxis with ganciclovir or acyclovir can decrease the risk of PTLD.[44]

Implications Within Canadian Health Care

1. The consequences of PTLD are significant and the population at risk of this complication is small given the rarity of EBV seronegativity in adults and the higher relative numbers, but low absolute numbers, in the pediatric population. Although high-quality data are not available regarding surveillance and prevention of PTLD,

the CST/CSN work group suggests that all seronegative transplant recipients undergo EBV monitoring. These patients also should be considered for antiviral prophylaxis with either valganciclovir or acyclovir until more compelling data to the contrary are forthcoming.

Herpes Simplex, Varicella Zoster, and Hepatitis B and Hepatitis C Viruses

These sections, especially the chapter on the herpesviridae, were based on fairly high-quality data that the work group was in agreement with. In addition, the hepatitis C recommendations referred to a previous KDIGO guideline for that subject and were all reasonable.[45]

Implications Within Canadian Health Care

1. The antiviral medications recommended in these chapters are expensive and funding varies substantially across provinces in Canada. The CST/CSN work group concurs with recommendations in these chapters and believes that provincial programs should fund the cost of these antivirals for patients without adequate private insurance.

Human Immunodeficiency Virus

The first recommendation in this chapter (not graded) was to screen all kidney transplant recipients for human immunodeficiency virus (HIV) infection. The work group agreed that this was mandatory before transplantation given the requirement for specialized care in the post-transplant period, when drug-drug interactions and infections may be amplified in HIV-infected patients. However, in the absence of known risk factors, it was unclear what was to be gained by screening all patients after transplantation.

Implications Within Canadian Health Care

1. Neither the Canadian Task Force on the Periodic Health Examination nor the US Preventive Services Task Force recommends routine screening for HIV.[46,47] In the absence of identifiable risk factors (outlined in[47]), the CST/CSN work group does not recommend routine screening of kidney transplant recipients for HIV after transplantation.

Commentary on Chapter 14: Other Infections

Most of the recommendations and suggestions in this chapter (Box 14) were believed by the committee to be reasonable. However, there is no evidence to support the recommendation that all patients with allograft pyelonephritis require hospital admission for IV antibiotic therapy. Several oral antibiotics have good bioavailability and achieve blood, urine, and tissue concentrations similar to those for IV antibiotics, allowing out-

Box 14. KDIGO Recommendations Concerning Other Infections

14.1: URINARY TRACT INFECTION

14.1.1: We suggest that all KTRs receive UTI prophylaxis with daily trimethoprim–sulfamethoxazole for at least 6 months after transplantation. (2B) *[CST/CSN workgroup concurs]*

14.1.2: For allograft pyelonephritis, we suggest initial hospitalization and treatment with intravenous antibiotics. (2C) *[see comments]*

14.2: PNEUMOCYSTIS JIROVECII PNEUMONIA

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

14.2.2: We suggest that all KTRs receive PCP prophylaxis with daily trimethoprim–sulfamethoxazole for at least 6 weeks during and after treatment for acute rejection. (2C) *[CST/CSN workgroup concurs]*

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

14.2.4: We recommend treatment with corticosteroids for KTRs with moderate to severe PCP (as defined by Pa_{O_2} <70 mm Hg in room air or an alveolar gradient of >35 mm Hg). (1C) *[CST/CSN workgroup concurs]*

14.3: TUBERCULOSIS

14.3.1: We suggest that TB prophylaxis and treatment regimens be the same in KTRs as would be used in the local, general population who require therapy. (2D) *[CST/CSN workgroup concurs]*

14.3.2: We recommend monitoring CNI and mTORi blood levels in patients receiving rifampin. (1C) *[CST/CSN workgroup concurs]*

14.3.2.1: Consider substituting rifabutin for rifampin to minimize interactions with CNIs and mTORi. (Not Graded) *[CST/CSN workgroup concurs]*

14.4: CANDIDA PROPHYLAXIS

14.4.1: We suggest oral and esophageal Candida prophylaxis with oral clotrimazole lozenges, nystatin, or fluconazole for 1-3 months after transplantation, and for 1 month after treatment with an antilymphocyte antibody. (2C) *[CST/CSN workgroup concurs]*

Abbreviations: CNI, calcineurin inhibitor; KTR, kidney transplant recipient; mTORi, mammalian target of rapamycin inhibitor; Pa_{O_2}, partial pressure of oxygen, alveolar; PCP, *Pneumocystis jirovecii* pneumonia; TB, tuberculosis; UTI, urinary tract infection.

patient treatment of appropriately selected low-risk patients. In addition, in Canada, IV antibiotics commonly are given in the outpatient setting through IV clinics or home IV programs. In Canada, there is a wide range of practice with respect to *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis. Although most centers use trimethoprim-sulfamethoxazole, the duration of prophylaxis is variable, with some centers stopping at 3 months while others continue it indefinitely. This variability in practice likely reflects different clinical experience with PCP cases.

Implications Within Canadian Health Care

1. Outpatient management of select transplant recipients with allograft pyelonephritis may be appropriate in certain circumstances and would represent an opportunity for cost-savings while still providing safe and efficacious care.
2. Given the lack of data and different clinical experience with PCP, the CST/CSN work group could not reach consensus on the duration of PCP prophylaxis. However, at a minimum, patients should receive prophylaxis for the first 3 months posttransplantation. The decision to stop prophylaxis at 3, 6, or 12 months or continue indefinitely will need to be based on local experience pending more rigorous data in this area.

Commentary on Chapter 15: Diabetes Mellitus

Screening for New-Onset Diabetes After Transplantation

The Canadian definition of screening for new-onset diabetes after transplantation (NODAT) parallels the definition of diabetes according to the Canadian Diabetes Association.[48] Lack of standardization of the glycated hemoglobin (hemoglobin A_{1c} [HbA_{1c}]) test precludes its use for the diagnosis of diabetes.[48] Risk factors for NODAT may be not only ethnicity specific, but also nation specific. There are some significant ethnicity-based differences between Canadian and United States–based populations. For example, Canadians of African ancestry may have arrived from the United States, but more commonly have arrived from Africa, the Caribbean, or Europe. Canadian blacks are at a 23% increased risk of NODAT.[49] Canada also has a large South Asian population and a substantial Aboriginal population, both of which are at increased risk of diabetes.[50,51]

Implications Within Canadian Health Care

1. Canadian physicians generally follow the Canadian Diabetes Association clinical practice guidelines for the diagnosis and treatment of diabetes. These practice guidelines do not recommend the HbA_{1c} test for the diagnosis of diabetes.
2. Canadian South Asians, Canadians of African descent, and Canadian Aboriginals may be at increased risk of NODAT based on the experience in other populations. Immunosuppression is another important risk factor for NODAT (see commentary on Chapter 2). The CST/CSN work group recommends that immunosuppression selection be individualized, taking into account the risk of NODAT as well as the underlying immunologic risk of the patient.

Managing NODAT or Diabetes Present at Transplantation

Recommendations in this section (Box 15) were not graded or were based on low quality of evidence. The suggestions regarding HbA_{1c} targets were reasonable, as was the suggestion to consider immunosuppression modification should NODAT develop. However, the work group does not agree with the suggestion regarding the use of aspirin for primary prevention. The text of the KDIGO document itself is at odds with this recommendation because it refers to recently published trials in this area showing no benefit. Finally, diabetes care in renal transplant recipients can be complex given the increasing number of medications available and the time required for appropriate management. Involvement with specialized diabetes clinical teams is suggested.

Implications Within Canadian Health Care

1. The CST/CSN work group does not suggest that diabetic kidney transplant recipients routinely receive aspirin for primary prevention. We agree with the KDIGO guideline that a randomized trial is needed to properly address this clinical question.
2. If locally available, the CST/CSN work group recommends the involvement of specialized diabetes clinical teams for the management of transplant recipients with diabetes.

Box 15. KDIGO Recommendations Concerning Diabetes Mellitus

15.1: SCREENING FOR NEW-ONSET DIABETES AFTER TRANSPLANTATION

15.1.1: We recommend screening all nondiabetic KTRs with fasting plasma glucose, oral glucose tolerance testing, and/or HbA_{1c} (1C) at least: weekly for 4 weeks (2D); every 3 months for 1 year (2D); and annually, thereafter. (2D) *[see comments]*

15.1.2: We suggest screening for NODAT with fasting glucose, oral glucose tolerance testing, and/or HbA_{1c} after starting, or substantially increasing the dose, of CNIs, mTORi, or corticosteroids. (2D) *[see comments]*

15.2: MANAGING NODAT OR DIABETES PRESENT AT TRANSPLANTATION

15.2.1: If NODAT develops, consider modifying the immunosuppressive drug regimen to reverse or ameliorate diabetes, after weighing the risk of rejection and other potential adverse effects. (Not Graded) *[CST/CSN workgroup concurs]*

15.2.2: Consider targeting HbA_{1c} 7.0-7.5%, and avoid targeting $HbA_{1c} \leq 6.0\%$, especially if hypoglycemic reactions are common.(Not Graded) *[CST/CSN workgroup concurs]*

15.2.3: We suggest that, in patients with diabetes, aspirin (65-100 mg/day) use for the primary prevention of CVD be based on patient preferences and values, balancing the risk for ischemic events to that of bleeding. (2D) *[see comments]*

Abbreviations: CNI, calcineurin inhibitor; CVD, cardiovascular disease; HbA_{1c}, hemoglobin A_{1c}; KTR, kidney transplant recipient; mTORi, mammalian target of rapamycin inhibitor; NODAT, new-onset diabetes after transplantation.

Commentary on Chapter 16: Hypertension, Dyslipidemias, Tobacco Use and Obesity

Hypertension

The work group agreed with the first 2 recommendations regarding blood pressure measurement (Box 16). Diagnosis and management of hypertension in Canada is based on the consensus recommendations of the Canadian Hypertension Education Program, which recommends a blood pressure target of 130/80 mm Hg for kidney transplant recipients.[52] The work group believed that the third suggestion (not graded) required comment. A recent meta-analysis (published shortly before the KDIGO guideline) of randomized trials in kidney transplant recipients found that calcium channel blockers were associated with a 25% decrease in graft loss (RR, 0.75; 95% CI, 0.57-0.99) and a significant improvement in GFR (mean difference, 4.5 mL/min; 95% CI, 2.2-6.7).[53] Direct comparisons between calcium channel blockers and ACE inhibitors were not conclusive. However, in the comparison of dihydropyridine to nondihydropyridine calcium channel blockers, the investigators found significantly lower serum creatinine levels with a trend toward improved GFR for the dihydropyridines. The investigators suggested that calcium channel blockers may be the preferred first-line antihypertensive for kidney transplant recipients.[53] A Canadian trial comparing ramipril with placebo in renal transplant recipients with proteinuria currently is underway and will address the KDIGO research recommendation regarding the effect of ACE inhibitors on patient and allograft survival.[54]

Implications Within Canadian Health Care

1. Given the recent evidence, the CST/CSN work group believes that calcium channel blockers should be used as first-line antihypertensive agents in kidney transplant recipients. Because of the potential for significant drug-drug interactions between some immunosuppressive agents and nondihydropyridines, as well as the suggestion of better kidney function with dihydropyridines, the work group prefers the latter subclass of calcium channel blockers as first line. For patients with significant proteinuria, ACE inhibitors and angiotensin receptor blockers are an option and will decrease proteinuria. However, it is not known whether use of these agents will improve patient or allograft survival.

Dyslipidemia

It is noted that the KDIGO statements concerning dyslipidemia (Box 16) are based on previously published Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines because there was no new evidence available at the time to warrant modification. However, the updated Canadian Cardiovascular Society guidelines have been published recently.[55] Substantial changes have been made to lipid targets in these recommendations based on levels of cardiovascular risk. Although transplant patients are not covered specifically in these guidelines, the work group believes that all renal transplant recipients, regardless of the presence or absence of specific cardiovascular risk factors, should be assumed to carry high cardiovascular risk and be treated as such. In the 2009 Canadian guidelines, the target low-

Box 16. KDIGO Recommendations Concerning Hypertension, Dyslipidemias, Tobacco Use, and Obesity

16.1: HYPERTENSION

16.1.1: We recommend measuring blood pressure at each clinic visit. (1C) *[CST/CSN workgroup concurs]*

16.1.2: We suggest maintaining blood pressure at <130 mm Hg systolic and <80 mm Hg diastolic if ≥18 years of age, and <90th percentile for sex, age, and height if <18 years old. (2C) *[CST/CSN workgroup concurs]*

16.1.3: To treat hypertension (Not Graded): use any class of antihypertensive agent; monitor closely for adverse effects and drug–drug interactions; and when urine protein excretion ≥1 g/day for ≥18 years old and ≥600 mg/m^2/24 h for <18 years old, consider an ACE-I or an ARB as first-line therapy. *[see comments]*

16.2: DYSLIPIDEMIAS

(These recommendations are based on KDOQI Dyslipidemia Guidelines and are thus Not Graded)

16.2.1: Measure a complete lipid profile in all adult (≥18 years old) and adolescent (puberty to 18 years old) KTRs (based on KDOQI Dyslipidemia Recommendation 1): 2-3 months after transplantation; 2-3 months after a change in treatment or other conditions known to cause dyslipidemias; at least annually, thereafter. *[CST/CSN workgroup concurs]*

16.2.2: Evaluate KTRs with dyslipidemias for secondary causes (based on KDOQI Dyslipidemia Recommendation 3) *[CST/CSN workgroup concurs]*

16.2.2.1: For KTRs with fasting triglycerides ≥500 mg/dL (≥5.65 mmol/L) that cannot be corrected by removing an underlying cause, treat with: Adults: therapeutic lifestyle changes and a triglyceride lowering agent (based on KDOQI Recommendation 4.1); Adolescents: therapeutic lifestyle changes (based on KDOQI Recommendation 5.1). *[CST/CSN workgroup concurs]*

16.2.2.2: For KTRs with elevated LDL-C: Adults: If LDL-C ≥100 mg/dL (≥2.59 mmol/L), treat to reduce LDL-C to <100 mg/dL (<2.59 mmol/L) (based on KDOQI Guideline 4.2); Adolescents: If LDL-C ≥130 mg/dL (≥3.36 mmol/L), treat to reduce LDL-C to <130 mg/dL (<3.36 mmol/L) (based on KDOQI Guideline 5.2). *[see comments]*

16.2.2.3: For KTRs with normal LDL-C, elevated triglycerides and elevated non-HDL-C: Adults: If LDL-C <100 mg/dL (<2.59 mmol/L), fasting triglycerides ≥200 mg/dL (≥2.26 mmol/L), and non- HDL-C ≥130 mg/dL (≥3.36 mmol/L), treat to reduce non-HDL-C to <130 mg/dL (<3.36 mmol/L) (based on KDOQI Guideline 4.3); Adolescents: If LDL-C <130 mg/dL (<3.36 mmol/L), fasting triglycerides ≥200 mg/dL (≥2.26 mmol/L), and non-HDL-C ≥160 mg/dL (≥4.14 mmol/L), treat to reduce non-HDL-C to <160 mg/dL (<4.14 mmol/L) (based on KDOQI Guideline 5.3). *[CST/CSN workgroup concurs]*

16.3: TOBACCO USE

16.3.1: Screen and counsel all KTRs, including adolescents and children, for tobacco use, and record the results in the medical record. (Not Graded). Screen during initial transplant hospitalization. Screen at least annually, thereafter. *[CST/CSN workgroup concurs]*

16.3.2: Offer treatment to all patients who use tobacco. (Not Graded) *[CST/CSN workgroup concurs]*

16.4: OBESITY

16.4.1: Assess obesity at each visit. (Not Graded). Measure height and weight at each visit, in adults and children. Calculate BMI at each visit. Measure waist circumference when weight and physical appearance suggest obesity, but BMI is <35 kg/m^2. *[see comments]*

16.4.2: Offer a weight-reduction program. *[CST/CSN workgroup concurs]*

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; KDOQI, Kidney Disease Outcomes Quality Initiative; KTR, kidney transplant recipient; LDL-C, low-density lipoprotein cholesterol.

density lipoprotein (LDL) cholesterol level for high-risk patients is <2.0 mmol/L.[55]

Implications Within Canadian Health Care

1. Transplant physicians have a choice between following the KDIGO guidelines or the Canadian Cardiovascular Society guidelines for the treatment of dyslipidemia. Given the recent evidence incorporated in the Canadian guidelines, the CST/CSN work group suggests that these guidelines be used for the management of kidney transplant recipients.

2. Based on this information, we suggest that kidney transplant recipients with an increased LDL cholesterol level be treated to a target <2.0 mmol/L.

Tobacco Use

This section had 2 recommendations about screening and management of tobacco cessation (Box 16). Although neither was graded, the work group believed that they were reasonable given the negative health consequences of tobacco use.

Obesity

KDIGO defines adult obesity on the basis of body mass index ≥30 kg/m^2, with a recommendation that waist circumference ≥102 cm in

men and ≥88 cm in women also be included. However, the 2009 Canadian Cardiovascular Society guidelines[55] emphasize abdominal obesity as a major cardiovascular risk factor by including the International Diabetes Federation classification of metabolic syndrome in the document.[56] Waist circumferences defined in this document are different from the KDIGO recommendation and are uniformly more stringent. These include values ≥94 cm in men of European descent; ≥90 cm in South Asian, Chinese, and Japanese men; and ≥80 cm in all women.[55] The document also recommends that South Asian values be used in Aboriginal populations.[55]

Implications Within Canadian Health Care

1. The 2009 Canadian Cardiovascular Society guidelines provide a country-specific ethnicity-specific set of recommendations for defining obesity that extend to metabolic syndrome. Given the ethnic diversity in the Canadian kidney transplant population, the CST/CSN work group recommends that the Canadian Cardiovascular Society guidelines be used for defining obesity and metabolic syndrome.

Commentary on Chapter 17: Cardiovascular Disease Management

This chapter had 2 recommendations (Box 17) regarding the management of cardiovascular disease that our group believed were reasonable and needed no further comment.

Commentary on Chapter 18: Cancer of the Skin and Lip

This chapter includes 2 recommendations and 4 suggestions regarding both the prevention and management of skin cancers in kidney transplant recipients (Box 18). All recommendations and suggestions are based on low- to moderate-level evidence, but are common sense and involve minimal intervention. The work group noted 2 areas of discussion that deviate from Canadian practice and require further comment. The KDIGO guidelines suggest that patients with a history of skin cancer be offered treatment with oral acitretin if there are no contraindications (18.6). Although acitretin is available in Canada, this medication rarely is prescribed by transplant physicians or dermatologists for renal transplant recipients in Canada, likely because of its unfavorable side-effect profile.

At the time of publication, the KDIGO guideline committee determined that there was unclear evidence to recommend an immunosuppressive medication change to decrease the incidence of skin cancer. Since then, 2 small trials have been reported that suggested that conversion to sirolimus from CNI-based immunosuppression therapy may decrease the incidence of skin cancer in renal transplant recipients with a history of nonmelanoma skin cancer (NMSC). A single-center, randomized, assessor-blinded, controlled trial re-

Box 17. KDIGO Recommendations Concerning Cardiovascular Disease Management

17.1: Consider managing CVD at least as intensively in KTRs as in the general population, with appropriate diagnostic tests and treatments. (Not Graded) *[CST/CSN workgroup concurs]*

17.2: We suggest using aspirin (65-100 mg/day) in all patients with atherosclerotic CVD, unless there are contraindications. (2B) *[CST/CSN workgroup concurs]*

Abbreviations: CVD, cardiovascular disease; KTR, kidney transplant recipient.

Box 18. KDIGO Recommendations Concerning Cancer of the Skin and Lip

18.1: We recommend that KTRs, especially those who have fair skin, live in high sun-exposure climates, have occupations requiring sun exposure, have had significant sun exposure as a child, or have a history of skin cancer, be told that their risk of skin and lip cancer is very high. (1C) *[CST/CSN workgroup concurs]*

18.2: We recommend that KTRs minimize life-long sun exposure and use appropriate ultraviolet light blocking agents. (1D) *[CST/CSN workgroup concurs]*

18.3: We suggest that adult KTRs perform skin and lip self-examinations and report new lesions to a healthcare provider. (2D) *[CST/CSN workgroup concurs]*

18.4: For adult KTRs, we suggest that a qualified health professional, with experience in diagnosing skin cancer, perform annual skin and lip examination on KTRs, except possibly for KTRs with dark skin pigmentation. (2D) *[CST/CSN workgroup concurs]*

18.5: We suggest that patients with a history of skin or lip cancer, or premalignant lesions, be referred to and followed by a qualified health professional with experience in diagnosing and treating skin cancer. (2D) *[CST/CSN workgroup concurs]*

18.6: We suggest that patients with a history of skin cancer be offered treatment with oral acitretin, if there are no contraindications. (2B) *[see comments]*

Abbreviation: KTR, kidney transplant recipient.

ported on patients switched to sirolimus therapy (n = 25) versus remaining on their present immunosuppression therapy (n = 19).[57] At 1 year, patients in the sirolimus arm showed improvement in premalignant skin dysplasia and a lower rate of new NMSC. A multicenter randomized trial involving 86 patients has shown similar results.[58] After a mean follow-up of approximately 19 months, those randomly assigned to sirolimus therapy (n = 39) compared with a CNI regimen (n = 47) had a lower yearly rate of NMSC and squamous cell carcinoma.

Implications Within Canadian Health Care

1. Acitretin is not commonly used in Canadian transplant recipients with skin cancer. Given that there is moderate evidence of efficacy based on randomized trials, the option of acitretin should be discussed and a decision to initiate therapy should be based on perceived risks and benefits to the patient.
2. Given recent evidence, the CST/CSN work group suggests that a switch to sirolimus therapy be considered in patients with a history of NMSC. The decision to switch will need to take into account patient preference, cost, and other clinical factors (eg, the presence of significant proteinuria).

Commentary on Chapter 19: Non-Skin Malignancies

This chapter contains no graded recommendations or suggestions (Box 19). The work group reviewed cancer screening guidelines published by Health Canada, Provincial Cancer Agencies, the Canadian Task Force on Preventative Health Care, and subspecialty medical societies. In almost all instances, Canadian guidelines for cancer screening align with those discussed in the KDIGO guideline. Regarding screening for cervical cancer, it is important to note that many provinces and the Society of Obstetricians and Gynecologists of Canada recommend Papanicolaou smears every 2-3 years in women with no history of cervical dysplasia and 3 negative test results.[59] Because cervical cancer may develop more rapidly and be more aggressive in transplant recipients, annual screening has been recommended.[60,61] Some provinces (Alberta, Manitoba, Ontario, and Nova Scotia) advocate for yearly screening in immunosuppressed individuals.

Box 19. KDIGO Recommendations Concerning Non-Skin Malignancies

19.1: Develop an individualized screening plan for each KTR that takes into account the patient's past medical and family history, tobacco use, competing risks for death, and the performance of the screening methodology. (Not Graded) *[CST/CSN workgroup concurs]*
19.2: Screen for the following cancers as per local guidelines for the general population (Not Graded): Women: cervical, breast and colon cancer; Men: prostate and colon cancer. *[see comments]*
19.3: Obtain hepatic ultrasound and alpha feto-protein every 12 months in patients with compensated cirrhosis. (Not Graded) *[CST/CSN workgroup concurs]*

Abbreviation: KTR, kidney transplant recipient.

Implications Within Canadian Health Care

1. Canadian kidney transplant recipients should undergo routine population-based screening for breast and colorectal cancer according to provincial and national guidelines. Given the increased risk, female transplant recipients should undergo cervical screening yearly after the onset of sexual activity.

Commentary on Chapter 20: Managing Cancer With Reduction of Immunosuppressive Medication

This chapter contains 2 suggestions related to a decrease in immunosuppressive medications in transplant recipients with cancer (Box 20). The work group agreed with KDIGO suggestions and

Box 20. KDIGO Recommendations Concerning Managing Cancer with Reduction of Immunosuppressive Medication

20.1: We suggest consideration be given to reducing immunosuppressive medications for KTRs with cancer. (2C) *[CST/CSN workgroup concurs]*
20.1.1: Important factors for consideration include (Not Graded): the stage of cancer at diagnosis; whether the cancer is likely to be exacerbated by immunosuppression; the therapies available for the cancer; whether immunosuppressive medications interfere with ability to administer the standard hemotherapy. *[CST/CSN workgroup concurs]*
20.2: For patients with Kaposi sarcoma, we suggest using mTORi along with a reduction in overall immunosuppression. (2C) *[CST/CSN workgroup concurs]*

Abbreviations: KTR, kidney transplant recipient; mTORi, mammalian target of rapamycin inhibitor.

recognizes that immunosuppressive medication for transplant recipients with cancer must be individualized.

Commentary on Chapter 21: Transplant Bone Disease

At the time of transplantation, kidney transplant recipients carry the skeletal manifestations of the complex disorder known as chronic kidney disease (CKD)–mineral and bone disorder (CKD-MBD). Normalizing renal function leads to an improvement in CKD-MBD, but ongoing abnormalities in bone turnover persist and range from high bone turnover associated with persistent secondary hyperparathyroidism to adynamic bone disease.[62,63] Measurements of bone mineral density (BMD) cannot recognize alterations in bone quality associated with CKD-MBD. The KDIGO work group emphasized that only bone histomorphometric evaluation accurately identifies the underlying pathobiologic state. It generally is accepted that BMD usually decreases in the first posttransplant year (particularly associated with high-dose glucocorticoid therapy) with a leveling off thereafter.[64,65] Unfortunately, evidence linking low BMD with fracture incidence in CKD or kidney transplantation is weak and inconsistent. Furthermore, if kidney transplant recipients experience worsening graft function, BMD cannot distinguish between the increasing diversity of the underlying CKD-MBD. For these reasons, we agree that BMD measurement be reserved for high-risk transplant recipients with estimated GFR >30 mL/min/1.73 m^2 and avoided for those with CKD stages 4-5T.

The KDIGO guideline identified vitamin D deficiency (defined as serum 25 hydroxyvitamin D level <40 nmol/L) as a very common finding, present in approximately half of all transplant patients both in the first year after transplant and later, whereas "insufficiency" (<75 nmol/L) affected three-fourths of this population (Box 21). In a recent report (n = 5,000), only 35% of Canadians were found to have a serum 25 hydroxyvitamin D level ≥75 nmol/L.[66] Unfortunately, serum 25 hydroxyvitamin D assays are expensive and may not be freely available in all Canadian jurisdictions for routine clinical care.

Our work group recognized the difficulties that the KDIGO guideline committee encountered in analyzing the evidence supporting the use of either vitamin D analogues or bisphosphonates in transplantation. There are no randomized trials that show the beneficial or harmful effects on patient-level outcomes, in particular, fractures, hospitalization, or mortality. Although both vitamin D analogues and bisphosphonates resulted in some increase in BMD, the limited bone histologic data available suggest that they predispose to the development of adynamic bone turnover.[67,68] Moreover, the KDIGO guideline was unable to provide guidance for the selection of patients using bone densitometric criteria given the difficulties of interpretation described. In patients with CKD stages 4-5T, we agree with the KDIGO guideline that patients should be managed as for patients with CKD stages 4-5 not on dialysis therapy. This topic has been reviewed in the CSN commentary on the KDIGO CKD-MBD guideline.[69]

Implications Within Canadian Health Care

1. Although nutritional vitamin D insufficiency/deficiency is so common in Canadian kidney transplant recipients as to warrant routine supplementation, to date there is no evidence for benefits resulting from supplementation to "sufficient" levels of serum 25 hydroxyvitamin D (>75 nmol/L) and the clinical harm has not been defined. An ongoing clinical trial in transplantation hopefully will address some of these questions.[70]

2. Bone histologic evaluation may provide relevant information about underlying CKD-MBD (allowing physicians to withhold bisphosphonate therapy from patients with pre-existing adynamic bone disease). In clinical practice, bone biopsy in transplant recipients rarely is available in Canada. Canadian physicians therefore must rely on surrogate markers of renal osteodystrophy (eg, levels of serum calcium, phosphate, parathyroid hormone, etc) before making decisions about therapeutic intervention.

3. In patients with CKD stages 1-3T who have no biochemical evidence of CKD-MBD, it is reasonable to assess and treat patients for their future fracture risk according to the recent guidelines established for the general population by Osteoporosis Canada.[71] This risk includes consideration of age, sex, prior osteoporotic fracture, BMD, and other significant risk factors, including glucocorticoid use. Management would in-

Box 21. KDIGO Recommendations Concerning Transplant Bone Disease

21.1: In patients in the immediate post-kidney transplant period, we recommend measuring serum calcium and phosphorus at least weekly, until stable. (1B) *[CST/CSN workgroup concurs]*

21.2: In patients after the immediate post-kidney transplant period, it is reasonable to base the frequency of monitoring serum calcium, phosphorus and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD. (Not Graded) *[CST/CSN workgroup concurs]*

21.2.1: Reasonable monitoring intervals would be (Not Graded): In CKD stages 1-3T, for serum calcium and phosphorus, every 6-12 months; and for PTH, once, with subsequent intervals depending on baseline level and CKD progression. In CKD stage 4T, for serum calcium and phosphorus, every 3-6 months; and for PTH, every 6-12 months. In CKD stage 5T, for serum calcium and phosphorus, every 1-3 months; and for PTH, every 3-6 months. In CKD stages 3-5T, measurement of alkaline phosphatases annually, or more frequently in the presence of elevated PTH. *[CST/CSN workgroup concurs]*

21.2.2: In CKD patients receiving treatments for CKD–MBD, or in whom biochemical abnormalities are identified, it is reasonable to increase the frequency of measurements to monitor for efficacy and side effects. (Not Graded) *[CST/CSN workgroup concurs]*

21.2.3: It is reasonable to manage these abnormalities as for patients with CKD stages 3-5. (Not Graded) *[CST/CSN workgroup concurs]*

21.3: In patients with CKD stages 1-5T, we suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and interventions. (2C) *[see comments]*

21.4: In patients with CKD stages 1-5T, we suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population. (2C) *[see comments]*

21.5: In patients with an eGFR greater than approximately 30 mL/min/1.73 m^2, we suggest measuring BMD in the first 3 months after kidney transplant if they receive corticosteroids or have risk factors for osteoporosis as in the general population (2D) *[see comments]*

21.6: In patients in the first 12 months after kidney transplant with eGFR greater than approximately 30 mL/min/1.73 m^2 and low BMD, we suggest that treatment with vitamin D, calcitriol/alfacalcidiol, or bisphosphonates be considered.(2D) *[see comments]*

21.6.1: We suggest that treatment choices be influenced by the presence of CKD–MBD, as indicated by abnormal levels of calcium, phosphorus, PTH, alkaline phosphatases, and 25(OH)D. (2C*) [see comments]*

21.6.2: It is reasonable to consider a bone biopsy to guide treatment, specifically before the use of bisphosphonates due to the high incidence of adynamic bone disease. (Not Graded) *[see comments]*

21.6.3: There are insufficient data to guide treatment after the first 12 months. (Not Graded) *[CST/CSN workgroup concurs]*

21.7: In patients with CKD stages 4-5T, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population and BMD does not predict the type of kidney transplant bone disease. (2B) *[CST/CSN workgroup concurs]*

21.8: In patients with CKD stages 4-5T with a known low BMD, we suggest management as for patients with CKD stages 4-5 not on dialysis. (2C) *[CST/CSN workgroup concurs]*

Abbreviations: BMD, bone mineral density; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral and bone disorders; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone.

clude routine supplementation with vitamin D (800-2,000 U/d) and calcium (1,000-1,500 mg/d of total elemental calcium intake), with specific pharmacotherapy based on overall risk of fracture, including bisphosphonate therapy when appropriate.

4. Bone densitometry should not be used routinely in patients with CKD stages 4-5T to form the basis of diagnostic and therapeutic decisions. Although there is very good evidence to support the efficacy and safety of therapies currently used to decrease fracture risk in the general population, there is little or no evidence to support their use in kidney transplant patients with advanced renal failure.

Commentary on Chapter 22: Hematological Complications

This section has one level-1 recommendation about using ACE inhibitors for the initial treatment of erythrocytosis (Box 22), which our work group agreed with. The other recommendations were not graded. The section on anemia is based largely on the *KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease,* as well as the 2007 update.[72-74] In the absence of specific trials in transplantation, the guidelines recommend treatment of anemia similar to that for patients with CKD not yet on dialysis therapy,

Box 22. KDIGO Recommendations Concerning Hematological Complications

22.1: Perform a complete blood count at least (Not Graded): daily for 7 days, or until hospital discharge, whichever is earlier; two to three times per week for weeks 2-4; weekly for months 2-3; monthly for months 4-12; then at least annually, and after any change in medication that may cause neutropenia, anemia or thrombocytopenia. *[CST/CSN workgroup concurs]*

22.2: Assess and treat anemia by removing underlying causes whenever possible and using standard measures applicable to CKD. (Not Graded) *[see comments]*

22.3: For treatment of neutropenia and thrombocytopenia, include treatment of underlying causes whenever possible. (Not Graded) *[CST/CSN workgroup concurs]*

22.4: We recommend using ACE-Is or ARBs for initial treatment of erythrocytosis. (1C) *[CST/CSN workgroup concurs]*

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease.

including the use of erythropoiesis-stimulating agents (ESAs). Although no maximum hemoglobin level target has been defined for transplant patients on ESA therapy, a recent cohort study found that hemoglobin level >140 g/L with an ESA was associated with a significant increase in mortality in renal transplant recipients.[75]

Implications Within Canadian Health Care

1. Pending specific data from transplant trials, the CST/CSN work group agrees that anemia should be managed in a manner similar to that for patients with CKD. Based on this evidence, a target hemoglobin level of 110 g/L is recommended for patients with CKD (acceptable range, 100-120 g/L).[76]

Commentary on Chapter 23: Hyperuricemia and Gout

This chapter has 3 suggestions and one level-1 recommendation (Box 23). The suggestions seem reasonable and our work group is in agreement with all of them. The level-1 recommendation deserves further comment. In general, we agree that the combination of allopurinol and azathioprine should be avoided because of the known interaction. However, there will be situations in which the use of other antiproliferative agents may not be possible. In these circumstances, decreased-dose azathioprine and low-dose allopurinol can be combined safely.[77,78] Treatment of asymptomatic hyperuricemia is not recommended in the general population or kidney transplant recipients. A recent secondary analysis of the Symphony Trial (n = 1,645) did not find an independent association between uric acid level and transplant kidney function at 3 years.[79]

Implications Within Canadian Health Care

1. The CST/CSN work group recommends that uric acid not be measured as part of routine posttransplant care given that nearly 80% of kidney transplant recipients have hyperuricemia and treatment is not recommended in the absence of symptoms (ie, gout, uric acid stones, or tophi). However, uric acid should be measured in those receiving treatment for or suspected of having gout, uric acid stones, or tophi.

Commentary on Chapter 24: Growth and Development

This section has 3 recommendations (Box 24) that the work group believed were reasonable and were in agreement with. Although recombinant human growth hormone (rhGH) is expensive and not approved for growth failure in transplant recipients, it is available and funded across most provinces for transplant recipients with growth retardation. With regard to the issue of steroid therapy, most Canadian pediatric transplant programs use steroid minimization protocols with low-dose alternate-day prednisone, with only a few programs using steroid avoidance or withdrawal in an effort to maximize growth potential.

Box 23. KDIGO Recommendations Concerning Hyperuricemia and Gout

23.1: We suggest treating hyperuricemia in KTRs when there are complications, such as gout, tophi, or uric acid stones. (2D) *[CST/CSN workgroup concurs]*

23.1.1: We suggest colchicine for treating acute gout, with appropriate dose reduction for reduced kidney function and concomitant CNI use. (2D) *[CST/CSN workgroup concurs]*

23.1.2: We recommend avoiding allopurinol in patients receiving azathioprine. (1B) *[see comments]*

23.1.3: We suggest avoiding NSAIDs and COX-2 inhibitors whenever possible. (2D) *[CST/CSN workgroup concurs]*

Abbreviations: CNI, calcineurin inhibitor; COX-2, cyclooxygenase 2; KTR, kidney transplant recipient; NSAID; nonsteroidal anti-inflammatory drug.

Box 24. KDIGO Recommendations Concerning Growth and Development

24.1: We recommend measuring growth and development in children (1C): at least every 3 months if <3 years old (including head circumference) (Not Graded); every 6 months in children ≥3 years until final adult height. (Not Graded) *[CST/CSN workgroup concurs]*

24.2: We recommend using rhGH 28 IU/m^2/week (or 0.05 mg/kg/day) in children with persistent growth failure after kidney transplantation. (1B) *[CST/CSN workgroup concurs]*

24.3: We suggest minimizing or avoiding corticosteroid use in children who still have growth potential. (2C) *[CST/CSN workgroup concurs]*

Abbreviation: rhGH, recombinant human growth hormone.

Implications Within Canadian Health Care

1. rhGH is used in Canadian pediatric transplant programs. Although short-term data support this practice, long-term studies are needed evaluating final adult height in the transplant population. Although steroid minimization protocols are used at many Canadian pediatric transplant programs, the work group is concerned about the lack of long-term data evaluating allograft survival.

Commentary on Chapter 25: Sexual Function and Fertility

This chapter had sections on sexual function and female and male fertility. All recommendations in this chapter (Box 25) were based on common sense or reasonable interpretations of the currently available data. Our work group agreed that pregnant kidney transplant recipients should be managed by an obstetrician with experience in high-risk pregnancies. Because such specialists may be centrally located within larger urban centers, this may require considerable travel for those in smaller cities or rural areas. In addition to mTOR inhibitors, our group wanted to note that valganciclovir has been associated with inhibition of spermatogenesis and subsequent infertility in animal models. The product monograph also states that in men, valganciclovir at the recommended doses may cause temporary or permanent inhibition of spermatogenesis. This information should be shared with male transplant recipients before initiating therapy.

Implications Within Canadian Health Care

1. The CST/CSN work group agrees with the KDIGO guideline suggesting that pregnancy be deferred until at least 1 year posttransplantation and to proceed only if kidney function is stable with minimal proteinuria (protein excretion <1 g/d). The work group realizes that high-risk obstetrical care may not be available in all areas

Box 25. KDIGO Recommendations Concerning Sexual Function and Fertility

25.1: SEXUAL FUNCTION

25.1.1: Evaluate adults for sexual dysfunction after kidney transplantation. (Not Graded) *[CST/CSN workgroup concurs]*

25.1.2: Include discussion of sexual activity and counseling about contraception and safe sex practices in follow-up of adult KTRs. (Not Graded) *[CST/CSN workgroup concurs]*

25.2: FEMALE FERTILITY

25.2.1: We suggest waiting for at least 1 year after transplantation before becoming pregnant, and only attempting pregnancy when kidney function is stable with <1 g/day proteinuria. (2C) *[CST/CSN workgroup concurs]*

25.2.2: We recommend that MMF and EC-MPS be discontinued or replaced with azathioprine before pregnancy is attempted. (1A) *[CST/CSN workgroup concurs]*

25.2.3: We suggest that mTORi be discontinued or replaced before pregnancy is attempted. (2D) *[CST/CSN workgroup concurs]*

25.2.4: Counsel female KTRs with child-bearing potential and their partners about fertility and pregnancy as soon as possible after transplantation. (Not Graded) *[CST/CSN workgroup concurs]*

25.2.5: Counsel pregnant KTRs and their partners about the risks and benefits of breastfeeding. (Not Graded) *[CST/CSN workgroup concurs]*

25.2.6: Refer pregnant patients to an obstetrician with expertise in managing high-risk pregnancies. (Not Graded) *[see comments]*

25.3: MALE FERTILITY

25.3.1: We suggest that male KTRs and their partners be advised that: male fertility may improve after kidney transplantation (2D); pregnancies fathered by KTRs appear to have no more complications than those in the general population. (2D) *[CST/CSN workgroup concurs]*

25.3.2: We recommend that adult male KTRs be informed of the possible risks of infertility from mTORi. (1C) *[CST/CSN workgroup concurs]*

25.3.2.1: We suggest that adult male KTRs who wish to maintain fertility should consider avoiding mTORi, or banking sperm prior to mTORi use. (2C) *[CST/CSN workgroup concurs]*

Abbreviations: EC-MPS, enteric-coated mycophenolate sodium; KTR, kidney transplant recipient; MMF, mycophenolate mofetil; mTORi, mammalian target of rapamycin inhibitor.

of the country. This may require significant travel or temporary relocation for pregnant transplant patients.

Commentary on Chapter 26: Lifestyle

This chapter has one level-1 recommendation (Box 26) that is reasonable and based on common sense, as well as extrapolation from the general population literature. Our work group was in agreement with this recommendation. However, implementation will be difficult given the level of inactivity and weight gain that is common in our transplant population.

Commentary on Chapter 27: Mental Health

This chapter has 1 recommendation (not graded; Box 27) suggesting that questioning about anxiety and depression be included in routine posttransplant care, which our work group was in agreement with.

CONCLUSION

The *KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients* provides answers to important clinical questions that will be useful to physicians, policy makers, and patients reviewing aspects of their own care. The guideline authors used a structured objective method to link recommendations to the strength of the evidence. As noted by Chapman,[80] perhaps the most important aspect of this guideline is that it highlights the tenuous body of evidence that guides our day-to-day management of kidney transplant recipients. This commentary has reviewed the KDIGO guideline and positioned the recommendations in the context of Canadian practice and the Canadian health care system. Although some positions taken in this commentary have differed from the original guideline, this usually has been the result of inadequacies in the data.[28] The CST and CSN recognize this limitation and agree that improvements in care will come only by expanding our evidence base with methodologically rigorous randomized trials that address outcomes relevant to renal transplant recipients.

Box 26. KDIGO Recommendations Concerning Lifestyle

26: We recommend that patients are strongly encouraged to follow a healthy lifestyle, with exercise, proper diet, and weight reduction as needed. (1C) *[CST/CSN workgroup concurs]*

Box 27. KDIGO Recommendations Concerning Mental Health

27: Include direct questioning about depression and anxiety as part of routine follow-up care after kidney transplantation. (Not Graded) *[CST/CSN workgroup concurs]*

ACKNOWLEDGEMENTS

Text from the *KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients* appearing in the boxes of this article is reproduced with kind permission of KDIGO.

Support: No financial support was required for the development of this commentary.

Financial Disclosure: In the interest of transparency and full disclosure, the Appendix includes conflict of interest information for all members of the work group.

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Appendix. Conflict of Interest Information for Work Group Members

Member	Type of Potential Conflict of Interest	Role	Period	Sponsor
Blydt-Hansen	Advisory Board	Consultant	2009	Astellas, Novartis
	Unrestricted research grant; investigator initiated	PI	2004-2009	Wyeth
Campbell	Unrestricted research grant; investigator initiated	Laboratory director	2009	Astellas
	Advisory Board	Consultant	2008-2009	Astellas, Novartis
Cantarovich	Advisory Board	Consultant	2008-2009	Astellas, Roche, Novartis
	Funding for industry-led clinical trial	Site investigator	2009-2010	Astellas
	Funding for industry-led clinical trial	Site investigator	2006-2008	Isotechnika
Cole	Advisory Board	Consultant	2007-2010	Novartis, BMS, Astellas
	Unrestricted educational grant for program		2004-2010	Roche, Wyeth
	Unrestricted research grant; investigator initiated	PI	2008-2010	Genzyme
	Fellows Symposium	Chair	2000-2010	Astellas
Gill	Advisory Board	Consultant	2009-2010	BMS, Novartis, Roche,
	Unrestricted research grant; investigator initiated	Site investigator	2008-2010	Genzyme
	Unrestricted research grant; investigator initiated	PI	2007-2008	Novartis
Gourishankar	Unrestricted research grant; investigator initiated	PI	2007-2009	Novartis
	Advisory Board	Consultant	2008-2009	Roche
	Unrestricted research grant; investigator initiated	Consultant	2008	Astellas
Hodsman	Advisory Board	Consultant	2006-2009	Shire

(Continued)

Appendix (Cont'd). Conflict of Interest Information for Work Group Members

Member	Type of Potential Conflict of Interest	Role	Period	Sponsor
House	Funding for industry-led clinical trial(s)	Site investigator	2001-2010	Astellas, Roche, Isotechnika, Novartis, Wyeth, Genzyme
	Unrestricted research grant; investigator initiated	PI	2001-2007	Wyeth
	Advisory Board	Consultant	2009	Genzyme
Hebert	Unrestricted research grant; investigator initiated	PI	2010	Astellas
Humar	Unrestricted research grant; investigator initiated	PI	2006-2009	Roche
	Advisory Board	Consultant	2006-2010	Roche
Kim	Unrestricted educational grant	PI	2009	Wyeth, Roche, Novartis
	Advisory Board	Consultant	2009	Astellas, Novartis
Knoll	Funding for industry-led clinical trial	Site investigator	2003-2009; 2002-2007	Astellas, Wyeth
	Unrestricted research grant; investigator initiated	PI	2009-2011	Roche
	Advisory Board	Consultant	2008-2009	Astellas, Roche, Genzyme, Novartis
Prasad	Funding for industry-led clinical trial	Site investigator	2007-2009	Astellas
	Unrestricted research grant; investigator initiated	PI	2007-2009	Roche, Novartis, Genzyme
	Advisory Board	Consultant	2007-2009	Astellas, Roche, Novartis, Wyeth

Note: Drs Fairhead, Karpinski, and Mainra declare that they have no relevant financial interests.
Abbreviations: BMS, Bristol-Myers Squibb; PI, principal investigator.