see commentary on page 271

KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary

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The 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline on the monitoring, management, and treatment of kidney transplant recipients is intended to assist the practitioner caring for adults and children after kidney transplantation. The guideline development process followed an evidence-based approach, and management recommendations are based on systematic reviews of relevant treatment trials. Critical appraisal of the quality of the evidence and the strength of recommendations followed the Grades of Recommendation Assessment, Development, and Evaluation (GRADE) approach. The guideline makes recommendations for immunosuppression and graft monitoring, as well as prevention and treatment of infection, cardiovascular disease, malignancy, and other complications that are common in kidney transplant recipients, including hematological and bone disorders. Limitations of the evidence, especially the lack of definitive clinical outcome trials, are discussed and suggestions are provided for future research. This summary includes a brief description of methodology and the complete guideline recommendations but does not include the rationale and references for each recommendation, which are published elsewhere.

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Since the first successful kidney transplantation in 1954, there has been an exponential growth in publications dealing with the care of kidney transplant recipients (KTRs). In addition, the science of conducting and interpreting both clinical trials and observational studies has become increasingly controversial and complex. Caring for KTRs requires specialized knowledge in areas as varied as immunology, pharmacology, nephrology, endocrinology, and infectious disease. The last two comprehensive clinical practice guidelines on the care of KTRs were published in 2000 by the American Society of Transplantation and the European Best Practices Guidelines Expert Group.[1,2] Both of these guidelines were based primarily on expert opinion, not rigorous evidence review. For these reasons, the international consortium of kidney guideline developers, Kidney Disease: Improving Global Outcomes (KDIGO),[3] concluded that a new comprehensive evidence-based clinical practice guideline for the care of KTRs was necessary. This summary includes a brief description of the methods used and the guideline recommendations. Further details are included in a separate publication.[4]

RESULTS

Here we present the guideline recommendations. The rationale for the recommendations and discussion of other important issues are provided in the full guideline.[4] Each recommendation is graded for strength of recommendation (Table 1) and overall quality of evidence (Table 2).

Table 1 | KDIGO nomenclature and description for grading recommendations

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

KDIGO, Kidney Disease: Improving Global Outcomes.
[a]The additional category 'Not Graded' was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

Table 2 | Final grade for overall quality of evidence

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

GUIDELINE RECOMMENDATIONS

1: INDUCTION THERAPY

1.1: We recommend starting a combination of immunosuppressive medications before, or at the time of, kidney transplantation. (*1A*)
1.2: We recommend including induction therapy with a biologic agent as part of the initial immunosuppressive regimen in KTRs. (*1A*)
  1.2.1: We recommend that an IL2-RA be the first-line induction therapy. (*1B*)
  1.2.2: We suggest using a lymphocyte-depleting agent, rather than an IL2-RA, for KTRs at high immunologic risk. (*2B*)

IL2-RA, interleukin 2 receptor antagonist; KTRs, kidney transplant recipients.

2: 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*)
2.2: We suggest that tacrolimus be the first-line CNI used. (*2A*)
  2.2.1: We suggest that tacrolimus *or* CsA be started before or at the time of transplantation, rather than delayed until the onset of graft function. (*2D tacrolimus; 2B CsA*)
2.3: We suggest that mycophenolate be the first-line antiproliferative agent. (*2B*)
2.4: We suggest that, in patients who are at low immunological risk and who receive induction therapy, corticosteroids could be discontinued during the first week after transplantation. (*2B*)
2.5: We recommend that if mTORi are used, they should not be started until graft function is established and surgical wounds are healed. (*1B*)

CNI, calcineurin inhibitor; CsA, cyclosporine A; mTORi, mammalian target of rapamycin inhibitor(s).

3: LONG-TERM MAINTENANCE IMMUNOSUPPRESSIVE MEDICATIONS

3.1: We suggest using the lowest planned doses of maintenance immunosuppressive medications by 2–4 months after transplantation, if there has been no acute rejection. (*2C*)
3.2: We suggest that CNIs be continued rather than withdrawn. (*2B*)
3.3: If prednisone is being used beyond the first week after transplantation, we suggest prednisone be continued rather than withdrawn. (*2C*)

CNI, calcineurin inhibitor.

4: 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*)
  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*)

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.

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*)

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*)

CCB, calcium-channel blocker; CNI, calcineurin inhibitor.

5: MONITORING IMMUNOSUPPRESSIVE MEDICATIONS

5.1: We recommend measuring CNI blood levels (*1B*), and suggest measuring at least:
- every other day during the immediate post-operative 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*)

5.1.1: We suggest monitoring CsA using 12-h trough (C_0), 2-h post-dose (C_2), or abbreviated AUC. (*2D*)

5.1.2: We suggest monitoring tacrolimus using 12-h trough (C_0). (*2C*)

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

5.3: We suggest monitoring mTORi levels. (*2C*)

AUC, area under concentration-time curve; CNI, calcineurin inhibitor; CsA, cyclosporine A; MMF, mycophenolate mofetil; mTORi, mammalian target of rapamycin inhibitor(s).

6: TREATMENT OF ACUTE REJECTION

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

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

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

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

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

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

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

OKT3, muromonab (anti-T-cell antibody).

7: TREATMENT OF CHRONIC ALLOGRAFT INJURY

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

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

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

CAI, chronic allograft injury; CNI, calcineurin inhibitor; CsA, cyclosporine A; eGFR, estimated glomerular filtration rate; mTORi, mammalian target of rapamycin inhibitor(s).

8: MONITORING KIDNEY ALLOGRAFT FUNCTION

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

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

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

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

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

GFR, glomerular filtration rate.

9: KIDNEY ALLOGRAFT BIOPSY

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

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

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

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

9.5: We suggest kidney allograft biopsy when there is:
- new onset of proteinuria *(2C)*;
- unexplained proteinuria $\geqslant$3.0 g per gram creatinine or $\geqslant$3.0 g/24 h. *(2C)*

10: 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)*

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

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

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

10.5: Treatment of recurrent kidney disease:

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

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

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

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

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

11: 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)*

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

KTRs, kidney transplant recipients.

12: VACCINATION

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

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

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

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

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

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

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

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

12.4: We suggest giving the following vaccines to KTRs who, due to age, direct exposure, residence or travel to endemic areas, or other epidemiological risk factors are at increased risk for the specific diseases:
- rabies, *(2D)*
- tick-borne meningoencephalitis, *(2D)*
- Japanese B encephalitis-inactivated, *(2D)*

- Meningococcus, *(2D)*
- Pneumococcus, *(2D)*
- Salmonella typhi-inactivated. *(2D)*

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

KTRs, kidney transplant recipients; HBsAb, antibody to hepatitis B surface antigen; HBV, hepatitis B virus.

13: 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)*

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)*

BKV, BK polyoma virus; KTRs, kidney transplant recipients; NAT, nucleic acid testing.

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)*

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

13.2.3: CMV treatment:

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

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

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

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

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)*

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

CMV, cytomegalovirus; KTRs, kidney transplant recipients; NAT, nucleic acid testing

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)*

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

13.3.3: We recommend that patients with EBV disease, including PTLD, have a reduction or cessation of immunosuppressive medication. *(1C)*

EBV, Epstein-Barr virus; KTRs, kidney transplant recipients; NAT, nucleic acid testing; PTLD, post-transplant lymphoproliferative disease.

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)*

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

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

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

13.4.4: We recommend that primary VZV infection (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)*

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

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

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

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

- varicella zoster immunoglobulin (or intravenous immunoglobulin) within 96 h 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)*

HSV, herpes simplex virus; KTRs, kidney transplant recipients; VZV, varicella zoster virus.

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]

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

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

13.5.4: Measure ALT in HCV-infected patients monthly for the first 6 months and every 3–6 months, thereafter. Perform imaging annually to look for cirrhosis and hepatocellular carcinoma. *(Not Graded)* [Based on KDIGO Hepatitis C Recommendation 4.4.1] (See Recommendation 19.3)

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

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

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

ALT, alanine aminotransferase; HCV, hepatitis C virus; KDIGO, Kidney Disease: Improving Global Outcomes; KTRs, kidney transplant recipients.

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)*

13.6.2: We suggest that interferon treatment should generally be avoided in HBV-infected KTRs. *(2C)*

13.6.3: We suggest that all HBsAg-positive KTRs receive prophylaxis with tenofovir, entecavir, or lamivudine. *(2B)*

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)*

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)*

13.6.4: We suggest treatment with adefovir or tenofovir for KTRs with lamivudine resistance (>5 $\log_{10}$ copies/ml rebound of HBV-DNA). *(2D)*

13.6.5: Screen HBsAg-positive patients with cirrhosis for hepatocellular carcinoma every 12 months with liver ultrasound and alpha feto-protein. *(Not Graded)* (See Recommendation 19.3).

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 $\geqslant 100$ mIU/ml. *(2D)*

ALT, alanine aminotransferase; HBsAb, antibody to hepatitis B surface antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; KTRs, kidney transplant recipients.

13.7: HUMAN IMMUNODEFICIENCY VIRUS

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

13.7.2: To determine antiretroviral therapy, refer HIV-infected KTRs to an HIV specialist, who should pay special attention to drug-drug interactions

and appropriate dosing of medications. *(Not Graded)*

HIV, human immunodeficiency virus; KTRs, kidney transplant recipients.

14: 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)*

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

KTRs, kidney transplant recipients; UTI, urinary tract infection.

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)*

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

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

14.2.4: We recommend treatment with corticosteroids for KTRs with moderate to severe PCP (as defined by $PaO_2 < 70$ mm Hg in room air or an alveolar gradient of > 35 mm Hg). *(1C)*

KTRs, kidney transplant recipients; PaO_2, partial pressure of oxygen in arterial blood; PCP, Pneumocystis jirovecii pneumonia.

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)*

14.3.2: We recommend monitoring CNI and mTORi blood levels in patients receiving rifampin. *(1C)*

14.3.2.1: Consider substituting rifabutin for rifampin to minimize interactions with CNIs and mTORi. *(Not Graded)*

CNI, calcineurin inhibitor; KTRs, kidney transplant recipients; mTORi, mammalian target of rapamycin inhibitor(s); TB, tuberculosis.

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)*

15: DIABETES MELLITUS

15.1: SCREENING FOR NEW-ONSET DIABETES AFER 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)*

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)*

CNI, calcineurin inhibitor; HbA_{1c}, hemoglobin A_{1c}; KTRs, kidney transplant recipients; mTORi, mammalian target of rapamycin inhibitor(s); NODAT, new-onset diabetes after transplantation.

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)*

15.2.2: Consider targeting HbA_{1c} 7.0–7.5%, and avoid targeting $HbA_{1c} \leqslant 6.0\%$, especially if hypoglycemic reactions are common. *(Not Graded)*

15.2.3: We suggest that, in patients with diabetes, aspirin (65–100 mg/d) 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)*

CVD, cardiovascular disease; HbA_{1c}, hemoglobin A_{1c}; NODAT, new-onset diabetes after transplantation.

16: HYPERTENSION, DYSLIPIDEMIAS, TOBACCO USE, AND OBESITY

16.1: HYPERTENSION

16.1.1: We recommend measuring blood pressure at each clinic visit. *(1C)*

16.1.2: We suggest maintaining blood pressure at < 130 mm Hg systolic and < 80 mm Hg diastolic if $\geqslant 18$ years of age, and < 90th percentile for sex, age, and height if < 18 years old. *(2C)*

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 $\geqslant 1$ g/d for $\geqslant 18$ years old and $\geqslant 600$ mg/m^2/24 h for < 18

years old, consider an ACE-I or an ARB as first-line therapy.

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

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.

16.2.2: Evaluate KTRs with dyslipidemias for secondary causes [Based on KDOQI Dyslipidemia Recommendation 3]

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].

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].

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].

HDL-C, high-density lipoprotein cholesterol; KDOQI, Kidney Disease Outcomes Quality Initiative; KTRs, kidney transplant recipients; LDL-C, low-density lipoprotein cholesterol.

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.

16.3.2: Offer treatment to all patients who use tobacco. *(Not Graded)*

KTRs, kidney transplant recipients.

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.

16.4.2: Offer a weight-reduction program to all obese KTRs. *(Not Graded)*

BMI, body mass index; KTRs, kidney transplant recipients.

17: 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)*

17.2: We suggest using aspirin (65–100 mg/d) in all patients with atherosclerotic CVD, unless there are contraindications. *(2B)*

CVD, cardiovascular disease; KTRs, kidney transplant recipients.

18: 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)*

18.2: We recommend that KTRs minimize life-long sun exposure and use appropriate ultraviolet light-blocking agents. *(1D)*

18.3: We suggest that adult KTRs perform skin and lip self-examinations and report new lesions to a health-care provider. *(2D)*

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)*

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)*

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

KTRs, kidney transplant recipients.

19: 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)*

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.

19.3: Obtain hepatic ultrasound and alpha feto-protein every 12 months in patients with compensated cirrhosis. *(Not Graded)* [See Recommendations 13.5.4 (HCV) and 13.6.5 (HBV).]

HBV, hepatitis B virus; HCV, hepatitis C virus; KTRs, kidney transplant recipients.

20: MANAGING CANCER WITH REDUCTION OF IMMUNOSUPPRESSIVE MEDICATION

20.1: We suggest consideration be given to reducing immunosuppressive medications for KTRs with cancer. *(2C)*

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 chemotherapy.

20.2: For patients with Kaposi sarcoma, we suggest using mTORi along with a reduction in overall immunosuppression. *(2C)*

KTRs, kidney transplant recipients; mTORi, mammalian target of rapamycin inhibitor(s).

21: TRANSPLANT BONE DISEASE

(See KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder [CKD–MBD].)

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

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)*

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.

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)*

21.2.3: It is reasonable to manage these abnormalities as for patients with CKD stages 3–5. *(Not Graded)*

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)*

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)*

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)*

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)*

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)*

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)*

21.6.3: There are insufficient data to guide treatment after the first 12 months. *(Not Graded)*

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)*

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)*

25(OH)D, 25-hydroxyvitamin D; BMD, bone mineral density; CKD, chronic kidney disease; CKD–MBD, chronic kidney disease–mineral and bone disorder; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; PTH, parathyroid hormone.

22: HEMATOLOGICAL COMPLICATIONS

22.1: Perform a complete blood count at least (*Not Graded*):
- daily for 7 days, or until hospital discharge, whichever is earlier;
- 2–3 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

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

22.3: For treatment of neutropenia and thrombocytopenia, include treatment of underlying causes whenever possible. *(Not Graded)*

22.4: We recommend using ACE-Is or ARBs for initial treatment of erythrocytosis. *(1C)*

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

23: HYPERURICEMIA AND GOUT

23.1: We suggest treating hyperuricemia in KTRs when there are complications, such as gout, tophi, or uric acid stones. *(2D)*

23.1.1: We suggest colchicine for treating acute gout, with appropriate dose reduction for reduced kidney function and concomitant CNI use. *(2D)*

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

23.1.3: We suggest avoiding NSAIDs and COX-2 inhibitors whenever possible. *(2D)*

CNI, calcineurin inhibitor; COX-2, cyclo-oxygenase-2; KTRs, kidney transplant recipients; NSAID, nonsteroidal anti-inflammatory drug.

24: 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 $\geqslant 3$ years until final adult height. *(Not Graded)*

24.2: We recommend using rhGH 28 IU/m^2/wk (or 0.05 mg/kg/d) in children with persistent growth failure after kidney transplantation. *(1B)*

24.3: We suggest minimizing or avoiding corticosteroid use in children who still have growth potential. *(2C)*

rhGH, recombinant human growth hormone.

25: SEXUAL FUNCTION AND FERTILITY

25.1: SEXUAL FUNCTION

25.1.1: Evaluate adults for sexual dysfunction after kidney transplantation. *(Not Graded)*

25.1.2: Include discussion of sexual activity and counseling about contraception and safe sex practices in follow-up of adult KTRs. *(Not Graded)*

KTRs, kidney transplant recipients.

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/d proteinuria. *(2C)*

25.2.2: We recommend that MMF and EC-MPS be discontinued or replaced with azathioprine before pregnancy is attempted. *(1A)*

25.2.3: We suggest that mTORi be discontinued or replaced before pregnancy is attempted. *(2D)*

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)*

25.2.5: Counsel pregnant KTRs and their partners about the risks and benefits of breastfeeding. *(Not Graded)*

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

EC-MPS, enteric-coated mycophenolate sodium; KTRs, kidney transplant recipients; MMF, mycophenolate mofetil; mTORi, mammalian target of rapamycin inhibitor(s).

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)*

25.3.2: We recommend that adult male KTRs be informed of the possible risks of infertility from mTORi. *(1C)*

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)*

KTRs, kidney transplant recipients; mTORi, mammalian target of rapamycin inhibitor(s).

26: LIFESTYLE

26: We recommend that patients are strongly encouraged to follow a healthy lifestyle, with exercise, proper diet, and weight reduction as needed. *(1C)* [See also Obesity, Recommendation 16.4.1]

27: MENTAL HEALTH

27: Include direct questioning about depression and anxiety as part of routine follow-up care after kidney transplantation. *(Not Graded)*

DISCUSSION

This guideline describes the prevention and treatment of complications that occur after kidney transplantation. It does not include pretransplant care. Specifically, it does not address issues pertinent to the evaluation and management of candidates for transplantation, or the evaluation and selection of kidney donors. Although many of the issues that are pertinent to KTRs are also pertinent to recipients of other organ transplants, we intend this guideline to be for KTRs only.

This guideline covers only those aspects of care likely to be different for KTRs than for patients in the general population. For example, we deal with the diagnosis and treatment of acute rejection, but not with the diagnosis and treatment of community-acquired pneumonia. It also makes recommendations pertinent to the management of immunosuppressive medications and their complications, including infections, malignancies, and cardiovascular disease. This guideline ends before the kidney fails, either by death of the recipient with a functioning graft or on return to dialysis or retransplantation. It does not deal with the preparation of KTRs for return to dialysis or retransplantation.

This guideline was written for doctors, nurses, coordinators, pharmacists, and other medical professionals who directly or indirectly care for KTRs. It was not developed for administrative or regulatory personnel *per se*. For example, no attempts were made to develop clinical performance measures. Similarly, this guideline was not written for patients directly, although carefully crafted explanations of guideline recommendations could potentially provide useful information for patients. The recommendations are meant to provide a basis for joint decision making between patients and physicians or other health care providers.

This guideline was written for transplant-care providers throughout the world. As such, it addresses issues that are important to the care of KTRs in both developed and developing countries, but nowhere was the quality of care compromised for utilitarian purposes. Nevertheless, we recognize that, in many parts of the world, treatment of end-stage kidney disease (chronic kidney disease stage 5) with dialysis is not feasible, and transplantation can only be offered as a lifesaving therapy if it is practical and cost-effective. Therefore, in providing a comprehensive, evidence-based guideline for the care of the KTRs, we were cognizant of the fact that programs in some areas of the world may need to adopt cost-saving measures to make transplantation possible.

This clinical practice guideline is based on the best information available as of March 2009. It is designed to provide information and assist decision-making. It is not intended to define a standard of care, and should not be construed as one, nor should it be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every health-care professional making use of these recommendations is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

METHODS

Organization of evidence-based recommendations

The KDIGO Co-Chairs appointed the Co-Chairs of the Work Group, who assembled the Work Group, including individuals with expertise in adult and pediatric nephrology, transplant surgery and medicine, critical-care medicine, cardiology, infectious diseases, oncology, and epidemiology, along with a patient advocate. An Evidence Review Team (ERT) at the Tufts Center for Kidney Disease Guideline Development and Implementation at Tufts Medical Center in Boston, MA, USA was contracted to provide expertise in guideline development methodology and systematic evidence review.

Literature searches

For each key clinical question that the Work Group developed, the ERT coordinated a systematic review of the literature. For each topic, the systematic review included the development of well-specified research questions, literature searches, data extraction of primary studies and existing systematic reviews, tabulation of data, assessment of the quality of individual studies, and assessment of the overall quality of the literature and summary conclusions. After review of the evidence with the ERT, the Work Group took the primary role of writing the recommendations and rationale narrative, and retained final responsibility for the content of the recommendation statements and the accompanying narrative.

The ERT, with assistance from the Cochrane Renal Group in Sydney Australia, performed literature searches in MEDLINE, Cochrane Central Registry for trials, and Cochrane database of systematic reviews from 1985 through February 2008. The Work Group added additional studies through November 2008. The electronic searches were designed to maximize sensitivity for studies of KTRs with conditions and/or interventions of interest. Study eligibility was based on population, intervention, comparator, outcome, and study design relevant to each clinical question. For most topics, the searches focused on randomized controlled trials with at least 100 participants and 6-month duration of follow-up; or multivariable analyses of large cohort studies. Exceptions were made for topics with sparse evidence or for trials in children. Unpublished and non-peer-reviewed articles were excluded. In addition, existing systematic reviews that used similar study eligibility criteria were included. For topics in which these existed, searches for *de novo* studies were limited to publication dates after the end of the searches within the systematic reviews.

Table 3 | Balance of benefits and harm

When there was evidence to determine the balance of medical benefits and harm of an intervention to a patient, conclusions were categorized as follows:

- **Net benefits**=the intervention clearly does more good than harm.
- **Tradeoffs**=there are important tradeoffs between the benefits and harm.
- **Uncertain**=it is not clear whether the intervention does more good than harm.
- **No net benefits**=the intervention clearly does not do more good than harm.

Summary of data and assessment of study quality

For each included study, detailed data extraction forms were completed. For each research question with sufficient data, summary tables were created, which contain a brief description of the outcome, baseline characteristics of the population, intervention, results, and methodological quality. The summary tables are available at http://www.kdigo.org.

Each trial was graded for study quality using a standardized system used for previous KDIGO guidelines that follows the approach recommended by the US Agency for Healthcare Research and Quality for its Comparative Effectiveness Reviews.[5–7] In brief, features of study design, reporting, and other considerations are assessed to estimate the likelihood of bias from low (A, good quality) to high (C, poor quality).

Use of the GRADE approach to assess the body of evidence

A structured approach, based on Grading of Recommendations Assessment, Development and Evaluation (GRADE), was used to grade the quality of the overall evidence and the strength of recommendations.[8–10] The 'quality of a body of evidence' refers to the extent to which our confidence in an estimate of effect is sufficient to support a particular recommendation.[10] The 'strength of a recommendation' indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm.

In brief, each clinical outcome was ranked by the Work Group as to its level of clinical importance. The quality of the overall body of evidence was then determined based on the quality grades for all outcomes of interest, taking into account explicit judgments about the relative importance of each outcome. There are four final categories for the quality of overall evidence, ranging from A to D (Table 2).[8] The net health benefit was determined based on the anticipated balance of benefits and harm across all clinically important outcomes. The assessment of net medical benefit was affected by the judgment of the Work Group and the ERT (Table 3).

The strength of a recommendation is graded Level 1, Level 2, or 'Not Graded' (Table 1). Recommendations can be for or against doing something. The strength of a recommendation is determined not just by the quality of the evidence, but also by other, often complex, judgments regarding the size of the net medical benefit, values and preferences, and costs. KDIGO also includes ungraded statements for any recommendation that meets any of the following criteria: it provides guidance based on common sense; it provides reminders of the obvious; it is not sufficiently specific to allow application of evidence to the issue, and therefore is not based on systematic, evidence review. Common examples include recommendations about frequency of testing, referral to specialists, and routine medical care.

Limitations of methods

Although the literature searches were intended to be comprehensive, they were not exhaustive. MEDLINE and various Cochrane databases were the only databases searched. However, important studies known to the domain experts that were missed by the electronic literature searches were added to retrieved articles and reviewed by the Work Group. Not all topics and subtopics covered by this guideline could be thoroughly and systematically reviewed. Decisions to restrict the topics were made to focus the systematic reviews on those topics in which existing evidence was thought to be likely to provide support for the guideline. Although nonrandomized studies were reviewed, the majority of the ERT and Work Group resources were devoted to review of randomized trials, as these were deemed to be most likely to provide data to support level 1 recommendations with very high- or high-quality (A or B) evidence.

DISCLOSURE

KDIGO makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived or actual conflicts of interest. This document is updated annually and information is adjusted accordingly. All reported information is printed in the full version publication of the guideline and is on file at the National Kidney Foundation (NKF), Managing Agent for KDIGO. Bertram L. Kasiske, MD (Work Group Co-Chair) has served as an Advisor/Consultant for Astellas, LithoLink, Novartis, and Wyeth. He has received Grant/Research support from Bristol-Myers Squibb, Genzyme, and Merck-Schering Plough. Martin G. Zeier, MD, FASN (Work Group Co-Chair) has received Grant/Research support from Astellas, Novartis, and Parexel. Jeremy R. Chapman, MD, FRACP, FRCP has served as an Advisor/Consultant for Astellas, Hoffmann-LaRoche, Novartis, and Wyeth. He has Grant/Research support from Bristol-Myers Squibb, Novartis, and Wyeth. Henrik Ekberg, MD, PhD has served as an Advisor/Consultant for Astellas, Bristol-Myers Squibb, Hoffmann-LaRoche, Life Cycle Pharma, Novartis, and Wyeth. He has also served as Speaker for Astellas and Hoffmann-LaRoche. Michelle A. Josephson, MD has served as an Advisor/Consultant for Digitas Health, MKSAP and Wyeth. She has also served as Speaker for Hoffmann-LaRoche and has received Grant/Research Support from Amgen, Astellas, and Wyeth. Bryce A. Kiberd, MD has served as Speaker for Hoffmann-LaRoche. Henri A. Kreis, MD has served as an Advisor/Consultant for Novimmune. John M. Newmann, PhD, MPH has served as an Advisor/Consultant for Arbor Research Collaborative and Renaissance Health Care. Flavio G. Vincenti, MD has received Grant/Research support from Astellas, Bristol-Myers Squibb, Genentech, Hoffmann-LaRoche, Novartis, and Wyeth.

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