REVIEW ARTICLE

The KDIGO review of the care of renal transplant recipient

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ABSTRACT

This review highlights the key messages from the KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guidelines for care of kidney transplant recipients, which were written to be global guidelines irrespective of the regulatory, fiscal, cultural, socioeconomic, or geographical environment. The distillation of 3168 randomized control trials, 7543 cohort studies, and 1609 reviews led to recommendations rated by the strength of supporting evidence and the quality of the data from A to D. Despite this, the quality of the evidence is surprisingly low for the majority of decisions that are routinely taken in all transplant units throughout the world, highlighting the needs for properly designed randomized controlled trials. The principle areas covered in the guidelines include immunosuppression, management of acute rejection, monitoring of the patient and graft, chronic allograft injury, kidney biopsy, nonadherence, vaccination, infectious diseases, cardiovascular risk management, malignancy, bone disease, pediatric growth, lifestyle, fertility, and mental health. This review highlights a number of these areas for consideration focusing on the different types of evidence that we use in daily clinical practice.

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Introduction The aim of this review is to highlight the key messages from the KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guidelines[1,2] for primary care physicians in their care of kidney transplant recipients (KTRs) and to place them into context for clinicians involved in kidney transplantation in Poland as others have in different reviews.[3,4,5]

The KDIGO guidelines were written as global guidelines not hampered or enhanced by the particular restrictions or opportunities of any particular regulatory, fiscal, cultural, socioeconomic, or geographical environment. But there are limitations imposed by this goal in that they do not take into account such realities of our clinical practice. It is thus important for physicians to interpret these guidelines in the light of the needs of their patient population.

Background These guidelines were written by a committee of 15 people from 9 countries, led by Bertram Kasiske from the United States and Martin Zeier from Germany, with support from an evidence review team of 5 full-time people based at Tufts Medical Center in Boston and lead by Ethan Balk. The publication involved distillation of 12,327 articles comprising 3168 randomized control trials (RCTs), 7543 cohort studies, and 1609 reviews. These papers were reduced to a final tally of 937 references. Each recommendation in the guidelines is rated by its strength of supporting evidence as Level 1 "We recommend", Level 2 "We suggest" or "Not graded". These levels are of importance since Level 1 implies that the authors decided that the evidence was such that most people would want that standard of care – definitely what you would want a relative to receive. Level 2 evidence might be suitable for some patients, and a health service might decide for or against such recommendations and could easily defend the decision.

The supporting articles are formally evaluated for the quality of the data from A to D. The detail of the grading system is available in the guidelines document, but it is important to note that less than 20% of the recommendations are supported by level A or B evidence.

The sum total of the advice is not enough to care for even a single patient after a renal transplant. Much of what we do in clinical practice has no basis in evidence, some because it is so obvious that it is inappropriate to question it, such as the decision to use a sharp knife for a surgical incision and to close the wound at the end of surgery. Other decisions are hard to design an appropriate study in order to prove best practice, for example we still have little evidence on which to base the frequency of posttransplant follow-up clinic visits.

Warning on the use of this review   The synthesis of the guidelines presented here is merely an interpretation of some aspects of the guidelines, and it is strongly recommended that the relevant sections of the guidelines are reviewed directly by physicians considering use of the advice to manage their own clinical practice. The guidelines are freely available on a number of internet sites including www.tts.org and www.kdigo.org.[6,7]

Immunosuppression   There is actually no RCT evidence that immunosuppression is required to maintain successful renal transplant function. However, there is substantial evidence on comparison of different therapies.

Induction therapy with a biologic agent, either lymphocyte-depleting agents or interleukin 2 receptor antagonist, reduces acute rejection but the evidence for efficacy and safety for lymphocyte depleting antibodies is more limited. Induction therapy with a lymphocyte-depleting antibody increases the incidence of serious adverse effects, but for those who are at high risk for acute rejection depleting biologics might be of benefit.

For maintenance immunosuppressive medication, the recommendation is to use a combination of drugs with different mechanism of action and at reduced doses for additive efficacy and limited toxicity. It is suggested that tacrolimus be used as the first-line calcineurin inhibitor (CNI) and mycophenolate as the first-line antiproliferative agent. It is important to achieve early therapeutic blood levels of a CNI to prevent acute rejection. Contrary to much original practice, initiation of a CNI should not be delayed even in the context of delayed graft function. Tacrolimus usage is associated with a lower risk of acute rejection with better graft survival during the first year of transplantation when compared with cyclosporin. Low-dose tacrolimus has been shown to minimize the otherwise significant risk of new-onset diabetes after transplantation (NODAT). Mycophenolate, compared with azathioprine, is associated with a lower risk of acute rejection and improves long-term graft survival in some cases. Avoidance or withdrawal of corticosteroid after the first week transplantation in patients expected to have a low immunological risk reduces steroid-related adverse effects without affecting graft survival. However, it is also associated with higher rate of steroid-sensitive acute rejections, therefore a long-term RCT, with adequate statistical power to detect differences in acute rejection and major adverse events, is needed to determine if the benefits of steroid avoidance outweigh the harms. Mammalian target of rapamycin inhibitors (mTORi) when used as replacement for antiproliferative agents or CNIs, or as add-on therapy, have not been shown to improve patient outcomes. It is suggested that the maintenance immunosuppressive medications be reduced to low dose to prevent toxicity by 2 to 4 months. Of note, RCTs have shown that CNI withdrawal leads to increased acute rejection without altering graft survival and that steroid withdrawal more than 3 months after transplantation increases the risk of acute rejection.

The guidelines contain advice on strategies designed to reduce the cost of immunosuppression including the use of concomitant agents that affect drug metabolism and the use of generic agents.

Treatment of acute rejection and chronic allograft injury   It is recommended that a biopsy should be obtained before treatment of acute rejection, despite the absence of RCT evidence, to show that obtaining a biopsy improves outcomes of suspected acute rejection as there are many conditions that can mimic acute graft rejection. Treatment of subclinical and borderline acute rejection diagnosed on protocol biopsy may improve graft survival. Most acute cellular rejection responds to treatment with corticosteroids. For patients who have a rejection episode, it is suggested that they should be commenced on prednisone if they are not on steroids, and/or mycophenolate if they are not receiving any antiproliferative agents. Acute cellular rejection that is unresponsive to corticosteroids or recurs should have treatment with an anti-T-cell antibody as it may prolong graft survival. Further rejection may be prevented with increased immunosuppressive medication. There are a number of measures used for treating antibody-mediated rejections, including plasma exchange, intravenous immunoglobulin, anti-CD20 antibody and anti-T-cell antibodies without substantial supporting evidence.

In long-term follow-up, it is also recommended that all KTRs with gradually declining kidney allograft function of unknown cause should have a biopsy to diagnose potentially reversible cause. Biopsies that revealed interstitial fibrosis and tubular atrophy have previously been labeled as "chronic rejection" or "chronic allograft nephropathy", but these are nonspecific diagnostic terms and should be avoided. The Banff 2005 workshop recommends that the term "chronic allograft injury" (CAI) should be used. There are many causes of CAI, including hypertension, CNI toxicity, chronic antibody-mediated rejection, and it is the most common cause of graft failure. About ¼ of KTRs at 1 year posttransplant have moderate to severe CAI on biopsy

and by 10 years about 90% of KTRs are expected to have CAI on biopsy. KTRs whose biopsy reveals reversible causes of graft dysfunction such as acute rejection, BK polyomavirus (BKV) nephropathy, or recurrent kidney disease may respond to appropriate treatments. It is suggested that KTRs with histological evidence of CNI toxicity on their kidney allograft biopsy should have their CNI reduced, withdrawn, or replaced. Replacement of CNI with mTORi is suggested in patients with CAI, but only if their estimated glomerular filtration rate (GFR) is >40 ml/min/1.73 m^2, and urine total protein excretion is <500 mg/g creatinine.

Graft monitoring   It is generally accepted that screening tests are needed to be performed routinely to allow prompt detection of kidney allograft dysfunction to allow timely diagnosis and treatment that may improve outcomes. The KDIGO guidelines provide suggestions as to the frequency of follow-up testing but acknowledge that there is only weak data to support the proposals. Serum creatinine is readily available in most laboratories and reliable for detecting acute changes of kidney function. The level of serum creatinine at year 1 after transplantation is a risk factor for subsequent outcomes, and may help determine the frequency of visits in the longer-term care. Unfortunately, serum creatinine is less reliable for detecting chronic changes in kidney function.

Formulas used to estimate GFR in chronic kidney disease population have not shown to be useful in KTRs. Measurement of GFR with urinary or plasma clearance techniques is the most accurate measure of allograft function in KTRs. However, the guidelines do not recommend their use in routine clinical practice due to cost, low patient acceptance, and variable availability. Measurement of cystatin C has also been used to monitor kidney function and is independent from body weight. However, more validation studies for cystatin C as estimation of GFR are required before it can be recommended to be used in KTRs.

Patients with proteinuria generally have lower kidney function compared with patients without proteinuria. Proteinuria is also associated with mortality and cardiovascular disease (CVD) events in KTRs. Hence, it is suggested that the measurement of urine protein excretion be performed once in the first month as the baseline, followed by every 3 months during the first year and annually thereafter.

Kidney allograft ultrasound examination is an important and noninvasive test to detect most common causes of allograft dysfunction, including arterial occlusion, venous thrombosis, urinary obstruction, and a urine leak. As mild-to-moderate calyceal distension in the kidney allograft is often detected on ultrasound examination in KTRs with normal kidney function, a baseline ultrasound examination of the kidney allograft should be performed to allow future comparisons.

Allograft biopsy is recommended in KTRs with a persistent, unexplained elevation in serum creatinine. It is also recommended in cases where there is a failure of function to return to baseline after treatment of an acute rejection to exclude new pathological process, such as coexistent acute tubular necrosis, drug toxicity or BKV nephropathy. As the incidence of acute rejection during delayed graft function (DGF) is higher than in patients without DGF, it is suggested that biopsy to diagnose superimposed acute rejection should be performed every 7 to 10 days while the patients are already receiving with dialysis, or when their serum creatinine does not fall from pretransplant values. However, it is suggested that allograft biopsies may reasonably be avoided by centers that have a very low overall incidence of acute rejection or when there are signs that DGF is resolving. Allograft biopsy is also suggested in KTRs whose kidney function fails to achieve the expected level, and in KTRs who developed new-onset unexplained proteinuria.

Acute rejection, CAI and CNI toxicity can occur in the absence of a measurable decline in kidney function. Several studies have shown that protocol biopsies can detect subclinical acute rejection as well as CAI and CNI nephrotoxicity. Data from observational studies has indirectly suggested that treatment of subclinical acute rejection diagnosed on protocol biopsies may be beneficial as subclinical rejection is associated with CAI and reduced graft survival. However the cost of protocol biopsies may be high in some centers and the guidelines suggest that further RCTs are needed to determine when the benefits of protocol biopsies outweigh harm.

Recurrent kidney disease   Recurrent glomerulonephritis was noted to be the third most frequent cause for graft failure 10 years after kidney transplantation and may present as increased serum creatinine, new-onset or increased proteinuria and/or hematuria. The risk of recurrence is particularly increased in KTRs with an original diagnosis of focal segmental glomerulosclerosis (FSGS), immunoglobulin A nephropathy, membranoproliferative glomerulonephritis, hemolytic-uremic syndrome (HUS), oxalosis and others. FSGS, HUS, and oxalosis may recur in the first few days to weeks after transplantation, whereas the timing is variable in the others. The guidelines summarize proposed screening methods, screening frequency and potential treatment for some of the common recurring glomerulonephritis.

Viral diseases   The guidelines provide some current recommendations on the management of viral disease in KTRs, such as BKV, cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes virus, hepatitis C virus, hepatitis B virus, and HIV. Of increasing interest, it is suggested that all KTRs be screened for BKV with quantitative plasma nucleic acid testing (NAT) at regular intervals, and that reduction of immunosuppressive medication

be considered if BKV plasma NAT is persistently greater than 10,000 copies/ml. Where NAT is not available, microscopic evaluation of urine for decoy cells is an acceptable alternative screening method. There are also several antiviral therapies for treatment of BKV nephropathy outlined in the guidelines, but no recommendation has been made due to the lack of definitive data on their effectiveness. In CMV disease, the emphasis is on adequate duration of prophylaxis to prevent the disease. It is suggested that KTRs with CMV disease should be monitored weekly with CMV plasma NAT or pp65 antigenemia. KTRs with serious CMV disease require intravenous ganciclovir rather than oral valganciclovir, which is an alternative treatment for KTRs with milder clinical symptoms. In EBV disease, it is suggested that high risk KTRs be monitored with NAT at regular intervals. KTRs with EBV-related disease such as posttransplant lymphoproliferative disease are recommended to have a reduction or cessation of immunosuppressive medication.

Cardiovascular disease   About 40% of KTRs experience at least one form of CVD event within 3 years after transplantation. With an annual rate of fatal or nonfatal CVD events of 3.5% to 5% (50-fold higher than the general population), it is prudent to manage their CVD risk factors in a manner similar to that proven to be of use in the general population. This approach includes abstinence from cigarette smoking as well as optimal management of diabetes, hypertension, and dyslipidemia. Most of the recommendations regarding the management of these CVD risk factors have been extrapolated from studies on the general population and those for dyslipidemia are based on the recent Kidney Disease Outcomes Quality Initiative Dyslipidemia Guidelines.

It is recommended that all nondiabetic KTRs should be screened for NODAT with fasting glucose, oral glucose tolerance testing, and/or HbA$_{1c}$. After diagnosis of NODAT, there should be consideration of modification of immunosuppressive drugs to reverse diabetes after weighing the risk of rejection and other adverse effects. However, it is important to note that there are only uncontrolled reports on the effects of changing immunosuppressive agents after the diagnosis of NODAT. Acetylsalicylic acid prophylaxis is recommended to prevent CVD based on the benefit seen in diabetics in the randomized trial of the general population.

Cancer   KTRs from studies performed around the world have been noted to have an increased risk of developing cancer, compared with the general population. There have been several cohort studies demonstrating the variability of risk for cancer with both age and sex. Young KTRs have a risk 15 to 30-fold greater than the general population of the same age to develop cancer, while those over 65 years have a two-fold increased risk. Once cancer has been diagnosed, KTRs have

poorer survival compared to the general population diagnosed with cancer. Therefore, it is reasonable to put a greater emphasis on preventative measures and screening of KTRs for cancer with the hypothesis of lower morbidity and mortality from early detection and interventions.

It is recommended that KTRs with high risk of developing skin and lip cancer, such as those with fair skin and living in sun-exposure climates, should be well informed of their risk before transplantation and measures that can be taken to reduce their risk. There is moderate-quality evidence for using acitretin as prophylaxis for formation of new skin cancers but its usage is also associated with adverse effects.

In KTRs, cancers that have a high or moderately increased standardized incidence ratio (SIR) are likely caused or exacerbated by immunosuppressive medication, and thus it is suggested that reduction of immunosuppressive medication should be considered. In distinction, reduction of immunosuppressive medication in KTRs with cancers that have a low SIR (e.g., ≤1.5) is less likely to affect patients' survival. It is important for a treating physician to balance the reduced quality of life from graft loss against the potential for prolonging patient survival as a result of immunosuppression reduction. In KTRs with Kaposi sarcoma, mTORi has been shown to be associated with dramatic reductions in lesion size.

Transplant bone disease   The risk of fractures following kidney transplantation is high and the causes of bone disease in KTRs are multifactorial. There are, however, insufficient data to identify who will benefit from treatment or to suggest any bone-specific therapies after transplantation. It is suggested that KTRs should be treated with calcium, calcitriol, or vitamin D analogs, and/or bisphosphonates to improve bone mineral density, but there is contrary evidence.

Psychosocial health   This important area of health is covered briefly in the guidelines, but there are limitations because there is an overall lack of studies and research in this aspect of care despite its importance. All KTRs are at risk for anxiety and depression because of complex medical conditions that require frequent tests and follow-ups, new medications such as corticosteroids, and the significant impact on lifestyle and work status, especially in the early phase of their transplantation. Delay in diagnosis and treatment of these conditions may result in medication nonadherence and subsequent severe adverse effects such as acute graft rejection. Studies are needed to determine the optimal approach to screening and managing depression and other mental disorders in KTRs.

Conclusion   These guidelines represent a major synthesis of the available data to support the care of KTRs. Despite the enormous work involved, the quality of evidence is surprisingly low for

the majority of decisions that are routinely taken in all transplant units throughout the world. There is a clear need for properly designed RCTs in a number of areas. The economic consequence of the guidelines has not been assessed and may change the decision of many physicians and patients. Finally, it is worth noting that the literature review on which the guidelines were based, spanned the period up to 2008, and that the subsequent 2 years have provided new studies and meta-analyses, which may alter the conclusions.

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Wytyczne KDIGO dotyczące opieki nad chorymi z przeszczepioną nerką

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STRESZCZENIE

W tym przeglądzie zawarto główne wnioski z wytycznych KDIGO (Kidney Disease: Improving Global Outcomes) dotyczących opieki nad biorcami przeszczepu nerki, będących w zamyśle autorów wytycznymi o znaczeniu globalnym, niezależnie od uwarunkowań prawnych, finansowych, kulturowych, społeczno-ekonomicznych czy geograficznych. Przegląd 3168 badań z randomizacją, 7543 badań kohortowych i 1609 przeglądów pozwolił na sformułowanie zaleceń, które w zależności od siły i jakości stojących za nimi danych naukowych podzielono na stopnie od A do D. Mimo to zaskakująco niska jest jakość danych, na których można się oprzeć w odniesieniu do większości decyzji klinicznych stale podejmowanych we wszystkich ośrodkach transplantologii na świecie, co podkreśla potrzebę przeprowadzenia prawidłowo zaprojektowanych badań z randomizacją. Główne zagadnienia omawiane w tych wytycznych to: immunosupresja, postępowanie w przypadku ostrego odrzucenia, monitorowanie chorego i przeszczepu, przewlekłe uszkodzenie alograftu, biopsja nerki, niestosowanie się do zaleceń, szczepienia, choroby zakaźne, kontrola ryzyka sercowo-naczyniowego, nowotwory złośliwe, choroba kości, wzrastanie u dzieci, styl życia, płodność i zdrowie psychiczne. W tym przeglądzie zwrócono uwagę na niektóre z powyższych zagadnień, podkreślając znaczenie jakości danych naukowych, jakie wykorzystujemy w codziennej praktyce klinicznej.