KDOQI US Commentary on the KDIGO Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation

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Evaluation of patients for kidney transplant candidacy is a comprehensive process that involves a detailed assessment of medical and surgical issues, psychosocial factors, and patients' physical and cognitive abilities with an aim of balancing the benefits of transplantation and potential risks of surgery and long-term immunosuppression. There is considerable variability among transplant centers in their approach to evaluation and decision-making regarding transplant candidacy. The 2020 KDIGO (Kidney Disease: Improving Guidelines Outcome) clinical practice guideline on the evaluation and management of candidates for kidney transplantation provides practice recommendations that can serve as a useful reference guide to transplant professionals. The guideline, covering a broad range of topics, was developed by an international group of experts from transplant and nephrology through a review of literature published until May 2019. A work group of US transplant nephrologists convened by NKF-KDOQI (National Kidney Foundation–Kidney Disease Quality Initiative) chose key topics for this commentary with a goal of presenting a broad discussion to the US transplant community. Each section of this article has a summary of the key KDIGO guideline recommendations, followed by a brief commentary on the recommendations, their clinical utility, and potential implementation challenges. The KDOQI work group agrees broadly with the KDIGO recommendations but also recognizes and highlights the decision-making challenges that arise from lack of high-quality evidence and the need to balance equity with utility of organ transplantation.

Introduction

Kidney transplantation is the preferred treatment option for patients with kidney failure. It offers the best chance of improving both quality and quantity of life but requires careful consideration of the risks and benefits. Patients with kidney failure often have serious medical comorbidities and challenging financial and psychosocial issues that increase the risk of complications and poor outcomes following transplantation. Key among these complications are the risk of infection, malignancy, postoperative cardiovascular complications, and complications arising from nonadherence to therapy after transplantation. Benefits of kidney transplantation have been demonstrated even among patients considered as "high-risk" such as those who are elderly, those with obesity, and those with longstanding diabetes with vascular and coronary artery disease. However, for such high-risk groups, the benefits

of transplantation may be smaller and come with higher risk of complications. Long-term success of transplantation depends on reducing postsurgical complications, carefully balancing the risks and benefits of immunosuppression over time, and developing strategies that ensure long-term adherence to transplant follow-up and medications. The comprehensive pretransplant evaluation of a potential transplant candidate has several objectives, but chief among them are: 1) identify absolute contraindications for transplantation; 2) recognize medical, surgical, psychosocial, and social risk factors that will require optimization prior to transplantation; 3) identify and update recommended screening and health maintenance procedures; 4) assess immunological risk; and 5) offer education, guidance, and counseling to patients about several aspects of kidney transplantation. Implementing this in an evidence-based manner requires incorporating and adopting new research findings from several disciplines of medicine. Additionally, the evaluation and decision-making processes needs to adapt to changes in organ transplant policies instituted at a national level.

The KDIGO (Kidney Disease: Improving Guidelines Outcome) clinical practice guideline on the evaluation and management of candidates for kidney transplantation published in April 2020 provides suggestions and recommendations that cover all major areas of pretransplant evaluation of kidney transplant candidates.[1] While many of the guidelines are backed by good-quality evidence, there was a lack of high-quality studies in some areas, which

necessitated recommendations based on expert opinion. In this article, a work group from NKF-KDOQI (National Kidney Foundation–Kidney Disease Quality Initiative) provides an overview of a select group of guideline recommendations, commenting on their clinical utility and applicability to kidney transplantation in the United States.

KDOQI Commentary Process

The KDOQI Steering Committee selected the commentary chair, who was given the mandate to assemble a work group comprising transplant nephrologists from a diverse group of academic transplant centers in the United States. The work group was asked to identify the important clinical areas to be addressed in this commentary. For each topic, this commentary presents the relevant KDIGO guideline statements (reproduced with permission of KDIGO), a short commentary, discussion of clinical utility, and consideration of implementation and its associated challenges. This content of this commentary was determined by discussion among the KDOQI work group, and all work group members reviewed and approved the commentary after reaching consensus. The article was also reviewed and approved by the NKF Scientific Advisory Board and KDOQI leadership.

Guideline Statements and Commentary

Transplant Recipients of Older Age

2.1: Consider age in the context of other comorbidities, including frailty, that may impact outcome when deciding about suitability for kidney transplantation *(Not Graded)*.

2.1.1: We recommend not excluding patients from kidney transplantation because of age alone *(1A)*.

Commentary

The KDIGO guideline highlights the need to evaluate the transplant candidacy of older individuals in the context of their physiologic reserve, mental health, and medical comorbidities rather than an age-based exclusion. Life expectancy in the United States for individuals age 65 is approximately 20 years, and has improved significantly over the last decade.[2] Individuals >75 years of age account for nearly 25% of those beginning kidney replacement therapy for kidney failure, and the elderly make up the fastest growing segment of the transplant population.[3] However, the likelihood of being waitlisted and successfully getting a transplant is substantially lower among older patients than among younger patients. While the US Renal Data System *Annual Data Report* shows a survival advantage of kidney transplantation over remaining on the waiting list in all age groups, this advantage diminishes with age, and many in the transplant and nephrology community still struggle with the decision of when to offer transplant to the elderly. Large cohort studies

demonstrate that the time to offset the increased risk of early posttransplant mortality is longer for older patients and varies with donor type and recipient risk factors.[4,5] For moderate- to high-risk older patients receiving a deceased-donor kidney, the offset does not occur until around 1 year after transplantation and is the longest for recipients of extended criteria kidneys.[5] Thus, assessment of comorbidity, including frailty (discussed later in this commentary), remains critical in the risk analysis and decision to transplant older individuals. The current approach to pretransplant evaluation remains focused on discrete comorbidities with an emphasis on cancer screening and cardiovascular evaluation for older individuals. There is increasing recognition of the need for more comprehensive assessments, and various scoring systems and comorbidity indices have been developed to assess combinations of factors as opposed to age alone as a single comorbidity. Attempts to quantify and assess frailty (walk speed, sit-to-stand test, grip strength), cognitive function, and social support are also gaining traction. Given the long waiting times for kidney transplantation, it is important to assess these at each evaluation to monitor for trends. The KDIGO guideline recommends not excluding patients solely based on age but does not provide specific guidance for accepting older recipients for transplantation.

It is equally important to recognize the impact of selective and timely acceptance of organ offers, balancing the benefits of transplantation with the use of an expanded donor pool, including high Kidney Donor Profile Index (KDPI), hepatitis C virus nuclear acid amplification test–positive (HCV NAAT+), donation after cardiac death (DCD), and Public Health Services (PHS) increased-risk organs. Finally, the KDIGO guideline does not address quality of life changes from transplantation, which, for some elderly patients, may be the primary reason for seeking transplantation.

Clinical Utility

As both life expectancy and, more importantly, active life expectancy has increased over the past decade, it is important to not exclude patients from kidney transplantation solely for chronologic age. A growing body of literature supports the benefits of kidney transplantation in the elderly. The assessment of frailty, cognitive function, and other comorbidities beyond age alone are important to consider during the evaluation of elderly recipients.

Implementation and Challenges

The first challenge begins with referral to transplantation; awareness among community nephrologists regarding the need for preemptive referral will increase timely evaluation of eligible candidates. Given the long waiting time for deceased-donor kidney transplantation, general nephrologists and the transplant team should educate and counsel elderly patients regarding the benefits of exploring living-donor kidney transplantation as an option.

In 2019, the Scientific Report on Transplant Registry (SRTR) added the deceased-donor kidney transplantation rate and waitlist mortality to their list of transplant center metrics. While these metrics are adjusted for age, they may not fully account for frailty and cognitive issues that are common yet vary among the elderly. This may also have the unintended consequence of decreasing access to listing and transplantation for older candidates. Some transplant centers may not be aggressive in listing older patients due to concerns for inferior outcomes, both on waiting list and after transplantation. A potential solution may be for SRTR to consider reporting transplant center program–specific reports separately for patients >70 years.

The initial evaluation of comorbidity, frailty, cognitive function, and social support are necessary before listing and require ongoing surveillance while on the transplant wait list. Assessment of frailty using gait speed, the sit-to-stand test, and hand grip strength require additional training and time for clinic personnel but may improve assessment of transplant candidacy. Educating patients regarding risks and benefits for nonstandard donor offers (high KDPI, DCD, PHS increased risk, HCV NAAT+) will also require additional time but may help reduce time to transplantation. Consideration of human leukocyte antigen (HLA)-A2 to -B transplants should also be made for appropriate patients. Calculators such as SRTR decision tool (www.srtr.org/reports-tools/kidney-transplant-decision-tool/) and the ones developed by Johns Hopkins University (www.transplantmodels.com/) may be used to estimate probabilities of clinical outcomes on the waiting list and after transplantation. These could help with shared decision-making. However, it is important to note that these models do not consider all comorbidity, social support, frailty, and cognitive issues. Also, even though the estimated survival benefit may vary based on age and the KDPI of transplanted kidney, the calculators always yield a survival benefit for transplantation (even with a marginal organ such as KDPI >85) compared to staying on the wait list or on dialysis. Hence, decisions regarding candidacy will still need to be individualized.

New optional care models introduced by the Centers for Medicare & Medicaid Services (Kidney Care First and Comprehensive Kidney Care Contracting Graduated, Professional, and Global Models) which incentivize cost-effective care of chronic kidney disease (CKD) patients, including those with kidney failure, will likely lead to additional scrutiny of the cost of transplant and post-transplant care in older recipients.[6,7]

Like the general population, the population with kidney failure is aging. Thus, there is a growing need to improve early referral and to address the medical, social, and psychological barriers to transplantation. This will lead to the timely and comprehensive evaluation of older patients to ensure their access to transplantation and will improve the quality and quantity of life that transplant offers.

Psychosocial Assessment

4.1: We suggest performing a psychosocial assessment in all candidates *(2D)*.

    4.1.1: Refer candidates to a health care professional experienced in the psychosocial aspects of kidney transplantation (eg, social worker, psychologist, psychiatrist, psychiatric nurse/nurse practitioner) to perform this assessment *(Not Graded)*.

    4.1.2: Use measurement tools completed by the patient and/or evaluating clinician to supplement the assessment *(Not Graded)*.

        4.1.2.1: We suggest not using measurement tools in isolation to determine transplant candidacy *(2D)*.

    4.1.3: Refer candidates with a diagnosable psychiatric or psychological condition, substance use disorder or nonadherence for pre-transplant counseling and services to enhance the likelihood of a favorable post-transplant outcome *(Not Graded)*.

4.2: We recommend not transplanting patients with an unstable psychiatric disorder that affects decision-making or puts the candidate at an unacceptable level of post-transplant risk *(1C)*.

4.3: We recommend not transplanting patients with ongoing substance use disorder that affects decision-making or puts the candidate at an unacceptable level of post-transplant risk *(1C)*.

4.4: We suggest that patients without current social support be considered for kidney transplantation if they are able to care for themselves and have an identified support plan in place prior to transplantation *(2D)*.

Commentary

Transplant success is highly dependent on patients' ability to adhere to clinic follow-up, laboratory tests, and medication intake. Presence of serious psychiatric or psychosocial barriers therefore pose a significant threat to successful posttransplant outcomes. Hence, the KDOQI work group agrees that patients with unstable psychiatric disorders and significant substance use disorders are not suitable for transplantation. Identification of underlying psychosocial issues is complex and will thus require assessment from a trained health care professional. The KDIGO guideline highlights the lack of evidence for using psychometric measurement tools as the sole decision-making criteria for transplantation but acknowledges that they can complement the assessment of a trained professional. Guideline statement 4.4 addresses the key issue of social or caregiver support, and recommends favoring transplantation for patients capable of self-management even if they lack current social support, provided they

have some pretransplant support plan. This statement is vague and does not provide clarity on the type of support system necessary. Psychosocial challenges among transplant candidates can be profound and often difficult to reverse completely, thus hindering the evaluation process, time to listing, and success after transplantation. Evaluating social support should include considering how the support system can complement the patient's ability for self-care and management of chronic health issues. Kidney disease in the United States disproportionately affects minorities and patients from lower socioeconomic strata. Thus, to avoid worsening inequities, it is imperative to consider patients' ability to manage posttransplant issues in situations with minimal or marginal social support. Notably, the KDIGO guideline does not address specific substance use disorders. Given the expansion of legalization of medical and recreational marijuana use, guidelines on approaching patients with marijuana use may have been useful. The legalization of marijuana in certain geographic areas makes it difficult to make a statement that is acceptable to all. Transplant centers vary in their approach to offering kidney transplantation for patients with ongoing marijuana use.[8] While concern has been raised regarding the use of marijuana and posttransplant adherence, interaction with immunosuppressants, posttransplant psychosocial issues, and clinical outcomes,[8-12] the KDOQI work group acknowledges that the evidence continues to evolve and further research is necessary before major recommendations can be made. The guideline also leaves out issues related to monitoring and psychosocial evaluations when patients are on the waiting list.

Clinical Utility

Psychosocial assessment of transplant candidates is a key component of pretransplant assessment and is performed routinely in all US transplant programs. There is high prevalence of cognitive impairment and psychiatric and substance use disorders among potential candidates as well as among those on the transplant wait list.[13] It is critical to adequately stabilize mood disorders pretransplant, particularly depression, given its association with inferior posttransplant outcomes.[14] Evidence, however, is mixed for the association between social support and poor outcomes following transplantation.[15-17] The studies reporting impact of social support may suffer from selection bias since patients with major issues are often not referred for transplantation or excluded at the time of evaluation.

Implementation and Challenges

It is accepted that psychosocial factors that may negatively affect transplant outcomes should be carefully screened for prior to transplantation. Programs may have different structural components to this assessment but generally use social workers to perform the initial psychosocial assessment, followed by referral of select patients for behavioral health evaluations. The thresholds at which psychiatric disorders are considered a contraindication for transplantation vary among transplant centers. Hence, the KDIGO guideline makes a broad but clear recommendation regarding the importance of assessing the impact of patient's psychiatric disorder on decision-making capabilities and risk of poor outcomes posttransplant. Though tools that assess transplant readiness are available, such as the Psychosocial Assessment of Candidates for Transplant (PACT), Stanford Integrated Psychosocial Assessment for Transplant (SIPAT), and Transplant Evaluation Rating Scale (TERS), it is unclear if they can be used as a standalone assessment.[18,19] The quantitative and predictive aspects of these scales have not been thoroughly evaluated and validated. Thus, while a threshold score on these scales cannot be used for deciding transplant candidacy, they can help standardize psychosocial evaluations. Additional tools such as Patient Health Questionnaire 9 (PHQ-9) for depression and the Montreal Cognitive Assessment (MOCA) can be used to screen select patients identified as high-risk on routine psychosocial assessment.

Transplant teams should also corroborate medical and psychosocial history and issues with other health care providers, including dialysis unit staff and social workers, and should review prior psychosocial evaluations. This will provide an additional layer of confirmation regarding the patient's ability to adhere to posttransplant regimens. A period of stability with regard to serious mood or psychotic disorders and without hospitalization for psychiatric illness is reasonable prior to active listing for transplantation.

Lack of social support accounts for 10%-20% of denials for kidney transplant listing.[20] There are no standardized criteria for defining adequate social support, and transplant programs and clinicians differ in their approach to use of social support criteria for determining transplant candidacy.[20] This lack of standardized criteria may accentuate disparities in access to transplantation. While evidence linking social support and transplant outcomes is not strong, findings suggest that social support does play an important role in facilitating good posttransplant outcomes.[15-17] Adequate social support is especially vital for patients with complex medical issues, older age, physical or mental impairments, and those with a language barrier. Thus, while programs may not all have a clear policy toward social support as a criterion for transplant candidacy, evaluating social support in the context of the overall psychosocial assessment will allow for an individualized approach. This will enable improving transplant access to some patients who may have marginal support systems but can otherwise demonstrate good ability to adhere to posttransplant follow-up.

Nonadherence to Therapy

5.1: Assess adherence and adherence barriers pre-transplantation to allow for appropriate education, counseling and post-transplant surveillance *(Not Graded).*

5.2: Refer candidates with a history of health-compromising nonadherent behavior or identified adherence barriers for adherence-based education and counseling pre-transplant *(Not Graded).*

5.3: We suggest that candidates with a history of graft loss due to nonadherence undergo adherence-based counseling prior to re-transplantation *(2D).*

5.4: We recommend that candidates with a history of non-adherence be considered for transplantation unless there is ongoing, health-compromising nonadherent behavior *(1D).*

Commentary

Nonadherence following transplantation is highly prevalent, increases with time after transplant, and is a major cause of rejection and graft loss. This may manifest in the domain of medication taking and/or missed laboratory tests and clinic appointments. The KDIGO guideline provides recommendations for a comprehensive pretransplant evaluation for nonadherence risk factors, suggests using adherence counseling and education for at-risk patients, and recommends avoiding transplantation in the presence of serious ongoing nonadherence behavior. These recommendations are in line with prior recommendations from other groups.[21,22] The guideline does not provide recommendations on specific methods to use for assessing nonadherence risk given the lack of reliable and validated tools. Consistent with other recommendations, the guideline recommends not excluding patients with prior allograft loss due to nonadherence provided there is no ongoing nonadherence behavior. The KDOQI work group agrees with this recommendation, particularly when prior nonadherence was secondary to adolescence or financial issues, provided patients demonstrate improved understanding and maturity and all financial barriers have been resolved satisfactorily. However, it should be emphasized that prior nonadherence does predict future nonadherence, and every effort at education, counseling, and rectifying barriers to nonadherence should be addressed prior to listing for transplantation.

Clinical Utility

Nonadherence, particularly to immunosuppressive medications, contributes to premature allograft loss with associated morbidity and mortality. Additionally, increased sensitization limits future transplant potential. Premature transplant failure is a major loss to society given the limited number of organs available for transplantation. Thus, transplant teams have a key role in assessing nonadherence risk, making decisions regarding transplantation, and providing appropriate tools for rectifying nonadherence.

Implementation and Challenges

Several factors contribute to nonadherence: poor health literacy, certain health beliefs, low socioeconomic status, cognitive impairment, limited social support, psychiatric disorders, and substance abuse. It is thus important to identify all potential barriers for posttransplant nonadherence prior to listing for transplantation. All efforts should be made to assess overall adherence patterns as they relate to dialysis, other medical visits, and medication-taking. While nonadherence on the waiting list can be gauged by assessing the number of inappropriately missed or shortened dialysis treatments, large interdialytic weight gain, and poor phosphorus, hypertension, and diabetes control, it is important to recognize that nonadherence to some aspects of dialysis regimen may not be always be associated with posttransplant nonadherence.[23,24]

The KDIGO guideline recommends adherence-based education and counseling but does not provide specifics about how such interventions should be implemented. Outside of the teaching provided as part of the transplant evaluation process, there is no specific adherence-based counseling that is available for clinical practice. Additionally, it is unclear if pretransplant adherence education will have long-lasting effects. There is evidence from nonkidney solid organ transplantation that techniques such as motivational interviewing may provide a longer duration of improvement in adherence.[25] Similar studies in kidney transplantation, however, are lacking, and further investigation is required. In addition, access to trained professionals providing adherence-based counseling may be limited. Programs should at least consider augmenting education and counseling at repeated intervals for specific patient groups with certain high-risk characteristics such as adolescents and those with limited support system and financial limitations to reduce risk of posttransplant nonadherence. Decisions regarding retransplantation for those with prior nonadherence are often challenging. Generally, in accordance with all guidelines, retransplantation for such patients is routinely practiced in the United States provided patients can demonstrate improved understanding and insight into posttransplant adherence needs and all contributing financial and social barriers are eliminated or reduced to an acceptable degree.

In summary, given the contribution of nonadherence to inferior outcomes and the numerous risk factors, it is crucial that transplant programs carefully evaluate and mitigate nonadherence risk through education and financial and social support to allow successful transplantation. Even with adequate pretransplant consideration, posttransplant nonadherence will remain an issue, though there is hope that innovative technological solutions (electronic health records and smartphone-based technologies) and behavioral interventions will help improve

adherence. Increasing research funding for studies evaluating nonadherence, including interventions, will pave a path toward improving long-term transplant outcomes. This will be particularly important in the ongoing social and economic crises resulting from the coronavirus disease 2019 (COVID-19) pandemic.

Transplant Recipients with Obesity

> 7.1: We recommend candidates to have their body habitus examined by a transplant surgeon at the time of evaluation and while on the waiting list *(1B)*.
>
> 7.1.1: We suggest that candidates not be excluded from transplantation because of obesity (as defined by body mass index or waist-to-hip ratio) *(2B)*.
>
> 7.1.2: We suggest weight loss interventions be offered to candidates with obesity prior to transplantation *(2D)*.

Commentary

Obesity-related guidelines are deliberately broad regarding consideration for transplantation in recognition of the dichotomy between survival advantage conferred by transplantation over dialysis for patients with obesity and the increased risks for suboptimal outcomes post–kidney transplant experienced by patients with versus without obesity.[26,27] In addition, a specific body mass index (BMI) cutoff is difficult to assign, as the experience and techniques of individual transplant centers and surgeons may influence acceptance criteria. The KDIGO guideline is generally in agreement with prior guidelines[21,22] but differs in not making recommendations based on specific obesity cutoffs for transplantation. The complexity of transplant surgical intervention and the increased risk of wound complications with obesity is reflected in the recommendation to have the patient's body habitus examined by a transplant surgeon prior to transplantation. The guideline also suggests offering weight-loss interventions for transplant candidates with BMI >35 kg/m^2 to reduce complications.

Although in overall agreement with the recommendations, the KDOQI work group feels that the KDIGO guideline should have gone a step further and offered recommendations regarding a BMI cutoff (of >40 kg/m^2) at which transplant candidacy needs to be evaluated and weight-loss interventions such as bariatric surgery should be considered. This is because patients with BMI >40 kg/m^2 are at high risk of staying inactive on the waiting list[28] and, even when transplanted, are at higher risk of perioperative complications, with survival benefit from transplantation being smaller.[27] Additionally, in the general population, there are recommendations for patients with diabetes mellitus and BMI >40 kg/m^2 to consider bariatric surgery as a potential weight-loss intervention.[29]

Finally, the guideline recommendations on obesity are centered around the risk for postsurgical issues and do not stress sufficiently the contribution of obesity to long-term metabolic complications, including elevated risk for new-onset diabetes after transplantation (NODAT).

Clinical Utility

Obesity prevalence is substantial, with 6.7% patients in the United States having class III obesity (BMI >40 kg/m^2). Based on data from the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study, the association of obesity with kidney failure appears to be mediated by metabolic syndrome.[30] While obesity is associated with lower risk of death among patients on maintenance dialysis (despite the independent association with cardiovascular disease), the impact of obesity on transplantation outcomes is complex. Despite a survival advantage of transplantation when compared with remaining on dialysis, obesity also correlates with poorer outcomes posttransplant. Patients with obesity have a higher risk of death, delayed graft function, rejection, wound complications, and prolonged hospitalization stays compared with those without obesity.[31] Thus, obesity remains an important issue for potential transplant candidates.

Implementation and Challenges

The exact underlying mechanisms for the paradoxical survival benefit conferred by obesity for dialysis patients are unclear, but it is hypothesized that patients with high BMI may have lower chronic inflammation, better nutritional status, and higher physical activity.[32-34] However, similar outcomes have not been shown after transplantation, and studies consistently have shown an increased risk of complications with higher BMI.[31] Most of the transplant programs in the United States have BMI cutoffs above which patients need to demonstrate sustained weight loss to be considered eligible for transplantation. It is well known that patients inactive on the waiting list due to obesity have a significant challenge in achieving the necessary weight loss to become eligible for transplantation.[28]

Programs should consider obesity in the context of coexisting comorbidities, body habitus, and functional status. Such an approach may allow for higher BMI cutoffs in active patients with no major cardiovascular or age-related comorbidities. Additionally, since some muscular patients may be disadvantaged by use of BMI criteria alone, careful attention and a case-based approach will be necessary to minimize this bias. Also, since patients on peritoneal dialysis can gain excessive weight, it may be prudent for transplant physicians to discuss with the referring nephrologists the potential for a switch to hemodialysis in select patients; this will need careful consideration of the benefits that come with home dialysis and dialysis access issues. As

recommended by a guideline developed by KDOQI and the Academy of Nutrition and Dietetics, patients may also benefit from medical nutrition therapy, which involves working with a registered dietitian nutritionist to optimize nutritional status and minimize risks due to nutrition-related comorbidity.[35,36]

The evolution of bariatric surgery techniques has been promising, and they offer an option for some patients to achieve the desired weight loss. While there are risks with surgical approaches to obesity, these risks do not appear to be significantly higher among carefully selected dialysis patients compared to the general population.[37] Bariatric surgery approaches to correct obesity may offer additional benefits far beyond better access to transplantation.[38] Single-center studies of transplant centers offering bariatric surgery options to transplant candidates with obesity have shown encouraging outcomes.[38,39] Finally, select centers are offering robotic transplantation for individuals with severe obesity, and this can be considered as an alternative option.[26]

Obesity continues to represent a substantial barrier to transplantation that requires a multidisciplinary approach for evaluation and potential interventions to control its risk associations, which may include bariatric surgical options. Solving the obesity challenge for potential transplant recipients remains a daunting task, at least in the near future.

Transplant Recipients With Frailty

> 7.2: We suggest that candidates be assessed for frailty at the time of evaluation and while on the waitlist to inform posttransplant risk and enable optimization strategies, such as pre-operative rehabilitation (2C).

Commentary

The KDIGO guideline recognizes the importance of frailty as an important negative prognostic factor in transplantation. Several studies have shown that frailty is highly prevalent and correlates with poor outcomes during waitlisting as well as following transplantation.[40-42] The guideline recognizes that frailty is currently not evaluated routinely and suggests incorporating this formally into the initial transplant evaluation. Given preliminary evidence that some patients may have modifiable frailty components, the guideline suggests considering strategies to optimize certain patients with frailty.[43]

The guideline refrains from making any specific recommendations regarding frailty assessment or the type of intervention for frail patients. Understandably, the guideline does not provide specific targets or metrics due to paucity of data. Though not included as a guideline statement, the KDIGO work group recommends against using frailty as a contraindication for transplantation, given that a significant proportion of frail patients also benefit from transplantation and have improvement in frailty scores posttransplant.

The KDOQI work group agrees with the recommendations and that the focus should be on identifying frailty with the aim toward risk modification. A formal approach to quantify frailty may inadvertently reduce access to some frail patients who may otherwise benefit from transplantation, unless it is shown that interventions can effectively modify frailty. In addition, frailty should not be included as a sole factor; instead, it should be evaluated with other concomitant comorbid conditions such as older age, diabetes, and obesity.

Clinical Utility

Frailty, which, by definition, is different than comorbidity burden, is a state of reduced physiological reserve and is related to age and associated comorbidities. It is particularly common in the context of kidney transplantation, with a prevalence of 10%-20% among patients on the waitlist and transplant recipients.[40,42] Frailty increases with age and dialysis vintage; in addition, it is more prevalent in patients who are female (3.3-fold higher) and kidney failure patients who are African American.[42] Frailty confers an increased risk of mortality and morbidity among patients while on the waitlist and after transplantation.[40,41] Post–kidney transplant frailty is associated with graft loss and mortality in addition to higher rates of delayed graft function and longer hospitalization. Hence, attempts to quantify frailty may prove useful by identifying patients who may benefit from strategies aimed at improving frailty scores.

Implementation and Challenges

There is widespread acceptance among the transplant community regarding the need to utilize frailty measurement of transplant candidates. In a recent survey conducted by the American Society of Transplantation (AST), 99% of transplant professionals (of all organ groups) felt frailty assessment is useful among transplant candidates.[44] Additionally, 24% reported utilizing frailty measurements routinely, while another 44% reported measuring frailty at least on some occasions.[44] Despite the widespread support for implementing routine frailty assessment, difficulties may arise regarding choice of frailty assessment tool given the plethora available.[45] Nevertheless, many respondents to the AST survey favored using tools that incorporated measures of physical strength (gait speed, grip strength, and sit-to-stand test) along with weight loss, suggesting that achieving some uniformity and standardization may not be very difficult.

The KDIGO guideline recommends not using frailty as a reason to exclude patients from transplantation. However, close to 70% of the survey respondents in the AST survey felt that results of the frailty assessment should be used to

make transplant candidacy decisions.[45] While this is not the intention of the guideline statement regarding frailty assessment, it is going to be difficult to separate the 2 aspects. In a large prospective study of patients from 3 US transplant centers, even without physicians knowing the results of a formal frailty assessment, frail patients were less likely to be waitlisted and less likely to receive a transplant, even after adjusting for other factors.[42] This suggests that physicians are able to identify frailty-related phenotypes even without a formal frailty assessment protocol. Adding a formal frailty assessment without an interventional strategy may thus run the risk of reducing access to transplantation for frail patients. Finally, transplant centers may not have adequate resources for long-term frailty management, and this needs further investigation.

Recurrent Glomerular Diseases: Focal Segmental Glomerulosclerosis

9.2.1: We recommend not excluding candidates with primary FSGS from kidney transplantation; however, the risk of recurrence should be considered and discussed with the candidate *(1B)*.

   9.2.1.1: Loss of a prior graft due to recurrent FSGS indicates a high risk of recurrence upon subsequent transplantation and this factor should be a major consideration in determining candidacy *(Not Graded)*.

9.2.2: We suggest genetic testing (eg, for podocin and nephrin gene mutations, among others) be performed in children and young adults with a clinical course consistent with genetic FSGS to inform the risk of recurrence *(2C)*.

9.2.3: We suggest avoiding routine use of pre-transplant plasma exchange or rituximab to reduce the risk of recurrent FSGS *(2D)*.

Commentary

Primary focal segmental glomerulosclerosis (FSGS) has a high risk of recurrence in the kidney allograft (30%-50% with first transplant) and high rates of irreversible graft loss. The risk of recurrence is higher, up to 80%, in candidates who have previously lost a transplant due to FSGS recurrence.[46] Pathogenesis of recurrent FSGS has not been fully explored, and, hence, risk factors associated with recurrence remain poorly defined. The identification of a hypothesized circulating factor has been elusive, and, thus, there are no confirmatory tests available for the diagnosis of recurrent FSGS. This also makes it difficult to appropriately risk-stratify candidates prior to kidney transplantation. Finally, specific therapeutic interventions before transplantation have failed to consistently reduce risk of recurrence.

Clinical Utility

The guideline recommendation about discussing the risk of recurrence with the patient is reasonable and clinically useful considering the lack of robust advances in the understanding of pathogenesis in recurrent FSGS and the high rate of recurrence among recipients with prior graft loss from recurrent FSGS.[47,48] The recommendation to order genetic tests for the young is also appropriate given the lower recurrence risk with many genetic forms of FSGS.[47,48] Furthermore, the recommendation to not avoid retransplant in patients with known prior recurrence despite higher rate of graft loss is balanced by poor median survival on long-term dialysis, especially in very young candidates. Currently, the lack of proven pretransplant interventions to prevent recurrence in patients with known prior recurrence of FSGS makes it difficult to advocate for treatment before transplantation.

Implementation and Challenges

The guideline recommendations are appropriate but generally limited by the lack of progress identifying the circulating factor and the continued ill-defined pathogenesis of recurrent FSGS in the clinical setting. Advances in genetic testing and the progressive reduction in the costs associated with next-generation and whole-exome sequencing has made genetic testing easier than before. Thus, implementing genetic testing for transplant candidates with a diagnosis of FSGS, particularly among young adults and those with a family history of FSGS, is reasonable and should be considered by transplant programs. This will allow for better risk stratification for recurrence after transplantation and could also potentially help in the evaluation of related kidney donor candidates. Since genetic variants of FSGS recur very rarely after transplantation, a positive genetic test could provide comfort to patients and confidence to the transplant team about proceeding with transplantation. Despite availability of better genetic tests, emphasis remains on pretransplant clinical risk assessment and counseling potential candidates regarding recurrence of FSGS.

Although the important negative impact of recurrent FSGS on graft survival was recognized decades ago, lack of progress in the elucidation of the pathogenesis in FSGS has left KDIGO with guideline recommendations that are similar to current clinical practice and easy to implement. Transplant programs do not consider FSGS an absolute contraindication for the first transplant, but many are rightfully hesitant to retransplant a patient with prior allograft failure due to FSGS recurrence. Additionally, given that recurrence occurs in <50% of the patients, is difficult to predict pretransplant, and efficacy of preemptive therapies remain unproven, it should be easy to implement KDIGO recommendations to not use preemptive plasmapheresis and rituximab to prevent FSGS recurrence. These recommendations may change over time as further exploration of the pathogenesis of recurrent FSGS paves the path for future diagnostic and therapeutic interventions.

Recurrent Glomerular Diseases: Membranous Nephropathy

9.3.1: We recommend not excluding candidates with MN from kidney transplantation; however, the risk of recurrence should be considered and discussed with the candidate *(1B)*.

9.3.1.1: We suggest not excluding candidates with prior graft loss due to MN; however, the risk of recurrence should be considered and discussed with the candidate *(2D)*.

9.3.2: We suggest that autoantibodies to phospholipase A2 receptor (PLA2R) be measured pre-transplant to inform the risk of recurrence in patients with MN *(2C)*.

9.3.3: We suggest not routinely using rituximab or alkylating agents to reduce the risk of recurrent MN *(2D)*.

Commentary

Membranous nephropathy (MN) is the most common cause of adult nephrotic syndrome. Clinical recurrence of MN is estimated to be around 10% and can go up to 50% with longer follow-up. Multiple autoantibodies have been implicated in the pathogenesis of MN; primary among these are autoantibodies to the phospholipase A_2 receptor (PLA$_2$R), which are seen in 60%-80% of patients with primary/idiopathic MN.[49] The KDOQI work group agrees with the KDIGO guideline recommendations for testing PLA$_2$R before transplantation to assess the risk for recurrent MN. The higher rate of remission associated with rituximab and cyclosporine in the treatment of primary MN is well established,[50] but similar data do not exist for the prevention and treatment of recurrent MN for transplant recipients.

Clinical Utility

Graft loss associated with recurrent MN occurs in ~10%-13% of cases. Therefore, counseling patients about disease recurrence is a valuable consideration. Additionally, measuring disease activity by assaying for anti-PLA$_2$R antibodies before transplantation may help assess risk of recurrent MN. Other antibodies have been identified recently among patients with PLA$_2$R-negative MN (eg, THSD7A [thrombospondin type 1 domain-containing 7A], NELL-1 [neural epidermal growth factor-like 1], and NEP [neutral endopeptidase]), and their measurement should be considered in specific cases. The recommendation against routine pretransplant treatment with rituximab or other alkylating agents is appropriate due to lack of sufficient supporting evidence.

Implementation and Challenges

The risk of allograft loss due to recurrent MN is not a major issue, and, thus, transplantation remains a treatment option for kidney failure patients with MN. PLA$_2$R testing before transplantation should be easy to implement since standardized tests are readily available. The guideline does not specify how and when these antibodies should be measured pretransplantation. Since studies demonstrate an association between presence and strength of anti-PLA$_2$R antibodies and posttransplant recurrence, it may be reasonable to monitor the levels in those who are positive for anti-PLA$_2$R antibodies.[51] However, it is currently unclear if patients with high or increasing levels of anti-PLA$_2$R antibodies should have a period of waiting time prior to kidney transplantation. Additional studies are required to integrate the testing of these antibodies in the management of recurrent MN. Prospective controlled studies on recurrent MN with special reference to prevention and treatment are lacking due to inherent difficulties in performing a randomized study for a rare disease. Thus, treatment for recurrent MN will be based on extrapolating results from MN in native kidneys. The risk-benefit balance of rituximab for recurrent MN with reference to infectious complications in an already immunocompromised population and its long-term efficacy need further evaluation.

Recurrent Glomerular Diseases: Membranoproliferative Glomerulonephritis

9.6. Immune complex-mediated membranoproliferative glomerulonephritis (IC-MPGN) and C3 glomerulopathy (C3G)

9.6.1 IC-MPGN

9.6.1.1: We recommend not excluding candidates with IC-MPGN from kidney transplantation; however, the risk of recurrence should be considered and discussed with the candidate *(1B)*.

9.6.1.2: We recommend investigation for an infective, autoimmune, or paraprotein-mediated cause of IC-MPGN prior to transplantation to guide treatment and inform risk of recurrence *(1C)*.

9.6.1.3: We suggest that, when possible, the cause of the IC-MPGN be treated prior to transplantation *(2C)*.

9.6.2 C3G, including dense deposit disease (DDD) and C3 glomerulonephritis (C3GN)

9.6.2.1: We recommend not excluding candidates with C3G from kidney transplantation; however, the risk of recurrence should be considered and discussed with the candidate *(1B)*.

9.6.2.2: We suggest that candidates with C3G be screened for genetic or acquired causes for the dysregulation of the complement alternative pathway to guide treatment and inform risk of recurrence *(2C)*.

9.6.2.3: Loss of a prior graft due to recurrent C3G indicates a high risk of recurrence upon subsequent transplantation and this factor should be a major consideration in determining candidacy *(Not Graded)*.

Commentary

Kidney transplant remains a viable treatment for patients with membranoproliferative glomerulonephritis (MPGN). The classification schema for MPGN has been updated to reflect pathophysiology and is now classified based on immunofluorescence findings into immune complex (IC) MPGN, complement-mediated MPGN (C3 glomerulopathy), and MPGN without IC or complement activation. IC-MPGN can further be classified based on polyclonal antibody (infections, autoimmune disorders) or monoclonal antibody (gammopathies), while C3 glomerulopathy has 2 subtypes based on structural characteristics observed on electron microscopy (dense deposit disease [DDD] and C3 glomerulonephritis [C3GN]). The pathogenesis of C3 glomerulopathies is secondary to unopposed activation of the alternative complement pathway from either a loss of function of one of the complement regulatory proteins (factor H [CFH] or factor I [CFI]) or from gain-of-function mutations in C3 that lead to resistance to regulation by CFH. It is critical to classify patients prior to transplantation at risk for recurrence, as the risk is variable according to the type of MPGN. Chances of recurrent MPGN are low among patients with polyclonal IC-MPGN and higher among those with monoclonal MPGN or C3 glomerulopathies.[50] In over 70% of cases, there can be recurrence of C3GN, which is often aggressive, seen early after transplantation, and associated with high rates of graft failure.[52]

Clinical Utility

It is imperative to subcategorize MPGN according to IC-MPGN, monoclonal antibody–related MPGN, and C3 glomerulopathy, as the outcome after transplant is different for each category. Subclassification also helps clinicians to approach specific treatment strategies to prevent recurrent MPGN. For example, management of systemic infections should remain the focus for the prevention of IC-MPGN, targeted therapy against monoclonal antibodies for monoclonal MPGN, and anticomplement therapy for C3 glomerulopathies.

Implementation and Challenges

Kidney failure patients with MPGN are not routinely investigated to characterize the type of MPGN based on its pathogenesis. It is important for the transplant team to take the lead in investigating the type of MPGN and convey the chances of recurrence to patients. While testing for a monoclonal paraprotein and autoimmune antibodies are relatively easy to accomplish, testing for complement-mediated C3 glomerulopathies may be challenging since such tests are only available at select laboratories. This arena continues to evolve rapidly, and newer therapies will change the landscape in the prevention and treatment of posttransplant MPGN including C3GN.

Recurrent Glomerular Diseases: Hemolytic Uremic Syndrome

9.11.1: We recommend not excluding candidates with HUS due to infection with a Shiga-toxin producing organism, usually *E. coli* (STEC-HUS), from kidney transplantation *(1A)*.

9.11.2: We recommend assessment of candidates with suspected atypical HUS (aHUS) for a genetic or acquired defect in complement regulation or other genetic causes of aHUS to inform risk of recurrence *(1B)*.

9.11.3: We recommend not excluding candidates with aHUS from kidney transplantation; however, the risk of recurrence should be considered and discussed with the candidate *(1B)*.

9.11.3.1: We recommend that if the candidate has an abnormality in complement regulation placing them at high risk of recurrence, kidney transplantation should not proceed unless a complement inhibitor can be administered or combined liver-kidney transplant can be performed *(1B)*.

Commentary

Hemolytic uremic syndrome (HUS) secondary to Shiga toxin from *Escherichia coli* is a rare cause of kidney failure without any recurrence after transplantation. However, atypical HUS (aHUS), although rare, has high rates of recurrence after kidney transplantation.[53] The pathogenesis of the disease is a defect in the complement system leading to unopposed activation of complements, resulting in microangiopathic lesions in the kidney. The recurrence rate is as high as 80% among those with a defect in CFH or CFI and with a prior history of recurrence.[53] Candidates with no identified genetic mutation are presumed to have an intermediate risk of recurrence. Disease penetrance even with identification of a pathogenic variant is approximately 50%, suggesting that an environmental factor like infection, pregnancy, or transplantation may be a necessary trigger[54]; however, a precipitating factor in many cases may not be apparent. Before the approval of monoclonal anti-C5 complement inhibitor, the recurrence risk was 50%, with graft loss occurring in 80%-90% of the cases.[53] Availability of effective complement inhibitors has revolutionized the prognosis in patients with aHUS. Transplant candidates with mutations affecting proteins primarily synthesized in the liver (CFH, CFI, C3, and CFB) serve as a basis for recommendation of a simultaneous liver and kidney transplantation for a subset of patients with aHUS.

Clinical Utility

Recurrent aHUS can be a catastrophic event with a high rate of graft loss. The outcome, though, can vary depending on the complement abnormality. It is critical to

identify the defect in the complement system, and, accordingly, patients should be counseled for recurrence and given appropriate therapy to prevent recurrence of aHUS.

Implementation and Challenges

Lack of easy access to genetic testing, its prohibitive cost, and variation in test results and interpretation from one laboratory to another makes it difficult for patients as well the transplant center to establish a clear protocol for aHUS. When testing is undertaken, a substantial portion can reveal no mutations or have a genetic variant of unknown significance. The heterogeneity in the mechanisms leading to dysregulation of the alternate pathway and epigenetics related to disease recurrence make counseling a patient challenging and underscore a need for further understanding of the pathogenesis. Currently available anti-complement inhibitors, while very effective, are very expensive, making it prohibitive for many patients and transplant centers to continue long-term therapy. A truncated form of therapy (continuing for a few years) has been attempted with varied success. Lowering the infusion burden with longer-acting anticomplement agents, oral inhibitors, and more selective alternative complement inhibitors that are in the pipeline perhaps may prove to be more useful options in the future.

Recurrent disease remains an important problem for young transplant recipients who do not have diabetes or autosomal dominant polycystic kidney disease. Many patients present at a late stage of CKD with atrophic kidneys and thus lack a definite histologic diagnosis for the kidney disease. Hence, it is prudent that all such kidney transplant recipients be monitored very closely for proteinuria after transplantation with prompt renal histological diagnosis to characterize the type of recurrent disease.

Recipient Vaccination

> 10.7.1: We recommend that the vaccination series be commenced using an accelerated schedule, if necessary, prior to kidney transplantation for any inactivated vaccines (Table 12) *(1B).*
>> 10.7.1.1: We suggest not excluding candidates who do not complete an inactivated vaccine series prior to kidney transplantation *(2D).*
> 10.7.2: We recommend that the vaccination series be completed prior to kidney transplantation for any live attenuated vaccines (Table 12) *(1B).*
>> 10.7.2.1: We recommend a 4-week delay in kidney transplantation if a live vaccine is administered (eg, MMR, VZV, shingles, yellow fever, oral typhoid, oral polio vaccine) *(1B).*

Commentary

The KDIGO guideline appropriately places emphasis on the importance of pretransplant vaccination for transplant candidates. The guideline recommends completing all necessary live attenuated vaccines prior to transplantation and waiting at least 4 weeks prior to moving forward with transplantation. While inactivated vaccines can be administered posttransplant, it is preferable to administer these pretransplant since responses to immunization are suboptimal posttransplant. Hence, the guideline recommends using an accelerated vaccination schedule for inactivated vaccines if necessary so that patients receive all necessary vaccines prior to transplantation. Given the long wait times to transplantation and high mortality and morbidity associated with maintenance dialysis, KDIGO recommends not to delay transplantation just to complete the vaccination series. However, as the risk for posttransplant varicella infection—although small—is real, exceptions could be considered in situations where patients have no demonstrable antibodies against varicella zoster virus. This aspect has to be discussed with the patient prior to transplantation without vaccination.[55,56]

There are relatively few contraindications to vaccination. Since infection is the second leading cause of death among transplant patients, prevention of infectious complications remains prudent, and vaccination is a very effective way to lower morbidity and mortality from certain infections.[57] Thus, the KDOQI work group agrees with the listed KDIGO recommendations including waiting 4 weeks after a live-virus vaccination before transplantation. To reduce the risk of infections from encapsulated bacteria, asplenic kidney transplant candidates should receive pretransplant pneumococcal, *Haemophilus*, and meningococcal vaccination, and patients who may need complement inhibitors in the peri- or posttransplant period should get meningococcal vaccination to reduce the risk of meningitis. Overall, these recommendations are similar to the 2019 guidelines from the AST Infectious Diseases Community of Practice.[58]

Clinical Utility

Vaccinations for vaccine-preventable illnesses are a highly cost-effective way to reduce morbidity and mortality. Kidney transplant recipients are higher risk for serious illnesses and invasive or disseminated disease, and, hence, appropriate and timely vaccination is paramount. The guideline statements thus offer clear and useful recommendations on vaccination schedules that can be followed both pre- and posttransplant as appropriate.

Implementation and Challenges

Obtaining an accurate vaccination history and checking serologies (such as for hepatitis viruses and varicella) at transplant evaluation and coordinating with dialysis centers and primary care physicians will ensure that vaccination is completed well in advance of transplantation. Hepatitis B vaccination is routinely provided to dialysis patients. For patients not on dialysis and for those with a need for expanded vaccination due to risk factors such as splenectomy or need for terminal complement inhibitors,

consultation with a transplant infectious disease specialist will help with timely vaccination. This will allow for better communication between transplant teams to ensure transplantation is delayed for at least 4 weeks after administration of a live attenuated virus vaccine.

The widespread availability of vaccines, statewide immunization registries, and transplant infectious disease–trained physicians at most transplant centers allow pre- and posttransplant options for getting the indicated vaccinations. Modern vaccines are well tolerated, and, even though adverse effects have been reported with all vaccines, these events are very rare. Diverse beliefs about vaccination in the United States, lack of easy access and universal insurance coverage for vaccination, and less than optimal attention toward giving pretransplant vaccinations may contribute to lower pretransplantation vaccination rates among kidney transplant recipients.[59] Thus, patient education is very important, and transplant centers can refer patients to the Centers for Disease Control and Prevention website, which maintains a vaccine information statement for every vaccine and for specific patient populations.[60]

Vaccination is a relatively simple way to decrease the burden of posttransplant infections, but there are challenges in implementing this for kidney failure patients and transplant recipients. Since the review of vaccination history mainly requires a review of records, e-consults or teleconsults by an infectious disease specialist as soon as the patient is listed for kidney transplantation may help improve the rate of vaccinations.[61] The Pfizer-BioNTech and Moderna mRNA vaccines for COVID-19 have recently been approved for use.[62] Although immunosuppressed patients were excluded from the clinical trials of these vaccines, it is hoped that they will still offer reasonable protection against COVID-19 to transplant recipients and for those with advanced kidney disease.

Cancer Screening

11.1.1: We recommend candidates undergo routine cancer screening, as per local guidelines for the general population (Table 13) *(1D)*.

  11.1.1.2: We suggest chest CT for current or former heavy tobacco users (≥ 30 pack-years) as per local guidelines, and chest radiograph for other candidates *(2C)*. (Same as rec. 12.2.1)

Commentary

The KDIGO guideline allows for variations in cancer screening practices "per local guidelines." With advances in screening technology and shifting emphasis toward cost-effectiveness and increasing recognition of the unintended consequences of false-positive testing and overdiagnosis, screening guidelines for cancers continue to evolve. In addition, guidelines in the United States are issued by many agencies, and, while generally consistent,

often include subtle variations.[63,64] Thus, the optimal screening strategy for some cancers remains incompletely defined. The guideline also specifically acknowledges the growing evidence regarding the benefit of lung cancer screening in high-risk populations and recommends screening chest computed tomography for patients with heavy smoking history.[65]

Clinical Utility

Given the increased risk of cancer in the setting of immunosuppression and the need to avoid transplanting patients with underlying cancers where early detection is possible, appropriate cancer screening is vital in the assessment of potential kidney transplant recipients. There are notable differences in US recommendations when compared to European best practices.[66] For example, table 13 of the KDIGO guideline lists biennial fecal immunochemical testing as the method of choice for colon cancer screening, followed by flexible sigmoidoscopy.[1] However, colonoscopy remains the first-line screening tool recommended by many groups in the United States due to its high sensitivity and the ability to remove precancerous lesions at the time of screening.[67,68] Flexible sigmoidoscopy is used less often in the United States and will miss right-sided colonic cancers. Similarly, while the KDIGO guideline suggests that women aged 40-49 years should have the choice to start annual breast cancer screening, the US Preventive Services Task Force guidelines give a lower level of recommendation for this age group.[69]

Implementation and Challenges

Communication and agreement between the transplant center, insurance companies, and referring physician is necessary but remains a challenge given evolving guidelines, increasing wait times, and the inevitable lag period in updating transplant center as well as insurance authorization screening protocols. There is a need to simplify and individualize screening without increasing risk for patients.

Potential Kidney Transplant Candidates With Prior Cancer

11.2.1: We recommend that candidates with active malignancy be excluded from kidney transplantation except for those with indolent and low-grade cancers such as prostate cancer (Gleason score ≤ 6), superficial nonmelanoma skin cancer, and incidentally detected renal tumors (≤ 1 cm in maximum diameter) *(1B)*.

11.2.2: Timing of kidney transplantation after potentially curative treatment for cancer is dependent on the cancer type and stage at initial diagnosis *(Not Graded)*.

Commentary

Oncology has witnessed significant improvements in the management of various cancers, a better understanding of

the natural history of certain malignancies, and marked improvements in survival of patients with certain cancers. This improvement is not reflected in the KDIGO recommended waiting times between cancer remission and kidney transplantation. This is likely due to the fact that much data on cancer outcomes are derived from the general population and not transplant patients receiving immunosuppression. For example, the KDIGO guideline recommends a waiting time of at least 2 years for individuals with Gleason score 7 prostate cancer and at least 2 years for stage 2 thyroid disease. Analyses of large databases in the general population have demonstrated nearly 100% 5-year survival for all but distant metastatic prostate and thyroid malignancies.[70,71] Similarly, 5-year survival rates for patients with localized renal cell cancer (stage IB or <7 cm) are now >90%.[72] Patients with these tumors, particularly if low-grade, could potentially be considered for transplant without additional waiting time, during which they would accumulate dialysis-associated morbidity and mortality risk. In addition, while some cancers may not be fully cured, new maintenance therapies (for example, for multiple myeloma) are changing previously deadly illness into chronic disease, not unlike the evolution that has taken place in HIV management. The prediction of cancer survival has begun to move away from pathologic and radiologic diagnosis to novel blood and tissue tumor markers as well as genetic analysis. While improvements in the management of kidney failure have remained incremental, understanding in cancer science has surged forward, and the risk of death associated with maintenance dialysis now exceeds that of many cancers.[73] If evidence accumulates that advances in cancer treatment options leading to better survival is true for the transplant population as well, it should in the future translate to shorter cancer-free intervals prior to transplant.

Clinical Utility

Transplant candidates with a history of prior malignancy is a common clinical scenario. Since cancer management continues to improve and dialysis-attributable mortality remains high, sometimes surpassing that of certain cancers, the recommended guidelines could be used as a practical starting point, and assessment of mortality from cancer versus remaining on maintenance dialysis can be individualized when considering a patient for transplantation.

Implementation and Challenges

The time course and influence of immunosuppression on cancer disease recurrence need to be balanced against the risk of poor outcomes on dialysis. One large challenge is that cancer survival data are largely gathered from the general, immunocompetent population; risks may be higher in the setting of immunosuppression and kidney failure. Oncologists, nephrologists, and transplant physicians offer different insight in the management of kidney failure and transplant patients with cancer. Dialogue between transplant centers and insurance providers must also take place to override the dogma of previously published cancer-free wait times. Prolonged wait time for transplant and improving outcomes with certain cancers has provoked many transplant physicians to accept patients with cancer for kidney transplantation.

The balance of risks and benefits of transplantation, dialysis, and cancer will continue to challenge transplant physicians. Advances in cancer diagnosis and treatment, as well as the outcome, will require transplant providers to continue to review their practices to optimize the care of patients with pre- and posttransplant cancer alike.

Coronary Artery Disease

13.3: We suggest that asymptomatic candidates at high risk for coronary artery disease (CAD) (eg, diabetes, previous CAD) or with poor functional capacity undergo noninvasive CAD screening *(2C)*.

    13.3.1: We recommend that asymptomatic candidates with known CAD not be revascularized exclusively to reduce perioperative cardiac events *(1B)*.

    13.3.2: We suggest that patients with asymptomatic, advanced triple vessel coronary disease be excluded from kidney transplantation unless they have an estimated survival which is acceptable according to national standards *(2D)*.

13.7: We suggest that patients with uncorrectable, symptomatic New York Heart Association (NYHA) Functional Class III/IV heart disease [severe CAD; left ventricular dysfunction (ejection fraction <30%); severe valvular disease] be excluded from kidney transplantation unless there are mitigating factors that give the patient an estimated survival which is acceptable according to national standards *(2D)*.

    13.7.1: Patients with severe heart failure (NYHA III/IV) who are otherwise suitable for kidney transplantation should be assessed by a cardiologist and considered for combined/simultaneous heart and kidney transplantation *(Not Graded)*.

Commentary

CAD is highly prevalent among kidney failure patients referred for kidney transplantation. Nearly all patients are routinely screened for CAD prior to listing and while on the transplant waiting list. Conclusive evidence that such a strategy improves patient outcomes, including postoperative cardiac events, is lacking. Nevertheless, several major society guidelines have recommended screening for CAD in at-risk patients undergoing elective surgery.[21,22,74–77] While cardiac and anesthesia guidelines recommend CAD screening only in those with

impaired functional status (defined as functional capacity of <4 metabolic equivalents), transplant-specific guidelines have recommended screening for CAD in at-risk patients irrespective of functional status. Similarly, KDIGO guideline statement 13.3 recommends screening for CAD in asymptomatic patients with poor functional status and for asymptomatic patients who have high risk of CAD (prior CAD, diabetes mellitus) irrespective of their functional status. When interpreting results and developing a treatment strategy for coronary disease, clinicians should, however, be aware that lack of coronary symptoms in patients with kidney failure is common and is possibly related to limited mobility, poor functional capacity, and concurrent autonomic neuropathy.

The KDIGO guideline does not recommend coronary revascularization for the sole purpose of reducing perioperative cardiac events (recommendation 13.3.1). The KDOQI work group agrees with this recommendation, given lack of data for reduction in perioperative cardiac events with preoperative coronary revascularization.[78] This recommendation, however, can be challenging to interpret, given that CAD screening will uncover ischemia and unknown coronary lesions. Also, though elective revascularization does not reduce perioperative cardiac events, patients with risk factors (ischemia, diabetes, decreased kidney function) are at higher risk for these events.[79] The KDIGO guideline should have included recommendations about when revascularization may be reasonably appropriate in transplant candidates found to have CAD. These can be found in the 2014 ACC/AHA (American College of Cardiology/American Heart Association) report and the criteria for appropriate use of coronary revascularization in patients with stable ischemic heart disease, released jointly in 2017 by several organizations.[80] KDIGO guideline statement 13.3.2 suggests that patients with advanced 3-vessel disease not be considered for transplantation except when their survival is considered acceptable. The KDOQI work group felt that this recommendation is somewhat vague and leaves individual transplant programs to decide on the candidacy of such patients based on their overall estimated risk of major adverse cardiovascular events over time and overall survival. There is a risk that this will lead to significant variation in how centers approach patients with 3-vessel disease.

KDIGO guideline statement 13.7 recommends not transplanting patients with moderate to severe symptoms (defined as NYHA class III or IV) and coexisting uncorrected valvular disease, CAD, or ejection fraction <30%. The guideline recommends that such patients should be evaluated for the possibility of a combined heart/kidney transplantation. The KDOQI work group agrees with these recommendations. Among patients with ejection fraction <30%, it may be reasonable to consider transplantation if patients have well compensated heart failure, have good functional status, and do not have significant and overt CAD or valvular lesions.

Clinical Utility

CAD remains the primary cause for early posttransplant mortality and for death with a functioning graft following transplantation.[81] Risk factors for CAD are highly prevalent among kidney transplant candidates, particularly among patients with hypertension, diabetes mellitus, and obesity. As a result, screening for CAD, even if patients are asymptomatic, is one of the most common tests performed in transplant candidates prior to and while on the waitlist. This will, on some occasions, uncover ischemia in asymptomatic patients that will necessitate further testing and invasive coronary evaluations.[82–84] However, evidence that such a strategy improves outcomes perioperatively and in the long term is lacking. While the primary reason for screening asymptomatic patients is to reduce perioperative coronary events, a second reason is to identify patients who may have severe underlying uncorrectable 3-vessel disease in whom transplantation is not advisable; this latter scenario, however, is uncommon, with a high number needed to screen.

Implementation and Challenges

The KDIGO guideline suggests that it may be reasonable to screen for CAD among asymptomatic patients with risk factors and those with poor functional capacity. However, the guideline strongly recommends against revascularization solely for the purposes of reducing perioperative cardiac events. This implies that revascularization should take into consideration other features of CAD that would make a decision to revascularize meet the AHA/ACC appropriate use criteria.[80] To add to the data showing no benefit with elective coronary revascularization in the general population, a recent large randomized study among patients with CKD showed no benefit with coronary intervention for moderate to severe ischemia when compared to optimal medical management.[85] However, once ischemia is noted on CAD screening and/or a significant coronary lesion is identified on angiography, transplant physicians, surgeons, and anesthesiologists are reluctant to proceed with transplant surgery without revascularization. This is particularly challenging if the lesion does not meet criteria for revascularization and/or if revascularization is not possible. Since exclusion of such patients may be inappropriate, consideration should be given to the extent of ischemia, location and degree of CAD lesions, ejection fraction, and patient characteristics (such as functional status, age, and comorbidities) to evaluate if transplantation can be pursued with optimal medical management. Finally, if ischemia is identified that requires a coronary angiogram but the patient is not on dialysis, then decisions will need to take into account

the availability of living donors, extent of ischemia, time to deceased-donor transplantation, and symptoms to decide on the timing of the angiogram. Consultation with cardiology teams will be highly valuable in these situations.

An additional downside of aggressive CAD screening is the need for invasive procedures and the potential for some patients to be deemed ineligible for transplantation despite being asymptomatic and in good functional status. This restricts the opportunity for successful transplantation for such recipients. A recent cost-benefit analysis suggested that no screening for CAD on the waiting list may be more cost-effective than routine screening of asymptomatic waitlisted kidney transplant candidates.[86] So, how should programs achieve a balance between avoiding unnecessary testing and also reducing risk of transplantation in the presence of severe untreated CAD? A reasonable starting point may be to consider the following goals while pursuing CAD testing: 1) to identify severe 3-vessel or left-main CAD that may benefit from revascularization according to the appropriate use criteria, 2) to identify severe advanced CAD and thus avoid transplantation in such patients, and 3) to not pursue coronary revascularization for minor levels of ischemia and nonsignificant coronary lesions and also not exclude such patients from transplantation.

Thus, the KDIGO guideline tackles only severe forms of disease such as 3-vessel disease and those that restrict life expectancy. The KDIGO work group was unable to make a strong recommendation in favor of or against testing asymptomatic individuals. This leaves testing, interpretation, intervention, and management for CAD to transplant centers. The issue surrounding CAD for kidney failure patients prior to transplant and while on the waitlist remains a complex issue and requires careful risk-benefit assessment of transplantation.

Pulmonary Hypertension

13.4: We suggest that asymptomatic candidates who have been on dialysis for at least two years or have risk factors for pulmonary hypertension (eg, portal hypertension, connective tissue disease, congenital heart disease, chronic obstructive pulmonary disease) undergo echocardiography *(2D)*.

13.5: Patients with an estimated pulmonary systolic pressure greater than 45 mm Hg by echocardiographic criteria should be assessed by a cardiologist *(Not Graded)*.

    13.5.1: We recommend not excluding candidates with uncorrectable pulmonary artery systolic pressure greater than 60 mm Hg (obtained from right heart catherization) from kidney transplantation; however, the risks of sudden deterioration or progression after transplantation should be a key consideration and the patient should have an estimated survival which is acceptable according to national standards *(1C)*.

Commentary

Pulmonary hypertension (PH) is highly prevalent among CKD patients, including those on dialysis, and is associated with worse patient and transplant outcomes after kidney transplantation.[87–90] Hence, the KDOQI work group agrees with the recommendation to screen patients who have been on dialysis for >2 years for the presence of PH. The guideline also suggests obtaining cardiology evaluation for echocardiographic evidence of moderate PH (pulmonary arterial systolic pressure [PASP] >45 mm Hg). These guidelines are in line with the 2012 AHA/ACC guidelines on cardiac evaluation for kidney transplant candidates.[77] However, the KDIGO guideline leaves out specifics on right heart catheterization for confirmation and subsequent management of PH. The KDIGO guideline does make a strong statement (level 1 recommendation) about not excluding from transplantation patients with severe PH (ie, PASP >60 mm Hg). The KDOQI work group, however, feels that the strong evidence for good outcomes among patients with severe PH is lacking, and a more guarded approach is prudent for patients with uncorrectable severe PH. Otherwise, the KDOQI work group broadly agrees with the listed recommendations but notes the paucity of data clearly characterizing posttransplant outcomes for different subtypes of PH and for patients with severe PH.

Clinical Utility

PH prevalence increases with CKD stage and is highest among hemodialysis patients, with some studies reporting a prevalence of up to 70%.[87] Several factors contribute to this increased prevalence, but, most commonly, it is related to increased intravascular volume and elevated left sided heart pressures. Additionally, patients on dialysis have additional coexisting risk factors such as obesity, sleep apnea, connective tissue disease, shunting of blood through dialysis access, cardiac disease, and fluctuating volume status. Diagnostic and management strategies are challenging given that the etiology of PH among kidney transplant candidates varies, with patients falling in several of the World Health Organization PH types.[91] Approved pharmacological treatments have mostly been directed at group 1 PH characterized by elevated pulmonary vascular resistance (>3 Woods units) and pulmonary capillary wedge pressure <15 mm Hg. Though PH is common, the prevalence of severe PH (defined as PASP >60 mm Hg) is uncommon but often indicates presence of causes other than just volume overload and left heart disease. Hence, the KDOQI work group agrees with the KDIGO guideline recommendation to obtain evaluation by cardiology or PH specialists.

Patients with PH have increased risk of delayed graft function, inferior graft function, and higher mortality.[88,89] However, studies have also shown PH improves after successful kidney transplantation, along with improvement in patient-reported symptoms.[92,93] This, combined with the poor outcomes for patients with PH who are on

dialysis, suggest that transplant should still be the favored strategy for PH patients with kidney failure. Thus, the KDOQI work group in general agrees with the KDIGO recommendation to not exclude patients from transplantation purely based on PASP criteria. However, a guarded approach is prudent, as these patients are at risk for poor outcome.

Implementation and Challenges

Obtaining a baseline echocardiography for PH screening in at-risk patients does not require additional resources, since the majority of transplant candidates undergo echocardiography at evaluation as part of assessment of left ventricular (LV) function and valvular issues. However, challenges may arise in ensuring adequate "dry weight" status at the time of echocardiography, particularly when volume issues are suspected to be contributing to PH. Performing echocardiography immediately postdialysis may help reduce need for right heart catheterization evaluation, but this is often challenging due to logistical barriers arising from dialysis schedules, caregiver support, and transportation issues. Additionally, the criteria for obtaining additional investigations and cardiology input are based on PASP criteria, which may not always correlate with right heart catheterization measurements.[94] However, use of PASP along with tricuspid jet peak velocity and other echocardiography features of PH such as right ventricular size, function, and thickness increases accuracy of PH recognition by echocardiography.[95]

Implementing the recommendation to not exclude patients with PASP >60 mm Hg may be more challenging, since the guideline does not provide specifics regarding evaluating such patients. How should programs consider patients with persistent elevation of PASP to >60 mm Hg? Patients with severe PH who have a precapillary component to PH should be trialed with pharmacological therapy under a PH expert to evaluate if pressures can be improved to <50 mm Hg. Additionally, the candidacy for kidney transplantation will have to consider the patient's overall functional status, right and left ventricular function, presence of concomitant cardiac conditions (such as CAD, valvular disease), systemic hypotension, and other comorbidities. Such patients with persistent severe PH despite volume management and pharmacological therapy are likely not transplant candidates at the majority of US centers.

Thus, prolonged waiting times and a complex interplay of risk factors determine the severity and persistence of PH, which poses problems for potential transplant recipients. Future research should focus on patients with persistent moderate PH to identify clinical characteristics that will help identify characteristics favorable to successful transplant outcomes.

Immunological Assessment

19.1: Communicate all sensitizing events (eg, blood product transfusion, including platelets, pregnancy or miscarriage) or clinical events that can impact panel reactive antibody (PRA) (eg, vaccination, withdrawal of immunosuppression, transplant nephrectomy, significant infection) to the human leukocyte antigen (HLA) laboratory *(Not Graded).*

19.2: Perform HLA antibody testing at transplant evaluation, at regular intervals prior to transplantation and after a sensitizing event or a clinical event that can impact PRA *(Not Graded).*

19.3: We recommend that HLA antibody testing be performed using solid phase assays *(1B).*

19.4: We recommend HLA typing of candidates at evaluation using molecular methods, optimally at all loci *(1D).*

19.5: We suggest not routinely testing candidates for non-HLA antibodies *(2C).*

19.6: We suggest not routinely testing candidates for complement-binding HLA antibodies *(2C).*

19.7: We suggest informing candidates about their access to transplantation based on blood type and histocompatibility testing results *(2C).*

    19.7.1: We recommend offering candidates with immunologically-reduced access to transplant access to a larger deceased donor pool, kidney exchange programs, and/or desensitization *(1C).*

    19.7.2: We suggest that antibody avoidance (eg, kidney exchange programs or deceased donor acceptable mismatch allocation) be considered before desensitization *(2C).*

Commentary

The first recommendation, to communicate all sensitization events to HLA laboratory directors, is important because of the limitations of HLA antibody testing. Solid-phase HLA antibody tests have inherent assay limitations and do not provide any measure of immunologic memory.[96] Currently, there are no readily available tests of immunologic memory outside of the research setting, and obtaining important sensitization history from the candidate provides some meaningful assessment of the potential for memory response. This key point was highlighted by a 2017 meeting report from the AST's STAR (Sensitization in Transplantation: Assessment of Risk) work group.[96]

The KDIGO guideline also contains recommendations about obtaining candidate serum at regular intervals to test new HLA antibodies. Lack of consensus regarding the of frequency of pretransplant testing remains an issue. The intent is to keep information on unacceptable antigens current to avoid unexpected positive crossmatches. This practice also ensures that HLA laboratories have fresh recipient serum available for a timely physical crossmatch when a deceased-donor organ is available for transplantation.

The KDOQI work group agrees with the recommendation that HLA antibody testing be done with solid-phase assays and that routine non-HLA antibody and complement binding antibodies be avoided, but the KDIGO guideline lacks important information about the role of adjunctive testing including flow cytometric and/or complement-dependent cytotoxicity crossmatches.[97,98] There is also no mention of the increasingly important role of the virtual crossmatch in an era of widespread HLA typing with molecular methods and sensitive single antigen bead HLA antibody testing.[99] The virtual crossmatch is very reliable among kidney transplant candidates who have no sensitization history and negative single antigen bead HLA antibody tests, but may be less reliable among sensitized candidates with a high calculated PRA (cPRA). These highly sensitized candidates may benefit from physical crossmatch testing and solid-phase assays with diluted serum to assess for factors such as prozone and bead saturation.[100,101]

The KDOQI work group also agrees that sensitized candidates should be offered access to larger deceased donor pools and kidney paired donation (KPD) programs if they have a potential living donor, but it must be acknowledged that patients with a very high cPRA (>99.9%) in the United States have disproportionately long wait times,[102,103] and transplantation in the context of HLA donor-specific antibody (DSA) and or positive crossmatch may provide patient survival benefit.[104]

Lastly, the term "desensitization" needs to be used carefully. Not all patients who undergo a transplant in the context of preformed DSA and/or positive crossmatch undergo therapy to remove antibody (desensitization); thus, HLA-incompatible transplant is not synonymous with desensitization.[98] There are also inadequate data to inform desensitization practices. Randomized controlled trials have not shown that desensitization is associated with improved long-term allograft survival. However, several retrospective studies have shown that kidney transplantation can be safely performed with a low degree of DSA and/or positive flow cytometric crossmatch without specific desensitization therapy and lead to acceptable short-term results among patients with limited options.[98] Moreover, it is important to acknowledge that, before sensitive single antigen bead and flow cytometric methods, kidney transplants were routinely (if inadvertently) performed in the context of low levels of alloantibody.

The KDIGO guideline does not contain recommendations regarding emphasizing patient education concerning sensitization events and the importance of immunosuppression adherence in avoiding sensitization. Recommendations regarding immunosuppression withdrawal among patients with a failing allograft are also missing; these patients are at high risk of developing HLA antibodies after immunosuppression withdrawal. An approach that takes into consideration residual kidney function, patient age, risk of side effects, and chances of a repeat transplant within a reasonable time period is necessary to tailor immunosuppression withdrawal. The KDOQI work group strongly believes that all transplant centers should focus heavily on educating transplant recipients about sensitizing events and the role of nonadherence in HLA sensitization. This will improve chances of a repeat transplant should the need arise.

Clinical Utility

The recommendations regarding obtaining an immunological assessment at the time of transplant evaluation and at regular intervals thereafter are prudent, but there are challenges to implementation. Routine anti-HLA testing is costly, and it can be difficult to contact patients to ensure that testing is performed regularly.

Implementation and Challenges

In the United States, there are disparities in access to KPD programs and transplant center expertise with HLA-incompatible transplantation (transplant in the context of DSA and/or positive crossmatch). Inadequate information exists to inform providers about the appropriate time to move forward with an HLA-incompatible transplant versus seeking KPD or remaining on dialysis. Solely focusing on the avoidance of DSA is overly simplistic. The compatibility between a donor and recipient should also consider characteristics including cytomegalovirus and Epstein–Barr virus serostatus, age and/or size mismatch, and the expected survival of a particular living-donor transplant. Factors such as exhausted dialysis access or the ability to get a preemptive transplant play into decisions to move forward with an HLA-incompatible transplant.

KPD programs in the United States also remain fragmented. Transplant programs with low volumes are likely to be disadvantaged. Small programs with internal KPD programs often have a small pool of candidates, and large multicenter programs such as the National Kidney Registry are based on donor-allocation schemes that tend to favor large programs with access to nondirected donors. The intent of these donor allocation schemes is to keep the donor pool large, but it has a potential to disadvantage recipients from certain centers.

A paucity of data exists to inform how to form chains to increase the longevity of allografts in general. The National Kidney Registry primarily focuses on avoiding HLA mismatch, which is certainly important, but it must be acknowledged that factors beyond HLA mismatching influence long-term allograft survival. Great benefit would come from a high-functioning national KPD program with an independent governing body focused on the ethical tenets of utility, justice, and respect for persons while maximizing the longevity of kidney transplants and avoiding disparities.[105] Lastly, certain centers have not uniformly adopted the virtual crossmatch, as it might decrease the financial reimbursement to HLA laboratories.

Development of HLA antibody before and after transplantation will continue to hinder transplant outcome. This barrier must be broken through immunological intervention, both by prevention and treatment of antibody-mediated rejection. Further scientific advances centered around HLA antibodies are needed to inform guidelines in this area.

Plasma Cell Dyscrasias, Monoclonal Gammopathy, and Multiple Myeloma

9.13.1 Multiple myeloma

9.13.1.1: We suggest that candidates with multiple myeloma be excluded from kidney transplantation unless they have received a potentially curative treatment regimen and are in stable remission (2D).

9.13.2 Monoclonal immunoglobulin deposition disease (MIDD)

9.13.2.1: We suggest that candidates with light chain deposition disease (LCDD) be excluded from kidney transplantation unless they have received a potentially curative treatment regimen and are in stable remission (2D).

9.13.2.2: We suggest that candidates with heavy chain deposition disease (HCDD) be excluded from kidney transplantation unless they have received a potentially curative treatment regimen and are in stable remission (2D).

9.13.2.3: We suggest that candidates with light and heavy chain deposition disease (LHCDD) be excluded from kidney transplantation unless they have received a potentially curative treatment regimen and are in stable remission (2D).

9.13.3 AL amyloidosis

9.13.3.1: We suggest that candidates with AL amyloidosis be excluded from kidney transplantation unless they have minimal extrarenal disease (eg, cardiac amyloid), have received a potentially curative treatment regimen and are in stable remission (2D).

17.6 Monoclonal gammopathy of undetermined significance (MGUS)

17.6.1: We suggest not excluding candidates with MGUS from kidney transplantation; however, a higher risk of post-transplant lymphoproliferative disease and other hematological malignancies should be considered and discussed with candidates (2D).

17.6.2: We suggest not excluding candidates with smoldering multiple myeloma from kidney transplantation; however, a significant risk of transformation into multiple myeloma should be considered and discussed with candidates (2D).

17.6.3: We recommend careful evaluation of candidates with MGUS for other types of plasma cell disorders prior to kidney transplantation (1D).

Commentary

Plasma cell dyscrasias (PCDs) have a substantial risk of recurrence and poor outcomes after kidney transplantation. Hence, the KDIGO work group recommends excluding patients with PCD from consideration for transplantation unless there has been a potentially curative treatment with achievement of stable remission. It is important to note that the quality of data and the strength of this recommendation are not strong (2D). Furthermore, no subclassification is considered to stratify the risk for recurrence. The KDIGO work group emphasizes the need for a multidisciplinary treatment approach involving hematologists and nephrologists. Good outcomes have been reported for patients with multiple myeloma and kidney failure. However, no clear recommendations are made regarding wait time between induction of remission for multiple myeloma and transplantation. The combination of living-donor kidney transplantation followed by autologous stem cell transplantation has been reported, but is sparingly used.[106]

LCDD, LHCDD, and HCDD can manifest with kidney disease and are frequently associated with MGUS (20%) and multiple myeloma (60%). Recent data suggest that reasonable outcomes can be obtained with kidney transplantation among patients with monoclonal immunoglobulin deposition disease using chemotherapy and autologous stem cell transplantation.[107] Similarly, good kidney transplant outcomes have been demonstrated for patients with AL amyloidosis.[108,109] However, there remains a risk of recurrence, which is particularly high if patients have not achieved a complete response to AL amyloidosis therapy; in a single-center study, the recurrence-free survival at 5 years was 0% for patients with partial response to AL amyloidosis therapy and 53.3% for those with very good partial response.[109] The risks of MGUS and smoldering myeloma progressing to overt multiple myeloma are low and are estimated to be 1% and 3% per year, respectively.[110] In general, no hematological treatment is recommended prior to progression to multiple myeloma.[111] The impact of transplantation despite low risk for of myeloma transformation remains controversial. Increased risk of posttransplant lymphoproliferative disease has been noted and should be kept in mind.[112]

Clinical Utility

The clinical utility of these KDIGO guideline statements is limited by lack of good data and heterogeneity of disease subtypes and spectrum of pathological renal manifestations. As highlighted by the KDIGO work group, it is imperative to consider a multidisciplinary approach that includes a collaboration between hematology and nephrology in these cases. The curative approach implied in the KDIGO guideline should not be taken literally, as very few true curative approaches exist for PCD.

Nevertheless, very notable therapeutic advances have been made that can induce clinical remission for a prolonged period of time and allow a successful kidney transplantation with better longevity and good quality of life. Although the combination of a kidney transplantation and stem cell transplantation is attractive given the potential for minimizing immunosuppression and achieving remission of PCD, it is rarely achievable on clinical grounds due to limited availability of donors and the differences in criteria for stem cell transplantation compared to those for kidney transplantation.

Substantial improvement in survival has also been noted in patients with AL amyloidosis in whom hematological remission was obtained prior to transplantation. The discussion on kidney transplantation for patients with MGUS and smoldering myeloma is based on concern about the risk of overt myeloma transformation, which is not more than 3% per year. By contrast, the annual mortality rate for all patients on the kidney transplant waitlist is around 5%-6%.

Implementation and Challenges

The KDIGO guideline is restrictive with regard to transplantation for the listed hematological conditions. Implementation considerations will become relevant only if transplantation for these clinical entities is permitted based on their pathologic findings, cause of renal manifestation, response to therapy, and risk of recurrence posttransplant. In addition, as newer therapies become available, their ability to suppress the hematological disease will also be relevant. Continuation of therapy for hematological diseases after transplantation may not always be curative but could potentially allow long-term suppression of clinical disease sufficient to allow good outcomes. Due to this complexity and lack of data to guide best practice, it is imperative that a multidisciplinary approach is taken in these cases. Finally, it is important to recognize that patients presenting for transplant evaluation with an unknown cause of kidney failure may have an unrecognized monoclonal gammopathy of renal significance (MGRS). Evaluating for a monoclonal protein among such patients, particularly when older than 40 years of age, may be reasonable. However, since MGRS is diagnosed by kidney biopsy, further evaluation to diagnose MGRS will be limited in patients with kidney failure. Such patients should be carefully monitored for signs of MGRS and consider kidney biopsy posttransplant.

It should be acknowledged that kidney transplant outcomes remain inferior for this subset of recipients. However, since kidney transplantation represents a better treatment option than long-term dialysis, this should remain an option, at least for select patients with favorable characteristics and a reasonable life expectancy. Recognizing that more data are needed, a more permissive approach regarding access to transplantation may be warranted for the subset of patients with stable PCDs, which may enhance overall patient survival as compared to long-term dialysis.

Combined Liver and Kidney Transplant

> 16.7.3: We recommend that candidates with cirrhosis or suspected cirrhosis be referred to a specialist with expertise in combined liver-kidney transplantation for evaluation *(1B)*.
>
> 16.7.3.1: We recommend that patients undergo isolated kidney transplantation if deemed to have compensated cirrhosis after specialist evaluation *(1B)*.

Commentary

The KDIGO guideline recommendation that patients can undergo isolated kidney transplant if deemed to have compensated cirrhosis is perhaps overly simplified. This guideline does not consider ongoing inciting factors such as untreated hepatitis C or alcoholism that must be addressed to avoid progression of liver disease. The importance of recognizing portal hypertension with high hepatic venous pressure gradients was also not considered. It is well known those with high hepatic venous pressure gradient (>10 mm Hg) can progress to decompensated cirrhosis with poor outcomes following kidney transplantation.[113] The recommendation about specialty consultation is important, but it is critical to acknowledge the differences in the nephrologist versus hepatologist perspective. The guideline appears to be written with a patient with known kidney disease and concomitant liver failure in mind. The KDIGO work group offers minimal guidance about when it is appropriate to consider a simultaneous kidney transplant among patients with end-stage liver failure. Decompensated liver failure with hepatorenal syndrome often presents as moderate to severe kidney dysfunction and many require dialysis. With timely liver transplantation, hepatorenal syndrome is often reversible. The prolonged acute kidney injury from hepatorenal syndrome, especially in patients who are older or who have diabetes or nonalcoholic steatohepatitis, can lead to permanent kidney damage. Moreover, other factors, including underlying CKD, infections with hemodynamic instability, and medications play a role in the development of kidney failure requiring kidney replacement therapy among patients with concomitant liver disease.

Clinical Utility

Optimizing organ utility is a must. The facts that liver transplant alone in the context of kidney failure is associated with inferior outcomes[114–116] and that unnecessary combined liver and kidney transplants contribute to improper kidney organ utilization must be balanced.[117] Currently, per the Organ Procurement and Transplant Network/United Network of Organ Sharing (OPTN/ UNOS) allocation policy, patients can be eligible for combined liver and kidney transplant if they have known CKD for ≥90 consecutive days with glomerular filtration rate (GFR) <35 mL/min, GFR <25 mL/min (including the

need for sustained dialysis) for 6 consecutive weeks, or in rare cases when a candidate has rare metabolic disease such as primary hyperoxaluria.[118] However, it should be remembered that meeting the GFR criteria alone should not automatically lead to a decision to perform combined liver and kidney transplantation without evaluating the potential for reversibility among patients with a high likelihood of having hepatorenal syndrome as the underlying etiology for kidney dysfunction. While native kidney biopsy has been investigated as a potential means of identifying patients in need of a combined liver and kidney transplant rather than a liver-alone transplant, data on this are limited.[119–121] It should be considered in select patients at low risk of kidney biopsy–related complications to make a decision regarding combined liver and kidney transplant versus liver-alone transplant.

Implementation and Challenges

OPTN/UNOS recognizes the issues that surround combined liver and kidney transplantation, including organ scarcity, fairness, and the occasional uncertainty about the medical need for a combined transplant. In response, OPTN/UNOS implemented a new "safety net" kidney allocation policy. Patients who are listed for kidney transplant within 60-365 days of a liver transplant are given additional priority for local kidney allocation if they meet specific medical requirements.[118] Critics of this new allocation system argue that it is too liberal and allows for transplantation among patients with acute kidney injury likely to recover.[117] Others argue that that this policy may lead to inferior outcomes among patients who would have been better served receiving organs simultaneously rather than liver followed by kidney transplantation. These recommendations stem from lack of data informing clinical practice and lack of availability of combined organ transplantation expertise at many transplant centers. Important issues regarding organ availability must always be considered. There is some evidence that survival with kidney-after-liver transplantation is similar to combined liver and kidney transplant and that kidney outcomes are better for the former.[122,123] This may serve as an impetus to increase the use of the safety net provision, since, despite the implementation of the new policy, the number of combined liver and kidney transplants has remained the same.

Lastly, in the United States, it is also important to recognize that there are certain patients in need of a simultaneous liver and kidney transplant who may never have access to organs regardless of their listing, particularly those patients with a low MELD (Model for End-Stage Liver Disease) score but obvious liver dysfunction. Examples include the patient with liver disease on dialysis who has frequent ascites or hepatic encephalopathy, but with low International Normalized Ratio and bilirubin.

In summary, candidates with combined kidney and liver disease are complex medically, and collaboration with an experienced transplant hepatologist is essential. When considering combined liver and kidney transplantation,

careful attention must be paid to issues surrounding organ scarcity and utilization.

Conclusion

In summary, this commentary highlights the clinical utility and implementation challenges of the KDIGO guideline for key areas pertaining to the evaluation and management of potential kidney transplant candidates. The KDIGO guideline statements and the strength of these recommendations are centered around evidence-based medicine. However, many diagnostic and therapeutic approaches employed in the evaluation and management of kidney transplant candidates have remained outside the reach of evidence-based medicine. Thus, while the KDIGO guideline is comprehensive, it is limited by the available evidence in many areas, because of which several guideline statements come as only suggestions or ungraded recommendations. Transplant professionals applying these guidelines should pay close attention to the strength of recommendation and the quality of evidence, and use their clinical judgement to make decisions that serve the best interest of transplant patients while also balancing utility and equity of kidney transplantation.

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