



# Transplantation®



**KDIGO Clinical Practice Guideline on the Evaluation and  
Management of Candidates for Kidney Transplantation**



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## DISCLAIMER

### SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon systematic literature searches last conducted in August 2017 supplemented with additional evidence review through May 2019. It is designed to assist decision making. It is not intended to define a standard of care, and should not be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when considering the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Healthcare professionals using these recommendations should decide how to apply them to their own clinical practice.

### SECTION II: DISCLOSURE

Kidney Disease: Improving Global Outcomes (KDIGO) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise from an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived as or are actual conflicts of interest. This document is updated annually and information is adjusted accordingly. All reported information is published in its entirety at the end of the document and is kept on file at KDIGO.

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## **KDIGO EXECUTIVE COMMITTEE**

Garabed Eknoyan, MD  
Norbert Lameire, MD, PhD  
Founding KDIGO Co-Chairs

David C. Wheeler, MD, FRCP  
Immediate Past Co-Chair

Michel Jadoul, MD  
KDIGO Co-Chair

Wolfgang C. Winkelmayer, MD, MPH, ScD  
KDIGO Co-Chair

Mustafa Arici, MD  
Tara I. Chang, MD, MS  
Jennifer E. Flythe, MD, MPH  
Masafumi Fukagawa, MD, PhD  
Morgan E. Grams, MD, MHS, PhD  
Fan Fan Hou, MD, PhD  
Meg J. Jardine, MBBS, PhD  
Markus Ketteler, MD  
Magdalena Madero, MD

Jolanta Malyszko, MD, PhD  
Ikechi G. Okpechi, MBBS, FWACP, PhD  
Rukshana Shroff, MD, FRCPCH, PhD  
Laura Sola, MD  
Paul E. Stevens, MB, FRCP  
Sydney C.W. Tang MBBS, MD, PhD, FRCP  
(L,E,G), FHKCP, FHKAM  
Marcello A. Tonelli, MD, SM, FRCPC  
Christina M. Wyatt, MD, MSc

### **KDIGO Staff**

John Davis, Chief Executive Officer  
Danielle Green, Executive Director  
Michael Cheung, Chief Scientific Officer  
Melissa Thompson, Chief Operating Officer  
Tanya Green, Events Director

## WORK GROUP MEMBERSHIP

### Work Group Co-Chairs

Steven J. Chadban, BMed (hons), PhD, FAAHMS,  
FRACP  
Royal Prince Alfred Hospital and  
Charles Perkins Centre, University of Sydney  
Sydney, Australia

Gregory A. Knoll, MD, MSc, FRCPC  
Department of Medicine  
The Ottawa Hospital and Ottawa Hospital  
Research Institute  
Ottawa, Canada

### Work Group

Curie Ahn, MD, PhD  
Seoul National University  
Seoul, South Korea

Julio Pascual, MD, PhD  
Hospital del Mar  
Barcelona, Spain

David A. Axelrod, MD, MBA, FACS  
University of Iowa  
Iowa City, IA, USA

Helen L. Pilmore, MD, FRACP  
Auckland City Hospital  
Auckland, New Zealand

Bethany J. Foster, MD, MSCE  
The Montreal Children's Hospital  
McGill University Health Centre  
Montreal, Canada

James R. Rodrigue, PhD, FAST  
Beth Israel Deaconess Medical Center  
Boston, MA, USA

Bertram L. Kasiske, MD, FACP  
Hennepin County Medical Center  
Minneapolis, MN, USA

Dorry L. Segev, MD, PhD  
Johns Hopkins University  
Baltimore, MD, USA

Vijay Kher, MD, DM, FAMS, FRCPE, FIMAS  
Medanta Kidney and Urology Institute  
Haryana, India

Neil S. Sheerin, BSc, PhD, FRCP  
Newcastle University  
Newcastle, United Kingdom

Deepali Kumar, MD, MSc, FRCPC, FAST  
University Health Network  
University of Toronto  
Toronto, Canada

Kathryn J. Tinckam, MD, MMSc, FRCPC, FAST  
University Health Network  
University of Toronto  
Toronto, Canada

Rainer Oberbauer, MD, PhD  
Medical University of Vienna  
Vienna, Austria

Germaine Wong, MD, PhD  
University of Sydney  
Sydney, Australia

### *Evidence Review Team*

Center for Evidence Synthesis in Health, Brown University School of Public Health  
Providence, RI, USA

Ethan M. Balk, MD, MPH, Project Director, Evidence Review Team Director  
Craig E. Gordon, MD, MS, Assistant Project Director, Evidence Review Team Associate Director  
Amy Earley, BS, Research Associate  
Valerie Rofeberg, ScM, Research Associate

## PREFACE

### INTRODUCTION

Transplantation is the kidney replacement therapy of choice for suitable patients with end-stage kidney disease (ESKD). However, not all patients are suitable candidates for transplantation, and suitability is often determined by the perceived risks of transplantation relative to the risks of not receiving a transplant. Estimation of risk is therefore a key part of the transplant candidate evaluation. Should a decision to proceed to transplantation be made, consideration of how to minimize risks and maximize the chances of a successful outcome are additional aspects of the candidate evaluation process.

This guideline systematically examines current evidence concerning the risks of transplantation associated with specific conditions and provides recommendations as to how clinicians may wish to deal with specific risk factors in isolation. In practice, patients are frequently complex and exhibit multiple risk factors for poor transplant outcomes. Ultimately the clinician will be required to synthesize the total risk burden that each candidate presents in deciding on suitability for transplantation.

### SCOPE

This guideline addresses the evaluation and management of possible candidates for kidney transplantation alone, from either a deceased or living donor. It covers the time period from the first consideration of the need for kidney replacement therapy to kidney transplant surgery. It considers adult and pediatric candidates. Education of the candidate and their family is beyond the scope of this guideline; however, we do wish to highlight the essential role of patient education in parallel with the evaluation process, as it is required to enable shared-decision making and consent regarding the decision to proceed to transplantation or not. This guideline does not address candidates for combined transplantation of a kidney and another organ but we have attempted to be as comprehensive as possible in addressing all clinically relevant conditions that may impact transplant candidacy. However, given the breadth of conditions relevant to transplantation and the rapidly evolving nature of data in medicine, it is likely that we may have omitted some issues and in other instances will have cited data that will be superseded. Please consult *Methods for Guideline Development* for further details.

### TARGET AUDIENCE

This guideline is intended for caregivers who refer and/or evaluate patients for possible kidney transplantation.

### BACKGROUND AND PRINCIPLES UNDERPINNING THE GUIDELINE

#### Ethics

Kidney transplantation, using organs obtained from either living or deceased donors, should be conducted in accordance with the Declaration of Istanbul,<sup>1</sup> which provides clear guidelines on ethical practice in this area.

#### Local considerations

As a global guideline, Kidney Disease: Improving Global Outcomes (KDIGO) necessarily seeks and considers all available evidence in producing guidelines which are of global relevance. However, the fact that the practice and outcomes of transplantation vary enormously across the globe—between continents, countries and even jurisdictions—requires the reader to consider their local practices and outcomes in interpreting and implementing the guideline. In particular, considerations should include:

1. **Superiority of transplantation over dialysis for the provision of kidney replacement therapy.** Existing data clearly demonstrate that on average, transplantation achieves superior medical outcomes (i.e., survival and quality of life) at lower cost as compared to dialysis, and transplantation is therefore considered to be the medically desirable and economically

dominant therapy. However, this conclusion is based upon data from high income countries with good access to both transplantation and dialysis.<sup>2</sup> This conclusion is likely to hold true for low- and middle-income countries from a medical perspective, though whether transplantation is cheaper than dialysis in this context is less certain and remains to be proven.

2. **Access to dialysis and transplantation.** In some areas, access to dialysis and/or transplantation may be restricted or absent. This may be due to the lack (or absence) of necessary infrastructure or services, cost of services to the patient, geographical inaccessibility, or other factors. Thus, access must be considered when interpreting these guidelines.
3. **Outcomes of dialysis and transplantation.** The decision to pursue transplantation in preference to dialysis for any given patient is based upon an expectation of superior outcomes following transplantation. To make this decision, knowledge of expected outcomes from dialysis and transplantation, at a local level, is required. For example, if local transplant outcomes yield a 60% patient survival at 2 years, whereas dialysis yields 70% survival, then transplantation may not be justified for an average patient with ESKD. In the absence of local data describing the outcomes of dialysis and transplantation, the decision to transplant or not must be made by adaptation of available data to the local context.
4. **Local risks involved in transplantation.** Regional and geographical variation in risk is evident following transplantation and should be considered in implementing the Guideline. The risk of infection after transplantation exhibits marked regional variation in type, frequency and severity. For example, the risk of post-transplant reactivation of latent tuberculosis (TB) is high among those from endemic areas, yet profoundly low among those from temperate climates. Cancer incidence is also affected by geography, genetics and lifestyle. For example, skin cancer is a common cause of death among Caucasian kidney transplant recipients in Australia, particularly among those residents with high sun exposure, yet skin cancers are far less common and are a rare cause of death in other areas of the world. Thus, local knowledge and understanding of likely risks and benefits are required to place the recommendations made within this Guideline into local context.

We thank the Work Group Co-Chairs, Drs. Greg Knoll and Steve Chadban, along with all the Work Group members who volunteered countless hours of their time to develop this guideline. We also thank the Evidence Review Team at the Brown University School of Public Health, KDIGO staff, and The Transplantation Society for their support which made this project possible.

Michel Jadoul, MD

Wolfgang C. Winkelmayer, MD, MPH, ScD

KDIGO Co-Chairs

**REFERENCE KEYS****KDIGO NOMENCLATURE AND DESCRIPTION FOR GRADING GUIDELINE RECOMMENDATIONS**

Within each recommendation, the strength of recommendation is indicated as **Level 1**, **Level 2**, or **Not Graded**, and the quality of the supporting evidence is shown as **A**, **B**, **C**, or **D**.

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

\*The additional category "Not Graded" is used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. Ungraded recommendations are generally written as simple declarative statements, but not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

Grade	Quality of Evidence	Meaning
<b>A</b>	High	We are confident that the true effect lies close to that of the estimate of the effect
<b>B</b>	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
<b>C</b>	Low	The true effect may be substantially different from the estimate of the effect
<b>D</b>	Very low	The estimate of effect is very uncertain, and often will be far from the truth

**CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO**

*CKD is defined as abnormalities of kidney structure or function, present for > 3 months, with implications for health. CKD is classified based on Cause, GFR category (G1-G5), and Albuminuria category (A1-A3), abbreviated as CGA.*

**Prognosis of CKD by GFR and albuminuria category<sup>3</sup>**

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m <sup>2</sup> ) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

**ALBUMINURIA CATEGORIES IN CKD<sup>3</sup>**

Category	AER (mg/24 hours)	ACR (approximate equivalent)		Terms
		(mg/mmol)	(mg/g)	
<b>A1</b>	< 30	< 3	< 30	Normal to mildly increased
<b>A2</b>	30-300	3-30	30-300	Moderately increased*
<b>A3</b>	> 300	> 30	> 300	Severely increased**

ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease

\*Relative to young adult level

\*\*Including nephrotic syndrome (albumin excretion usually > 2200 mg/24 hours [ACR > 2200 mg/g; > 220 mg/mmol])

**CONVERSION FACTORS OF CONVENTIONAL UNITS TO SI UNITS**

	<b>Conventional Unit</b>	<b>Conversion Factor</b>	<b>SI Unit</b>
Creatinine	mg/dl	88.4	μmol/l

Note: Conventional unit x conversion factor = SI unit

## ABBREVIATIONS AND ACRONYMS

ACC	American College of Cardiology
ADPKD	Autosomal dominant polycystic kidney disease
AGREE	Appraisal of Guidelines for Research and Evaluation
AHA	American Heart Association
aHUS	Atypical hemolytic uremic syndrome
ANCA	Anti-neutrophil cytoplasmic antibody
Anti-GBM	Anti-glomerular basement membrane
Anti-HBc	Antibody to hepatitis B core antigen
Anti-HBs	Antibody to hepatitis B surface antigen
ANZDATA	Australia and New Zealand Dialysis and Transplant
APLA	Antiphospholipid antibody
APS	Antiphospholipid syndrome
ASHI	American Society for Histocompatibility and Immunogenetics
AST	American Society of Transplantation
BMD	Bone mineral density
BMI	Body mass index
C3G	C3 glomerulopathy
C3GN	C3 glomerulonephritis
CAD	Coronary artery disease
CFB	Complement Factor B
CFH	Complement Factor H
CFI	Complement Factor I
CI	Confidence interval
CKD	Chronic kidney disease
CKD G4, CKD G5	Chronic kidney disease GFR category 4; chronic kidney disease GFR category 5
CKD-MBD	Chronic kidney disease-mineral and bone disorder
CMV	Cytomegalovirus
COGS	Conference on Guideline Standardization
cPRA	Calculated panel reactive antibody
CST	Canadian Society of Transplantation
CT	Computed tomography
CVD	Cardiovascular disease
DAA	Direct-acting antiviral
DDD	Dense deposit disease
DM	Diabetes mellitus
DOAC	Direct oral anticoagulant
DSA	Donor-specific antibody
EBNA	EBV nuclear antigen
EBV	Epstein-Barr virus
ECD	Expanded-criteria donor
ECG	Electrocardiogram
EDS	Ehlers-Danlos Syndrome
eGFR	Estimated glomerular filtration rate
EGD	Esophagogastroduodenoscopy
ERA-EDTA	European Renal Association-European Dialysis and Transplantation Association
ERT	Evidence Review Team
ESC	European Society of Cardiology
ESKD	End-stage kidney disease
FI	Frailty Index
FSGS	Focal segmental glomerulosclerosis
FVL	Factor V Leiden
GFR	Glomerular filtration rate
GRADE	Grades of Recommendation, Assessment, Development and Evaluation
HbA <sub>1c</sub>	Glycated hemoglobin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus

HCDD	Heavy chain deposition disease
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HIT	Heparin-induced thrombocytopenia
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HR	Hazard ratio
HSV	Herpes simplex virus
HTLV	Human T-cell lymphotropic virus
HUS	Hemolytic uremic syndrome
ICA	Intracranial aneurysm
IC-MPGN	Immune complex-mediated MPGN
IgAN	IgA nephropathy
IU	International unit
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
KHA-CARI	Kidney Health Australia-Caring for Australasians with Renal Impairment
LCDD	Light chain deposition disease
LHCDD	Light and heavy chain deposition disease
LN	Lupus nephritis
LVEF	Left ventricular ejection fraction
MDRO	Multidrug resistant organisms
MET	Metabolic equivalent
MGUS	Monoclonal gammopathy of undetermined significance
MI	Myocardial infarction
MIDD	Monoclonal immunoglobulin deposition disease
MMR	Measles, mumps, or rubella
MN	Membranous nephropathy
MPGN	Membranoproliferative glomerulonephritis
NAT	Nucleic acid test(ing)
NODAT	New-onset diabetes after transplantation
NYHA	New York Heart Association
OR	Odds ratio
PAD	Peripheral arterial disease
PASP	Pulmonary artery systolic pressure
PCD	Plasma cell dyscrasia
PLA2R	Phospholipase A2 receptor
PPD	Purified protein derivative
PRA	Panel-reactive antibody
PTH	Parathyroid hormone
RCT	Randomized controlled trial
RR	Relative risk
siRNA	small interfering RNA
STEC-HUS	Shiga toxin-associated hemolytic uremic syndrome
TB	Tuberculosis
TIA	Transient ischemic attack
TSANZ	Transplantation Society of Australia and New Zealand
UK	United Kingdom
UNOS	United Network for Organ Sharing
US	United States
UTI	Urinary tract infection
VCA	Viral capsid antigen
VZV	Varicella-zoster virus

# KDIGO Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation

Steven J. Chadban, BMed, PhD,<sup>1\*</sup> Curie Ahn, MD, PhD,<sup>2</sup> David A. Axelrod, MD, MBA,<sup>3</sup> Bethany J. Foster, MD, MSCE,<sup>4</sup> Bertram L. Kasiske, MD,<sup>5</sup> Vijah Kher, MD, DM,<sup>6</sup> Deepali Kumar, MD, MSc,<sup>7</sup> Rainer Oberbauer, MD, PhD,<sup>8</sup> Julio Pascual, MD, PhD,<sup>9</sup> Helen L. Pilmore, MD,<sup>10</sup> James R. Rodrigue, PhD,<sup>11</sup> Dorry L. Segev, MD, PhD,<sup>12</sup> Neil S. Sheerin, BSc, PhD,<sup>13</sup> Kathryn J. Tinckam, MD, MMSc,<sup>7</sup> Germaine Wong, MD, PhD,<sup>14</sup> and Gregory A. Knoll, MD, MSc,<sup>15\*</sup>

**Abstract:** The 2020 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation is intended to assist health care professionals worldwide who evaluate and manage potential candidates for deceased or living donor kidney transplantation. This guideline addresses general candidacy issues such as access to transplantation, patient demographic and health status factors, and immunological and psychosocial assessment. The roles of various risk factors and comorbid conditions governing an individual's suitability for transplantation such as adherence, tobacco use, diabetes, obesity, perioperative issues, causes of kidney failure, infections, malignancy, pulmonary disease, cardiac and peripheral arterial disease, neurologic disease, gastrointestinal and liver disease, hematologic disease, and bone and mineral disorder are also addressed. This guideline provides recommendations for evaluation of individual aspects of a candidate's profile such that each risk factor and comorbidity are considered separately. The goal is to assist the clinical team to assimilate all data relevant to an individual, consider this within their local health context, and make an overall judgment on candidacy for transplantation. The guideline development process followed the Grades of Recommendation Assessment, Development, and Evaluation (GRADE) approach. Guideline recommendations are primarily based on systematic reviews of relevant studies and our assessment of the quality of that evidence, and the strengths of recommendations are provided. Limitations of the evidence are discussed with differences from previous guidelines noted and suggestions for future research are also provided.

**Keywords:** albuminuria; adherence; bone and mineral metabolism; candidates; CKD-MBD; clinical practice guideline; cancer; cardiac disease; compatibility; diabetes mellitus; end-stage kidney disease; evidence-based recommendation; gastrointestinal disease; genetic kidney disease; hematuria; hematological disorders; HLA; immunological assessment; infectious diseases; KDIGO; kidney transplantation; liver disease; malignancy; mineral and bone disorder; neurologic disease; obesity; pediatric; perioperative; peripheral arterial disease; pulmonary disease; psychosocial; systematic review; tobacco

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<sup>1</sup> Royal Prince Alfred Hospital and Charles Perkins Centre, University of Sydney, Sydney, Australia.

<sup>2</sup> Seoul National University, Seoul, South Korea.

<sup>3</sup> University of Iowa, Iowa City, IA.

<sup>4</sup> The Montreal Children's Hospital, McGill University Health Centre, Montreal, Canada.

<sup>5</sup> Hennepin County Medical Center, Minneapolis, MN.

<sup>6</sup> Medanta Kidney and Urology Institute, Haryana, India.

<sup>7</sup> University Health Network, University of Toronto, Toronto, Canada.

<sup>8</sup> Medical University of Vienna, Vienna, Austria.

<sup>9</sup> Hospital del Mar, Barcelona, Spain.

<sup>10</sup> Auckland City Hospital, Auckland, New Zealand.

<sup>11</sup> Beth Israel Deaconess Medical Center, Boston, MA.

<sup>12</sup> Johns Hopkins University School of Medicine, Baltimore, MD.

<sup>13</sup> Newcastle University, Newcastle, United Kingdom.

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<sup>14</sup> University of Sydney, Sydney, Australia.

<sup>15</sup> The Ottawa Hospital and Ottawa Hospital Research Institute, Ottawa, Canada.

\*Guideline Work Group Co-Chairs

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## SUMMARY OF RECOMMENDATION STATEMENTS

### SECTION 1: ACCESS TO TRANSPLANTATION

1.1: We recommend that all patients with chronic kidney disease (CKD) G4-G5 (glomerular filtration rate [GFR] < 30ml/min/1.73 m<sup>2</sup>) who are expected to reach end-stage kidney disease (ESKD) (excluding those listed in Rec 1.1.3) be informed of, educated about, and *considered* for kidney transplantation regardless of socioeconomic status, sex, gender identity, or race/ethnicity (1D).

- 1.1.1: Refer potential kidney transplant candidates for evaluation at least 6 to 12 months before anticipated dialysis initiation to facilitate identification/work-up of living donors and plan for possible pre-emptive transplantation (*Not Graded*).
- 1.1.2: Refer potential candidates already on dialysis when medically stable and kidney failure deemed irreversible (*Not Graded*).
- 1.1.3: We recommend not referring patients for kidney alone transplant evaluation with the following conditions (*1D*):
- Multiple myeloma (Rec 9.13.1.1), light chain deposition disease or heavy chain deposition disease (Recs 9.13.2.1, 9.13.2.2 and 9.13.2.3) unless they have received a potentially curative treatment regimen and are in stable remission;
  - AL amyloidosis with significant extrarenal involvement (Recs 9.13.3.1 and 13.8);
  - Decompensated cirrhosis (consider for combined liver-kidney transplant; Recs 10.5.2.4.2, 16.7.2);
  - Severe irreversible obstructive or restrictive lung disease (Rec 12.5);
  - Severe incorrectable and symptomatic cardiac disease that is deemed by a cardiologist to preclude transplantation (Rec 13.7);
  - Progressive central neurodegenerative disease (Rec 15.4).
- 1.1.3.1: Document the reason(s) for not referring patients for transplant evaluation (*Not Graded*).
- 1.1.3.2: Inform patients about the reason(s) for not referring for transplant evaluation (*Not Graded*).
- 1.1.4 We recommend *delaying* transplant evaluation in patients with the following conditions until properly managed (*1D*):
- An unstable psychiatric disorder that affects decision-making or puts the candidate at an unacceptable level of post-transplant risk (Rec 4.2);
  - Ongoing substance use disorder that affects decision-making or puts the candidate at an unacceptable level of post-transplant risk (Rec 4.3);
  - Ongoing, health-compromising nonadherent behavior despite education and adherence-based counseling (Rec 5.4);
  - Active infection (excluding hepatitis C virus infection) that is not properly treated (Rec 10.1.1);
  - Active malignancy except for those with indolent and low-grade cancers such as prostate cancer (Gleason score  $\leq 6$ ), and incidentally detected renal tumors ( $\leq 1$  cm in maximum diameter) (Rec 11.2.1);
  - Active symptomatic cardiac disease (eg, angina, arrhythmia, heart failure, valvular heart disease) that has not been evaluated by a cardiologist (Rec 13.2);
  - Active symptomatic peripheral arterial disease (Rec 14.5);
  - Recent stroke or transient ischemic attack (Rec 15.1);
  - Active symptomatic: peptic ulcer disease (Rec 16.2.2); diverticulitis (Rec 16.3.1), acute pancreatitis (Rec 16.4.1), gallstone/gallbladder disease (16.5.1), inflammatory bowel disease (Rec 16.6.1);

- Acute hepatitis (Rec 16.7.2);
- Severe hyperparathyroidism (Rec 18.2).

- 1.2: Use a multidisciplinary team, which includes at a minimum a transplant physician, transplant surgeon and a health care professional experienced in the psychosocial aspects of transplantation, to evaluate and decide about suitability for kidney transplantation (*Not Graded*).
- 1.3: Approve patients for kidney transplantation that have an estimated survival which is acceptable according to national standards (*Not Graded*).
- 1.3.1: Inform patients of their option to seek a second opinion from another transplant center if they are declined (*Not Graded*).
- 1.4: We recommend pre-emptive transplantation with a living kidney donor as the preferred treatment for transplant-eligible CKD patients (*1A*).
- 1.4.1: We recommend pre-emptive transplantation (living or deceased donor) in adults when the estimated glomerular filtration rate (eGFR) is  $< 10$  ml/min/1.73 m<sup>2</sup> or earlier with symptoms (*1D*).
- 1.4.2: We recommend pre-emptive transplantation (living or deceased donor) in children when the eGFR is  $< 15$  ml/min/1.73 m<sup>2</sup> or earlier with symptoms (*1D*).

## SECTION 2: 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*).

## SECTION 3: PEDIATRIC ISSUES

- 3.1: We suggest performing a neurocognitive assessment in pediatric candidates who experienced end-stage kidney disease before the age of 5 years (*2D*).
- 3.2: We suggest performing an academic assessment in pediatric candidates of school age who are experiencing academic difficulties (*2D*).

## SECTION 4: 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).

## SECTION 5: ADHERENCE

- 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 nonadherence be considered for transplantation unless there is ongoing, health-compromising non-adherent behavior (1D).

## SECTION 6: TOBACCO

- 6.1: Assess past and present use of tobacco products by candidates at transplant evaluation and while on the waiting list (Not Graded).
- 6.2: We recommend counseling all candidates to avoid tobacco products before and indefinitely after transplantation (1B).
- 6.3: We recommend offering a tobacco cessation program to candidates who are using tobacco products (1B).
- 6.4: We recommend that candidates abstain from tobacco use, at a minimum 1 month prior to waitlisting or living donor transplantation (1B).
- 6.5: We suggest chest computed tomography (CT) for current or former heavy tobacco users ( $\geq 30$  pack-years) as per local guidelines to screen for occult lung cancer (2C).

## SECTION 7: SURGICAL ISSUES INCLUDING 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).
- 7.2: We suggest that candidates be assessed for frailty at the time of evaluation and while on the waitlist to inform post-transplant risk and enable optimization strategies, such as pre-operative rehabilitation (2C).
- 7.3: We suggest that candidates be assessed for medical conditions that inhibit wound healing, including obesity, undernutrition, tobacco use, and prior abdominal surgeries, to inform risks of delayed wound healing and hernia formation (2B).

- 7.4: Candidates should not be excluded from consideration for kidney transplantation because of their need for anticoagulation, antiplatelet therapy or a history of heparin-induced thrombocytopenia (HIT) (Not Graded).
  - 7.4.1: Single antiplatelet agents (eg, aspirin, clopidogrel, ticagrelor) can be continued while waiting for deceased donor transplant (Not Graded).
  - 7.4.2: Delay transplantation for the mandated period of treatment with dual antiplatelet therapy (eg, aspirin plus clopidogrel) when the risk of stopping medication (eg, stent thrombosis) or operating while on treatment (eg, surgical bleeding) exceeds the anticipated benefit of transplantation (Not Graded).
    - 7.4.2.1: Antiplatelet agents (except aspirin) should be stopped 5 days prior to living donor transplantation (unless cessation is contraindicated) and during the perioperative period for deceased donor transplantation (Not Graded).
  - 7.4.3: Do not transplant patients on direct-acting oral anticoagulants (DOACs; eg, apixaban, rivaroxaban) except when there is specific expertise using DOACs perioperatively and access to DOAC reversal agents (Not Graded).
    - 7.4.3.1: Switch to an alternative anticoagulant (eg, warfarin) prior to waitlisting or living donor transplantation if recommended by a thrombosis expert/hematologist or if there is no expertise using DOACs perioperatively or access to DOAC reversal agents (Not Graded).
  - 7.4.4: Use non-heparin based agents for perioperative anticoagulation in candidates with a history of HIT (Not Graded).
- 7.5: Assess vascular anatomy and patency for patients with significant peripheral arterial disease (Section 14), prior transplant procedures, venous dialysis catheters, pelvic surgery, or deep venous thrombosis (Not Graded).
- 7.6: Evaluate native kidney size in patients with polycystic kidney disease (Not Graded).
  - 7.6.1: We suggest staged or simultaneous native nephrectomy and transplantation for candidates with polycystic kidney disease that is symptomatic (eg, recurrent pain, recurrent infection), a suspicion of malignancy, or if the patient has insufficient room for a transplant (2D).
- 7.7: Refer to a urologist experienced in transplant issues for patients at increased risk for or those with a history of urologic malignancy, recurrent urinary tract infections, dysfunctional voiding, prior bladder augmentation/division, an ileal conduit, significant structural anomalies of the kidneys or urinary tract, or nephrolithiasis (Not Graded).
  - 7.7.1: We suggest cystoscopy to screen for bladder carcinoma in candidates at increased risk, such as those with high-level exposure to cyclophosphamide or heavy smoking ( $\geq 30$  pack-years) (2D).
  - 7.7.2: We suggest that pre-transplant unilateral or bilateral nephrectomy be considered for pediatric candidates with high urine volumes ( $> 2.5$  ml/kg/hour) or heavy proteinuria associated with hypoalbuminemia (2D).

## SECTION 8: DIABETES

- 8.1: We recommend that candidates with type 1 or type 2 diabetes mellitus (DM) be considered for kidney transplantation (1B).

8.1.1: We suggest candidates with ESKD and type 1 DM be considered for simultaneous pancreas-kidney transplantation in regions where this procedure is available (2A).

8.2: We suggest testing for abnormal glucose metabolism by oral glucose tolerance test in candidates who are not known to have diabetes (2A).

## SECTION 9: CAUSE OF END-STAGE KIDNEY DISEASE (ESKD)

### 9.1 Cause of ESKD and kidney transplantation

9.1.1: We recommend that the cause of ESKD in candidates be determined, where possible, to inform risks and management after kidney transplantation (1A).

9.1.2: Advise candidates about the disease-specific risk of recurrence and resultant risk of graft loss (Not Graded).

### 9.2 Focal segmental glomerulosclerosis (FSGS)

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).

### 9.3 Membranous nephropathy (MN)

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).

### 9.4 IgA nephropathy (IgAN)

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

### 9.5 IgA vasculitis

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

### 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).

### 9.7 Lupus nephritis (LN)

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

9.7.2: We recommend that lupus activity should be clinically quiescent on no or minimal immunosuppression prior to transplantation (1D).

9.7.3: We recommend evaluation for secondary antiphospholipid antibodies prior to transplantation to inform perioperative management (1C).

### 9.8 Antiphospholipid syndrome (APS)

9.8.1: We recommend not excluding candidates with APS from kidney transplantation; however, the risks of post-transplant thrombosis and perioperative anticoagulant therapies should be considered and discussed with the candidate (1B).

9.8.2: We suggest that APS should be clinically quiescent prior to transplantation (2D).

9.8.3: Continue anticoagulation (eg aspirin, warfarin) at the time of activation on the transplant waitlist (Not Graded).

### 9.9 Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis

9.9.1: We recommend not excluding candidates with ANCA-associated vasculitis from kidney transplantation; however, the risk of recurrence should be considered and discussed with the candidate (1B).

9.9.2: We suggest that ANCA-vasculitis should be clinically quiescent prior to transplantation (2D).

- 9.10 Anti-glomerular basement membrane (anti-GBM) disease**
- 9.10.1: We recommend not excluding candidates with anti-GBM disease from kidney transplantation (*1B*).
- 9.10.2: We recommend that anti-GBM antibody titers be measured in candidates and that transplantation is only performed when antibodies are undetectable (*1D*).
- 9.11 Hemolytic uremic syndrome (HUS)**
- 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*).
- 9.12 Systemic sclerosis**
- 9.12.1: We recommend not excluding candidates with systemic sclerosis from kidney transplantation in the absence of severe pulmonary, gastrointestinal, or other life-threatening extrarenal disease (*1C*).
- 9.13 Plasma cell dyscrasias (PCDs)**
- Please consult Section 17.6 Hematologic Disorders for recommendations related to monoclonal gammopathy of undetermined significance (MGUS)
- 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*).

**9.14 AA amyloidosis**

9.14.1: We recommend not excluding candidates with AA amyloidosis from kidney transplantation after adequate treatment of the underlying cause and in the absence of severe extrarenal organ involvement (*1D*).

**9.15 Fibrillary/immunotactoid glomerulonephritis**

9.15.1: We recommend not excluding candidates with fibrillary or immunotactoid glomerulonephritis from kidney transplantation; however, the risk of recurrence should be considered and discussed with the candidate (*1D*).

**9.16 Hyperoxaluria (oxalosis), primary and secondary**

9.16.1: We suggest that candidates with primary hyperoxaluria type 1 be considered for combined or sequential liver-kidney transplantation (*2C*).

9.16.2: We suggest genetic testing to identify the cause of primary hyperoxaluria to inform treatment decisions (*2C*).

9.16.3: We suggest not excluding candidates with correctable hyperoxaluria—pyridoxine-responsive or secondary—from kidney transplantation alone; however, the risk of recurrence should be considered and discussed with the candidate (*2D*).

9.16.4: We recommend the use of strategies to lower total body oxalate burden prior to transplantation in patients with hyperoxaluria, including intensive dialysis, diet modification, and pyridoxine treatment as appropriate on a case-by-case basis (*1D*).

**9.17 Cystinosis**

9.17.1: We recommend not excluding candidates with cystinosis from kidney transplantation in the absence of severe extrarenal manifestations (*1C*).

**9.18 Fabry disease**

9.18.1: We recommend not excluding candidates with Fabry disease from kidney transplantation in the absence of severe cardiac or other systemic extrarenal organ involvement (*1C*).

**9.19 Sickle cell disease**

9.19.1: We recommend not excluding candidates with sickle cell disease from kidney transplantation in the absence of active, severe extrarenal sickle cell disease (*1C*).

**9.20 Sarcoidosis**

9.20.1: We recommend not excluding candidates with renal sarcoidosis from kidney transplantation in the absence of severe extrarenal disease (*1C*).

**9.21 Alport syndrome**

9.21.1: We recommend not excluding candidates with Alport syndrome from kidney transplantation (*1C*).

**SECTION 10: INFECTIONS****10.1 Active infections**

10.1.1: We recommend that kidney transplantation be delayed until active infections (bacterial, fungal, viral [except hepatitis C], parasitic) are treated (1C).

**10.2 Colonization**

10.2.1: Follow local protocols for detection and management of colonization with drug-resistant organisms (*Not Graded*).

10.2.2: We recommend not excluding patients from kidney transplantation with asymptomatic bacterial, parasitic or fungal colonization (1C).

**10.3 Specific Infections****10.3.1 Urinary tract infections (UTIs)**

10.3.1.1: We recommend treating symptomatic UTIs prior to kidney transplantation (1B).

10.3.1.2: We suggest not routinely performing prophylactic nephrectomy for recurrent pyelonephritis or cyst infections (2D).

**10.3.2 Tuberculosis (TB)**

10.3.2.1: We suggest complete treatment of active TB prior to kidney transplantation, as per World Health Organization or local guidelines (2C).

10.3.2.2: We recommend screening for latent TB at the time of candidate evaluation in low TB prevalence areas with a chest radiograph along with a purified protein derivative (PPD) skin test or interferon-gamma release assay (1C).

10.3.2.3: We suggest starting treatment of latent TB prior to or immediately following kidney transplantation in low TB prevalence areas (2C).

10.3.2.4: We suggest screening for latent TB at the time of candidate evaluation as per local guidelines in intermediate and high TB prevalence areas with post-transplantation vigilance for active TB (2C).

**10.4 Screening for periodontal disease**

10.4.1: We suggest dental evaluation, as per local general population guidelines, to screen for dental/periodontal disease prior to kidney transplantation (2C).

**10.5 Screening for viral infections (see Table 11)****10.5.1 Human immunodeficiency virus (HIV)**

10.5.1.1: We recommend screening all patients for HIV infection, using HIV serology (1A).

10.5.1.2: We recommend not excluding patients with controlled HIV infection from kidney transplantation (1C).

10.5.1.3: Kidney transplant candidates with HIV should be managed in a center with experience in this area (*Not Graded*).

10.5.2 Hepatitis C virus (HCV) [*This section is adapted from 2018 KDIGO HCV Guideline*]

10.5.2.1: We recommend screening all patients for HCV infection (1A). (*KDIGO HCV Guideline Recommendation 1.1.4*)

10.5.2.2: We recommend using an immunoassay followed by nucleic acid testing (NAT) if immunoassay is positive (1A). (*KDIGO HCV Guideline Recommendation 1.1.1.1*)

10.5.2.3: We recommend kidney transplantation as the best therapeutic option for patients with CKD G5 irrespective of presence of HCV infection (1A). (*KDIGO HCV Guideline Recommendation 4.1.1*)

10.5.2.4: We suggest that all candidates with HCV infection be evaluated for severity of liver disease and presence of portal hypertension (if indicated) prior to acceptance for kidney transplantation (Figure 3) (2D). (*KDIGO HCV Guideline Recommendation 4.1.2*)

10.5.2.4.1: We recommend that patients with HCV and compensated cirrhosis (without portal hypertension) undergo isolated kidney transplantation (1B). (*KDIGO HCV Guideline Recommendation 4.1.2.1*)

10.5.2.4.2: We recommend referring patients with HCV and decompensated cirrhosis for combined liver-kidney transplantation (1B) and deferring HCV treatment until after transplantation (1D). (*KDIGO HCV Guideline Recommendation 4.1.2.2*)

10.5.2.5: Timing of HCV treatment in relation to kidney transplantation (before vs. after) should be based on donor type (living vs. deceased donor), waitlist times by donor type, center-specific policies governing the use of kidneys from HCV-infected deceased donors, HCV genotype, and severity of liver fibrosis (*Not Graded*). (*KDIGO HCV Guideline Recommendation 4.1.3*)

10.5.2.5.1: We recommend that all patients with HCV who are candidates for kidney transplantation be considered for direct-acting antiviral (DAA) therapy, either before or after transplantation (1A). (*KDIGO HCV Guideline Recommendation 4.1.3.1*)

10.5.2.5.2: We suggest that candidates with HCV with a living kidney donor can be considered for treatment before or after transplantation according to HCV genotype

- and anticipated timing of transplantation (2B). (KDIGO HCV Guideline Recommendation 4.1.3.2)
- 10.5.2.5.3: We suggest that if receiving a kidney from an HCV-positive donor improves the chances for transplantation, the HCV NAT-positive patient can undergo transplantation with an HCV-positive kidney and be treated for HCV infection after transplantation (2B). (KDIGO HCV Guideline Recommendation 4.1.3.3)
- 10.5.3 Hepatitis B virus (HBV) [See Section 10.7 for related recommendations on HBV vaccinations]**
- 10.5.3.1: We recommend screening for HBV infection with HBsAg, anti-HBs, and anti-HBc (1A).
- 10.5.3.2: We recommend screening with HBV DNA for patients with a positive HBsAg or anti-HBc (1A).
- 10.5.3.3: We recommend that patients from hepatitis D virus (HDV) endemic areas be screened with HDV serology if they are positive for HBsAg or anti-HBc (1A).
- 10.5.3.4: We recommend that HBsAg positive and/or HBV DNA positive candidates be referred to a specialist with expertise in the management of liver disease and HBV infection to determine appropriate antiviral treatment (1D).
- 10.5.3.4.1: We recommend that HBsAg positive and/or HBV DNA positive candidates undergo isolated kidney transplantation if they do not have decompensated cirrhosis and are stable on antiviral therapy after specialist evaluation (1B).
- 10.5.3.5: We recommend not excluding anti-HBc antibody positive (HBsAg negative) patients from kidney transplantation (1C).
- 10.5.3.5.1: We recommend that anti-HBc antibody positive (HBsAg negative) patients not receive antiviral prophylaxis given that the risk of reactivation is low (1D).
- 10.5.3.5.2: We suggest that anti-HBc antibody positive (HBsAg negative) patients have a plan in place for post-transplant monitoring of HBsAg and HBV DNA for a minimum of 1-year post-transplantation (2C).
- 10.5.4 Cytomegalovirus (CMV)**
- 10.5.4.1: We recommend screening for CMV with CMV IgG (1C).
- 10.5.5 Epstein-Barr virus (EBV)**
- 10.5.5.1: We recommend screening for EBV with EBV viral capsid antigen (VCA) IgG and/or EBV nuclear antigen (EBNA) IgG (1C).
- 10.5.6 Herpes simplex virus (HSV)**
- 10.5.6.1: We suggest screening for HSV with HSV IgG (2C).
- 10.5.7 Varicella-zoster virus (VZV)**
- 10.5.7.1: We recommend screening for VZV with VZV IgG (1C).
- 10.5.7.1.1: We recommend varicella immunization for VZV seronegative candidates at least 4 weeks prior to transplantation (1C).
- 10.5.8 Measles, mumps, and rubella (MMR)**
- 10.5.8.1: We suggest screening for MMR using IgG serology (2C).
- 10.5.8.1.1: We suggest MMR immunization for MMR seronegative candidates at least 4 weeks prior to transplantation (2C).
- 10.5.9 BK virus**
- 10.5.9.1: We recommend not screening for BK virus infection in candidates (1C).
- 10.5.9.1.1: We recommend not excluding patients for repeat transplantation if a previous graft was lost due to BK nephropathy (1C).
- 10.5.10 Human T-cell lymphotropic virus (HTLV)**
- 10.5.10.1: We recommend screening for HTLV 1/2 with IgG serology in candidates from endemic areas as per World Health Organization (1C).
- 10.6 Screening for non-viral infections**
- 10.6.1 Syphilis**
- 10.6.1.1: We recommend screening for syphilis (*Treponema pallidum*) with serology at the time of candidate evaluation and treatment prior to transplantation if infection is identified (1C).
- 10.6.2 Strongyloides**
- 10.6.2.1: We suggest screening for strongyloidiasis with serology at the time of evaluation in candidates from endemic areas, and treatment prior to transplantation if infection is identified (2C).
- 10.6.3 Chagas disease**
- 10.6.3.1: We recommend screening for Chagas disease with serology at the time of evaluation in candidates from endemic areas, and treatment prior to transplantation if infection is identified (1C).
- 10.6.4 Malaria**
- 10.6.4.1: We recommend screening for malaria with a malaria blood smear at the time of evaluation in candidates who have recently travelled to endemic areas, and treatment prior to transplantation if infection is identified (1C).
- 10.7 Vaccinations**
- 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).
- 10.7.3: We recommend that splenectomized candidates or those at increased risk for post-transplant splenectomy receive pre-transplant pneumococcal, hemophilus, and meningococcal vaccination (1B).
- 10.7.4: We recommend that candidates requiring complement inhibitors perioperatively or post-transplant undergo meningococcal vaccination (1B).
- 10.7.5: We suggest administering the following vaccines to candidates who, due to age, direct exposure, residence or travel to endemic areas, or other epidemiological risk factors, are at increased risk for the specific diseases:
- Rabies (2D)
  - Tick-borne meningoencephalitis (2D)
  - Japanese encephalitis (inactivated) (2D)
  - Meningococcus (2D)
  - *Salmonella typhi* (inactivated) (2D)
  - Yellow fever (2D)

## SECTION 11: MALIGNANCY

### 11.1 Cancer screening

- 11.1.1: We recommend candidates undergo routine cancer screening, as per local guidelines for the general population (Table 13) (1D).
- 11.1.1.1: We suggest chest imaging prior to transplantation in all candidates (2C). (Same as Rec 12.2)
- 11.1.1.2: We suggest chest CT for current or former heavy tobacco users ( $\geq 30$  pack-years) as per local guidelines, and chest radiograph for other candidates (2C). (Same as Rec 12.2.1)
- 11.1.2: Screen candidates at increased risk for renal cell carcinoma (eg  $\geq 3$  years dialysis, family history of renal cancer, acquired cystic disease or analgesic nephropathy) with ultrasonography (Not Graded).
- 11.1.3: We suggest cystoscopy to screen for bladder carcinoma in candidates at increased risk, such as those with high-level exposure to cyclophosphamide or heavy smoking ( $\geq 30$  pack-years) (2D).
- 11.1.4: We recommend screening for hepatocellular carcinoma in candidates with cirrhosis prior to transplantation using techniques

(eg, ultrasound,  $\alpha$ -fetoprotein) and frequency as per local guidelines (1C).

- 11.1.5: We recommend screening for bowel cancer in candidates with inflammatory bowel disease as per local guidelines (1C).

### 11.2 Potential kidney transplant candidates with a 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  $\leq 6$ ), superficial non-melanoma skin cancer, and incidentally detected renal tumors ( $\leq 1$  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).
- 11.2.3: We recommend no waiting time for candidates with curatively treated (surgically or otherwise) non-metastatic basal cell and squamous cell carcinoma of the skin; melanoma *in situ*; small renal cell carcinoma ( $< 3$  cm); prostate cancer (Gleason score  $\leq 6$ ); carcinoma *in situ* (ductal carcinoma *in situ*, cervical, others); thyroid cancer (follicular/papillary  $< 2$  cm of low grade histology); and superficial bladder cancer (1C).
- 11.2.3.1: For other cancers, we suggest following waiting time parameters as outlined in Table 14 (2D).
- 11.2.3.2: We suggest that the recommended waiting time from cancer to kidney transplantation begins upon completion of potentially curative treatment (2D).
- 11.2.4: Decisions about transplantation for candidates in remission from cancer should be made collaboratively with oncologists, transplant nephrologists, patients, and their caregivers (Not Graded).
- 11.2.4.1: For relevant cancers, supplement estimates of prognosis using genomic profiling, other molecular genomic tests, and phenotyping in consultation with the patient's oncologist (Not Graded).
- 11.2.5: We recommend not excluding candidates with a history of metastatic cancer provided that potentially curative therapy has been administered and complete remission achieved; however, the risk of recurrence should be a major consideration and discussed with the candidate and their oncologist (1D).
- ### 11.3 Hematologic malignancy (See Sections 17.7, 17.8 and 17.9)
- 11.3.1: Acute leukemia and high-grade lymphoma, including post-transplant lymphoproliferative disease
- 11.3.1.1: Avoid transplanting patients with leukemia or lymphoma until they have received curative therapy, achieved remission and remained cancer free for a period to be determined in consultation with the patient, a hematologist/oncologist and the transplant program (Not Graded).

### 11.3.2: Myelodysplasias, chronic leukemia and chronic/low-grade lymphoma

- 11.3.2.1: Decisions about kidney transplantation in patients with myelodysplasia should be made in collaboration with a hematologist (*Not Graded*).
- 11.3.2.2: Advise consultation with a hematologist with transplant experience in determining transplant candidacy since many lesions may be deemed to be at high risk of accelerated progression or transformation post-transplant (*Not Graded*).
- 11.3.3: Decisions about kidney transplantation in patients with a prior history of hematologic malignancy who are now in remission should be made in collaboration with a hematologist (*Not Graded*).

## SECTION 12: PULMONARY DISEASE

- 12.1: Assess candidates with lung disease in collaboration with a pulmonary specialist to determine suitability for transplantation (*Not Graded*).
- 12.2: We suggest chest imaging prior to transplantation in all candidates (2C). (Same as Rec 11.1.1.1)
- 12.2.1 We suggest chest CT for current or former heavy tobacco users ( $\geq 30$  pack-years) as per local guidelines, and chest radiograph for other candidates (2C). (Same as Rec 11.1.1.2)
- 12.3: We recommend pulmonary function testing in candidates with impaired functional capacity, respiratory symptoms, or known pulmonary disease (1C).
- 12.4: We recommend counseling all candidates to avoid tobacco products before and indefinitely after transplantation (1B). (Same as Rec 6.2)
- 12.5: We recommend excluding patients with severe irreversible obstructive or restrictive lung disease from kidney transplantation (1C).

## SECTION 13: CARDIAC DISEASE

- 13.1: Evaluate all candidates for the presence and severity of cardiac disease with history, physical examination, and electrocardiogram (ECG) (*Not Graded*).
- 13.2: Patients with signs or symptoms of active cardiac disease (eg, angina, arrhythmia, heart failure, symptomatic valvular heart disease) should undergo assessment by a cardiologist and be managed according to current local cardiac guidelines prior to further consideration for a kidney transplant (*Not Graded*).
- 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 non-invasive 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).

- 13.4: 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 catheterization) 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).
- 13.6: Patients with severe valvular heart disease should be evaluated and managed by a cardiologist according to local cardiac guidelines (*Not Graded*).
- 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*).
- 13.8: Perform cardiac imaging in patients with systemic amyloidosis. Exclude such patients from kidney transplantation if significant cardiac amyloid is confirmed (*Not Graded*). (see Rec 9.13.3.1)
- 13.9: We suggest that candidates who have a myocardial infarction be assessed by a cardiologist to determine whether further testing is warranted and when they can safely proceed with kidney transplantation (2B).
- 13.10: We suggest that transplantation be delayed an appropriate amount of time after placement of a coronary stent as recommended by the patient's cardiologist (2B).
- 13.11: We suggest that maintenance aspirin,  $\beta$ -blockers, and statins be continued while on the waiting list and perioperatively, according to local cardiac guidelines (2A).

## SECTION 14: PERIPHERAL ARTERIAL DISEASE (PAD)

- 14.1: Evaluate all candidates for presence and severity of peripheral arterial disease (PAD) with history and physical examination (*Not Graded*).
- 14.2: We suggest that candidates without clinically apparent PAD, but who are at high risk for PAD, undergo non-invasive vascular testing (2D).

- 14.3: Candidates with clinically apparent PAD should undergo imaging and management of their PAD in consultation with a vascular surgeon prior to transplantation (*Not Graded*).
- 14.4: We suggest that candidates with clinically apparent PAD, abnormal non-invasive testing, or prior vascular procedures, undergo non-contrast CT imaging of the abdomen/pelvis to evaluate arterial calcification and improve operative planning (*2D*).
- 14.5: Exclude candidates with non-healing extremity wounds with active infection from transplantation until the infection is resolved (*Not Graded*).
- 14.6: We suggest not excluding patients with prior aorto-iliac procedures including iliac artery stent placement from kidney transplantation if there is sufficient native artery available for vascular anastomosis (*2D*).
- 14.7: We suggest not excluding patients with severe aorto-iliac disease or distal vascular disease from kidney transplantation; however, the risk of progression after transplantation should be a key consideration and the patient should have an estimated survival which is acceptable according to national standards (*2D*).

## SECTION 15: NEUROLOGIC DISEASE

- 15.1: We suggest waiting at least 6 months after a stroke or 3 months after a transient ischemic attack (TIA) before kidney transplantation (*2D*).
- 15.2: We recommend not screening asymptomatic candidates for carotid artery disease (*1D*).
- 15.3: We suggest screening candidates with autosomal dominant polycystic kidney (ADPKD) disease for intracranial aneurysms only if they are at high risk due to prior history of or a family history of subarachnoid hemorrhage (*2D*).
- 15.4: Patients with progressive central neurodegenerative disease should not undergo kidney transplantation if survival and quality of life are not expected to be substantially improved by transplantation (*Not Graded*).
- 15.5: Assess mental status in candidates with known or suspected cognitive impairment (*Not Graded*).
- 15.5.1: We recommend not excluding candidates from kidney transplantation because of non-progressive intellectual, developmental, or cognitive disability (*1D*).
- 15.6: Patients with symptomatic peripheral neuropathy should be assessed by a neurologist (*Not Graded*).
- 15.6.1: We suggest people with progressive peripheral neuropathy attributed to uremia be considered for urgent kidney transplantation, if available (*2D*).
- 15.6.2: We recommend not excluding candidates from kidney transplantation because of peripheral neuropathy (*1D*).

## SECTION 16: GASTROINTESTINAL AND LIVER DISEASE

- 16.1: Evaluate all candidates for the presence of gastrointestinal disease, including liver disease, with a targeted history and physical examination (*Not Graded*).

### 16.2 Peptic ulcer disease

- 16.2.1: We recommend that candidates with symptoms suggestive of active peptic ulcer disease undergo esophagogastroscope and *H. pylori* testing prior to kidney transplantation (*1C*).
- 16.2.2: Delay kidney transplantation in candidates with endoscopically-proven peptic ulcer disease until symptoms have resolved (*Not Graded*).
- 16.2.3: We recommend not screening candidates with a history of peptic ulcer disease with esophagogastroscope (*1C*).
- 16.2.4: We recommend not excluding candidates with a history of peptic ulcer disease from kidney transplantation (*1D*).

### 16.3 Diverticulitis

- 16.3.1: Delay kidney transplantation in candidates with active diverticulitis until symptoms have resolved (*Not Graded*).
- 16.3.2: We recommend not screening asymptomatic candidates for diverticulosis (*1C*).
- 16.3.3: We recommend not performing prophylactic colectomy in patients with a history of diverticulitis or asymptomatic diverticulosis (*1C*).
- 16.3.4: We recommend not excluding candidates with a history of diverticulitis from kidney transplantation (*1C*).

### 16.4 Pancreatitis

- 16.4.1: Delay kidney transplantation in candidates with acute pancreatitis a minimum of three months after symptoms have resolved (*Not Graded*).
- 16.4.2: We suggest not excluding candidates with a history of acute or chronic pancreatitis from kidney transplantation (*2C*).

### 16.5 Cholelithiasis

- 16.5.1: Delay kidney transplantation in candidates with symptomatic gallstone or gallbladder disease until symptoms have resolved (*Not Graded*).
- 16.5.2: We recommend that candidates with a history of cholecystitis undergo cholecystectomy before kidney transplantation (*1C*).
- 16.5.3: We recommend not screening asymptomatic candidates for cholelithiasis (*1C*).
- 16.5.4: We recommend not performing prophylactic cholecystectomy in candidates with asymptomatic cholelithiasis (*1C*).
- 16.5.5: We recommend not excluding candidates with asymptomatic cholelithiasis from kidney transplantation (*1A*).

### 16.6 Inflammatory bowel disease

- 16.6.1: Delay kidney transplantation in candidates with active symptomatic inflammatory bowel disease (*Not Graded*).
- 16.6.1.1: Determine timing of transplantation for such patients in consultation with a gastroenterologist (*Not Graded*).
- 16.6.2: We recommend screening for bowel cancer in candidates with inflammatory bowel disease as per local guidelines (*1C*). (Same as Rec 11.1.5).
- 16.6.3: We recommend not excluding candidates with a history of inflammatory bowel disease from kidney transplantation (*1D*).

## 16.7 Liver disease

- 16.7.1: Screen kidney transplant candidates for liver disease with a total bilirubin, alanine aminotransferase, international normalized ratio, and albumin (*Not Graded*).
- 16.7.2: Delay kidney transplantation until acute hepatitis, of any cause, has resolved and a long-term strategy for managing liver disease has been implemented (*Not Graded*).
- 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*).

For liver disease associated with HBV or HCV infection, see Sections 10.5.2 and 10.5.3

- 16.7.4: We recommend screening for hepatocellular carcinoma in candidates with cirrhosis prior to transplantation using techniques (eg, ultrasound, alpha-fetoprotein) and frequency as per local guidelines (*1C*). (Same as Rec 11.1.4).

## SECTION 17: HEMATOLOGIC DISORDERS

- 17.1: We recommend not routinely screening for thrombophilia in candidates (*1C*).
  - 17.1.1: We suggest screening for thrombophilia only in candidates who have experienced a venous thromboembolic event, recurrent arteriovenous access thromboses, non-atherosclerotic arterial thrombosis, or family history of venous thromboembolism to identify candidates at higher risk of graft thrombosis (*2C*).
- 17.2: We suggest testing for antiphospholipid antibodies (APLAs) in patients with systemic lupus erythematosus or features of antiphospholipid syndrome (APS) (*2C*).
- 17.3: Candidates should not be excluded from consideration for kidney transplantation because of their need for anticoagulation, antiplatelet therapy or a history of HIT (*Not Graded*). [same as Rec 7.4]
  - 17.3.1: Single antiplatelet agents (eg, aspirin, clopidogrel, ticagrelor) can be continued while waiting for deceased donor transplant (*Not Graded*). [same as Rec 7.4.1]
  - 17.3.2: Delay transplantation for the mandated period of treatment with dual antiplatelet therapy (eg, aspirin plus clopidogrel) when the risk of stopping medication (eg, stent thrombosis) or operating while on treatment (eg, surgical bleeding) exceeds the anticipated benefit of transplantation (*Not Graded*). [same as Rec 7.4.2]
    - 17.3.2.1: Antiplatelet agents (except aspirin) should be stopped 5 days prior to living donor transplantation (unless cessation is contraindicated) and during the perioperative period for deceased donor transplantation (*Not Graded*). [same as Rec 7.4.2.1]
  - 17.3.3: Do not transplant patients on direct-acting oral anticoagulants (DOACs; eg, apixaban, rivaroxaban) except when there is specific expertise using DOACs perioperatively and access to DOAC reversal agents (*Not Graded*). [same as Rec 7.4.3]
    - 17.3.3.1: Switch to an alternative anticoagulant (eg warfarin) prior to waitlisting or living donor transplantation if recommended by a thrombosis expert/hematologist or if there is no expertise using DOACs perioperatively or access to DOAC reversal agents (*Not Graded*). [same as Rec 7.4.3.1]
  - 17.3.4: Use non-heparin based agents for perioperative anticoagulation in candidates with a history of HIT (*Not Graded*). [same as Rec 7.4.4]
- 17.4: Evaluate transplant suitability of patients with significant cytopenias based on cause and severity (*Not Graded*).
- 17.5: We recommend that candidates with sickle cell disease or thalassemia not be excluded from kidney transplantation [see sections on recurrent disease: Section 9.19: sickle cell disease]. (*1C*)
- 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*).
- 17.7 Acute leukemia and high-grade lymphoma, including post-transplant lymphoproliferative disease (Same as Section 11.3.1)
  - 17.7.1: Avoid transplanting patients with leukemia or lymphoma until they have received curative therapy, achieved remission and remained cancer free for a period to be determined in consultation with the patient, a hematologist/oncologist and the transplant program (*Not Graded*).
- 17.8 Myelodysplasias, chronic leukemia and chronic/low-grade lymphoma (Same as Section 11.3.2)
  - 17.8.1: Decisions about kidney transplantation in patients with myelodysplasia should be made in collaboration with a hematologist (*Not Graded*).
  - 17.8.2: Advise consultation with a hematologist with transplant experience in determining transplant candidacy since many lesions may be deemed to be at high risk of accelerated progression or transformation post-transplant (*Not Graded*).

- 17.9: Decisions about kidney transplantation in patients with a prior history of hematological malignancy who are now in remission should be made in collaboration with a hematologist (*Not Graded*) (Same as Rec 11.3.3).

## SECTION 18: BONE AND MINERAL METABOLISM

- 18.1: Measure serum parathyroid hormone (PTH) at the time of transplant evaluation (*Not Graded*).
- 18.2: We suggest not transplanting patients with severe hyperparathyroidism until they are adequately treated (medically or surgically) as per KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) guideline (2D).
- 18.3: Bone mineral density (BMD) should not be measured as part of the transplant evaluation (*Not Graded*).

## SECTION 19: 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).

## METHODS FOR GUIDELINE DEVELOPMENT

### AIM

The overall aim of this project was to develop an evidence-based clinical practice guideline for the management of patients being evaluated for kidney transplantation. The guideline consists of recommendation statements, rationale text, and a summary of systematically generated evidence on relevant pre-defined clinical topics. The general guideline development method is described below.

## OVERVIEW OF PROCESS

The development process for the *KDIGO 2020 Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation* included the following steps:

- Appointing Work Group members and the evidence review team (ERT)
- Discussing process, methods, and results
- Developing and refining topics
- Identifying populations, interventions or predictors, and outcomes of interest
- Selecting topics for systematic evidence review
- Standardizing quality assessment methodology
- Developing and implementing literature search strategies
- Screening abstracts and retrieving full-text articles on the basis of pre-defined eligibility criteria
- Creating data extraction forms
- Extracting data and performing critical appraisal of the literature
- Grading the methodology and outcomes in individual studies
- Tabulating data from individual studies into summary tables
- Grading quality of evidence for each outcome across studies, and assessing the overall quality of evidence across outcomes with the aid of evidence profiles
- Grading the strength of recommendations on the basis of the quality of evidence and other considerations
- Finalizing guideline recommendations and supporting rationale
- Sending the guideline draft for public review in October 2018
- Editing the guideline
- Publishing the final version of the guideline

The overall process for conducting the systematic reviews and developing the clinical practice guideline follow international standards, including those from the Institute of Medicine (now known as Health and Medicine Division, National Academies of Sciences, United States [US]).<sup>4,5</sup>

The Work Group Co-Chairs and ERT met for a two-day meeting to review the guideline development process, evidence review topics, and systematic review findings. Following this, the Work Group, ERT, and KDIGO support staff met for two separate meetings to review the available evidence, formulate recommendation statements, evaluate the quality of the evidence and strength of recommendations, deliberate on rationale for recommendations, and develop consensus. The draft clinical practice guideline underwent public review, after which revisions to recommendations and text were made where appropriate.

## Commissioning of Work Group and ERT

The KDIGO Co-Chairs appointed the Work Group Co-Chairs, who then assembled the Work Group of domain experts, including individuals with expertise in adult and pediatric nephrology, transplant nephrology, transplantation surgery, transplantation medicine, transplant immunology, and cancer epidemiology. The Brown University Center for Evidence Synthesis in Health in Providence, Rhode Island, USA, was contracted as the ERT to conduct systematic evidence review and provide expertise in guideline development methodology. The ERT consisted of

physician–methodologists and experienced research associates with expertise in nephrology and evidence-based clinical practice guideline development.

### Defining scope and topics

The Work Group Co-Chairs and the ERT defined the overall scope and goals of the guideline including lists of populations, interventions, predictors, comparators, outcomes, and analyses of interest. Together, they then drafted a preliminary list of topics and key clinical questions. The Work Group and the ERT further developed and refined each topic and specified screening criteria, literature search strategies, and data extraction forms.

### Establishing the process for guideline development

The ERT performed systematic literature searches and organized abstract and article screening. The ERT also coordinated the methodological and analytical processes and defined and standardized the methodology for performing literature searches, data extraction, and summarizing the evidence. The Work Group took the primary role of writing and grading the recommendation statements and rationale text and retained final responsibility for their content.

### Formulating questions of interest

Questions of interest were formulated according to the PICOTS criteria (Population, Intervention/Predictor, Comparator, Outcome, Timing, and Study Design). Details of the PICOTS criteria are presented in Table 1.

### Ranking of outcomes

The Work Group ranked outcomes of interest on the basis of their importance for informing clinical decision making (Table 2).

### Literature searches and article selection

Systematic search strategies were developed by the ERT with input from the Work Group Co-Chairs. Modules were created for kidney transplantation, study designs, and terms for each of the systematic review topics. Separate searches were conducted for each topic (or sets of related topics). Searches were conducted in Medline (via PubMed), EMBASE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. No date or language restrictions were entered into the searches. The full literature search strategies are provided in the Supplemental Appendix A. The final searches were conducted in August 2017. The search for gammopathies was conducted in May 2019. Searches were supplemented by articles provided by Work Group members through September 2019.

For selection of studies, all members of the ERT screened each set of abstracts in duplicate using an open-source, online screening program Abstrackr (<http://abstrackr.cebm.brown.edu/>). To establish relevance and consensus among reviewers, the entire team screened and achieved consensus on a series of initial batches of 100 abstracts. A total of 45,914 citations were screened (Figure 1). Journal articles reporting original data or systematic reviews were selected for evidence review, based on *a priori* criteria for eligible evidence. Of these, 762 were selected for consideration for

inclusion. After review of the full-text articles, 190 were included, as enumerated in Table 3.

### Data extraction

Data extraction was done by ERT research associates. Extracted data from each study was reviewed by another ERT member to confirm accuracy. The ERT designed forms to capture data on design, methodology, eligibility criteria, study participant characteristics, interventions, comparators, predictors, outcomes, and results of individual studies. Methodology and outcomes were also systematically assessed for risk of bias (see the section on risk of bias assessment below) and recorded during the data extraction process.

### Summary tables

Summary tables were developed for each reviewed topic with eligible studies. Summary tables contain outcomes of interest, relevant population characteristics, description of intervention and comparator (or predictor), results, and quality grading for each outcome. Categorical and continuous outcomes were tabulated separately.

Work Group members reviewed and confirmed all summary table data and quality assessments. Summary tables are available at [www.kdigo.org](http://www.kdigo.org).

### Evidence profiles

Evidence profiles were constructed to assess the quality and record quality grades and descriptions of effect (or association) for each outcome across studies, as well as the quality of overall evidence and description of net benefits or harms of the intervention or comparator across all outcomes. These profiles aim to make the evidence synthesis process transparent. Decisions in the evidence profiles were based on data from the primary studies listed in corresponding summary tables and on judgments of the ERT and Work Group. Each evidence profile was initially constructed by the ERT and then reviewed, edited, and confirmed by the Work Group and/or Work Group Chairs. The work products created by the ERT for summarizing the evidence base are listed in Table 3, together with the number of included studies.

### Grading of quality of evidence for outcomes of individual studies

Methodological quality (internal validity) refers to the design, conduct, and reporting of outcomes of a clinical study. A previously devised three-level classification system for quality assessment was used to grade the overall study quality and quality of all relevant outcomes in the study (Table 4). Grading of individual studies was done by one of the reviewers, then confirmed by another, with discrepancies discussed in conference.

We based the methodological quality of each study on predefined criteria. For randomized controlled trials (RCTs) and other comparative studies, the ERT used the Cochrane risk of bias tool,<sup>6</sup> which asks about risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. For observational studies, we also used selected questions from the Newcastle Ottawa Scale about comparability of cohorts,

**TABLE 1.**  
**Systematic review topics and screening criteria**

**Clinical outcomes: Transplant vs. continued waitlist**

Population	Adult or child eligible for potential kidney transplant
Intervention	Kidney transplantation ( <i>de novo</i> , retransplant, any donor)
Comparator	Continuation on waitlist for kidney transplantation. Exclude if include patients not on transplant waitlist (not awaiting transplantation).
Predictors	Age subgroups, obesity subgroups, HIV, HBV
Outcome	Mortality (all cause), HIV or HBV outcomes as relevant
Study design	Multivariate (adults, HBV), any design (pediatrics, HIV)
Minimum duration of follow-up	None
Minimum <i>N</i> of Subjects	100 (adults), Any (pediatrics)

**Prediction model studies**

Population	Received kidney transplant, in large registry or national database or equivalent. Exclude multi-organ transplantation.
Predictors	Pre-transplantation (or at time of transplant) variables only: eGFR, albumin, BMI (particularly at extremes), SGA or other nutrition markers, malnutrition, age (particularly at extremes), tobacco use, PRA, history of cardiac disease, heart disease status/measures, diabetes, aortoiliac disease, diabetic peripheral vascular disease, pulmonary disease, specific CKD, cancer history, morbidity indexes, substance use disorder, intellectual disability. Exclude organ donor factors.
Outcome	All predictors: Mortality (all cause), graft failure/loss Predictor-specific: Mortality (cause-specific), cancer recurrence, new-onset diabetes
Design	Registry study (or equivalent), multivariable analyses
Minimum <i>N</i> of subjects	100
Registry dates	Latest enrollment in registry in or after 2007

**CKD recurrence after transplantation**

Population	Kidney transplantation due to known, specific (listed) causes of CKD
Predictor	Specific causes of CKD
Outcome	CKD recurrence after transplantation (percentage with recurrence)
Design	Longitudinal
Minimum duration of follow-up	None
Minimum <i>N</i> of subjects	Variable based on population frequency of specific causes of CKD

**Prevention of CKD recurrence**

Population	Kidney transplantation due to FSGS, HUS, membranous nephropathy, or MPGN
Intervention	Treatments for CKD at or around time of transplantation, including plasma exchange/plasma-pheresis, rituximab, eculizumab, immunoabsorption, and immunosuppression
Outcome	Mortality (all-cause), graft failure/loss, GFR, proteinuria, recurrent disease (by biopsy)
Design	Longitudinal
Minimum duration of follow-up	None
Minimum <i>N</i> of subjects	None

**Tuberculosis**

Population	CKD G4-G5 with active tuberculosis
Intervention	Short course tuberculosis treatment
Comparator	Long (typical) course tuberculosis treatment (or no comparator)
Outcome	Mortality (all-cause and TB), TB reactivation, graft failure/loss
Study design	Longitudinal
Minimum duration of follow-up	None
Minimum <i>N</i> of Subjects	50

**Nephrectomy (for recurrent UTI or BK virus)**

Population	CKD G4-G5 with recurrent UTI or Kidney transplant recipient with failed/failing graft due to BK virus
Intervention	Nephrectomy (native or allograft kidney)
Comparator	No nephrectomy (or no comparator)
Outcome	Mortality (all-cause), graft failure/loss, GFR, recurrent UTI or BK nephropathy
Study design	Any
Minimum duration of follow-up	None
Minimum <i>N</i> of Subjects	None

Continued

**TABLE 1. (Continued)****HIV**

Population	Kidney transplant candidates who receive transplants
Intervention	HIV+
Comparator	HIV-
Outcome	Mortality (all-cause), graft failure/loss, HIV and infectious outcomes, GFR
Study design	Comparative (HIV+ vs. HIV-)
Minimum duration of follow-up	None
Minimum <i>N</i> of Subjects	100

**Tuberculosis testing**

Population	CKD G4-G5 who receive transplants
Intervention	Any TB test (pre-transplantation)
Outcome	Test performance characteristics, Post-transplant TB outcomes
Study design	Any
Minimum duration of follow-up	None
Minimum <i>N</i> of Subjects	20

**Vaccination**

Population	CKD G4-G5 who receive transplants
Intervention	Vaccination for/with Pneumovax (Pneumovax 13), influenza, HBV, measles, shingles
Outcome	Immunogenicity, post-transplant vaccine effectiveness (disease incidence)
Study design	Any
Minimum duration of follow-up	None
Minimum <i>N</i> of Subjects	20

**Prostate cancer**

Population	Kidney transplant candidate with non-metastatic prostate cancer who receive transplants
Intervention	Prostatectomy (at time of kidney transplantation)
Comparator	None needed
Outcome	Mortality (all-cause), graft failure/loss, prostate cancer outcomes
Study design	Longitudinal
Minimum duration of follow-up	None
Minimum <i>N</i> of Subjects	10

**Cancer, active**

Population	Kidney transplant candidates with known, specific, treated cancer who receive transplants
Predictor	Wait-time for transplantation after cancer cure or treatment
Outcome	Mortality (all-cause, cancer), graft failure/loss, cancer recurrence
Study design	Longitudinal
Minimum duration of follow-up	None
Minimum <i>N</i> of Subjects	100

**Monoclonal gammopathy**

Population	Kidney transplant candidates who receive transplants
Predictor	Testing for gammopathies
Outcome	MGUS or MGRS (pre- or post-Txp), hematologic outcomes (post-Txp), kidney/graft outcomes (post-transplant), survival (post-Txp)
Study design	Longitudinal
Minimum duration of follow-up	None
Minimum <i>N</i> of Subjects	None

**Cancer screening**

Population	Kidney transplant candidates with no known cancer who receive transplants
Intervention	Cancer screening (any cancer, method)
Outcome	Mortality (all-cause, cancer), graft failure/loss, cancer
Study design	Longitudinal
Minimum duration of follow-up	None
Minimum <i>N</i> of Subjects	100

**Echocardiography**

Population	Kidney transplant candidates asymptomatic for CHF, valvular disease, or other indications for echocardiography who receive transplants
Intervention	Echocardiography measures

Continued

**TABLE 1. (Continued)**

Outcome	Mortality (all-cause, cardiac), graft failure/loss, cardiac disease, pulmonary hypertension, left ventricular function (overall or categorical, not specific measures)
Study design	Longitudinal
Minimum duration of follow-up	None
Minimum <i>N</i> of Subjects	100 (adults), any (pediatrics)
<b>Cardiac revascularization</b>	
Population	CKD G5 (dialysis) with severe CAD who receive transplants
Intervention	Cardiac revascularization
Outcome	Mortality (all-cause, cardiac), graft failure/loss
Study design	Longitudinal
Minimum duration of follow-up	None
Minimum <i>N</i> of Subjects	10
<b>Cerebrovascular disease screening</b>	
Population	CKD G4-G5 who receive transplants
Intervention	Extracranial cerebrovascular testing (as screening)
Outcome	Mortality (all-cause, cerebrovascular), graft failure/loss, stroke
Study design	Longitudinal
Minimum duration of follow-up	None
Minimum <i>N</i> of Subjects	100
<b>ADPKD-related cerebral aneurysm screening</b>	
Population	ADPKD
Intervention	Intracranial aneurysm screen/test
Outcome	Mortality (all-cause, cerebrovascular), stroke, intracranial aneurysm
Study design	Any
Minimum duration of follow-up	None
Minimum <i>N</i> of Subjects	None
<b>Hepatitis B treatment</b>	
Population	CKD G5 (dialysis) with HBV who receive transplant
Intervention	HBV treatment
Outcome	HBV cure (HBV DNA-)
Study design	Longitudinal
Minimum duration of follow-up	None
Minimum <i>N</i> of Subjects	10
<b>Perioperative testing, diabetes</b>	
Population	Undergoing kidney transplantation
Intervention	Diabetes testing (OGTT, FBG/FPG, RBG)
Outcome	Perioperative complications, NODAT, change in perioperative management
Study design	Any
Minimum duration of follow-up	None
Minimum <i>N</i> of Subjects	100
<b>Perioperative testing, thrombophilia</b>	
Population	Kidney transplant candidates or CKD G5 (dialysis) with history of VTE, recurrent AV access thrombosis, or arterial thrombosis, or family history of VTE
Intervention	Thrombophilia tests
Outcome	Mortality (all-cause, thrombosis-related), graft loss/failure, VTE, perioperative complications, change in perioperative management
Study design	Any
Minimum duration of follow-up	None
Minimum <i>N</i> of Subjects	200
<b>Psychosocial testing</b>	
Population	Kidney transplant candidates who receive transplants
Intervention	Psychosocial scales/instruments, including: Psychosocial Assessment of Candidates for Transplantation (PACT), Stanford Integrated Psychosocial Assessment for Transplant (SIPAT), Transplant Evaluation Rating Scale (TERS)
Outcome	Mortality (all-cause), graft failure/loss, adherence

Continued

**TABLE 1. (Continued)**

Study design	Longitudinal
Minimum duration of follow-up	Any
Minimum <i>N</i> of Subjects	10
<b>Retransplantation with history of nonadherence</b>	
Population	History of graft failure/loss due to nonadherence
Intervention	Retransplantation
Comparator	None necessary
Outcome	Mortality (all cause), graft failure/loss
Design	Longitudinal
Minimum duration of follow-up	None
Minimum <i>N</i> of subjects	100
<b>Chest CT</b>	
Population	CKD G4-G5
Intervention	Low-radiation chest CT
Outcome	Mortality (all-cause, lung cancer), lung cancer diagnosis
Study design	Any
Minimum duration of follow-up	Any
Minimum <i>N</i> of Subjects	10
<b>Dual antiplatelet agents</b>	
Population	Kidney transplant candidates who receive transplants
Intervention	Dual antiplatelet treatment
Comparator	Single antiplatelet treatment
Outcome	Perioperative complications, Thombosis outcomes
Study design	Comparative
Minimum duration of follow-up	None
Minimum <i>N</i> of Subjects	10/arm
<b>Hyperparathyroidism</b>	
Population	Kidney transplant candidates who receive transplants with hyperparathyroidism (with or without hypercalcemia)
Intervention	Parathyroidectomy
Comparator	No surgery (or no comparator)
Outcome	Mortality (all-cause), graft failure/loss, parathyroidectomy post-transplant
Study design	Any
Minimum duration of follow-up	None
Minimum <i>N</i> of Subjects	20
<b>Peripheral artery disease testing</b>	
Population	CKD G4-G5 with clinically-apparent PAD who receive transplant
Intervention	Peripheral artery disease testing
Outcome	Perioperative complications, Change in management, PAD post-transplantation
Study design	Any
Minimum duration of follow-up	Any
Minimum <i>N</i> of Subjects	10

ADPKD, autosomal dominant polycystic kidney disease; AV, arteriovenous; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CT, computed tomography; eGFR, estimated glomerular filtration rate; FBG/FPG, fasting blood/plasma glucose; FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate; HBV, hepatitis B infection (DNA+, surface antigen +); HIV, human immunodeficiency virus infection; HUS, hemolytic uremic syndrome; MGRS, monoclonal gammopathy of renal significance; MGUS, monoclonal gammopathy of undetermined significance; MPGN, membranoproliferative glomerulonephritis; NODAT, new-onset diabetes after transplantation; OGTT, oral glucose tolerance test; PAD, peripheral artery testing; PRA, panel reactive antibodies; RBG, random blood glucose; SGA, subjective global assessment (nutrition assessment tool); TB, tuberculosis; UTI, urinary tract infection; VTE, venous thromboembolism.

**TABLE 2.****Hierarchy of outcomes**

Hierarchy	Outcome
Critical importance	Mortality, graft loss, intracranial aneurysm rupture, stroke
High importance	Graft loss (cause specific), cancer, infection, intracranial aneurysm, LV function, recurrent kidney disease
Moderate importance	NODAT, nonadherence, uncomplicated UTI

LV, left ventricular; NODAT, new-onset diabetes after transplantation; UTI, urinary tract infection.

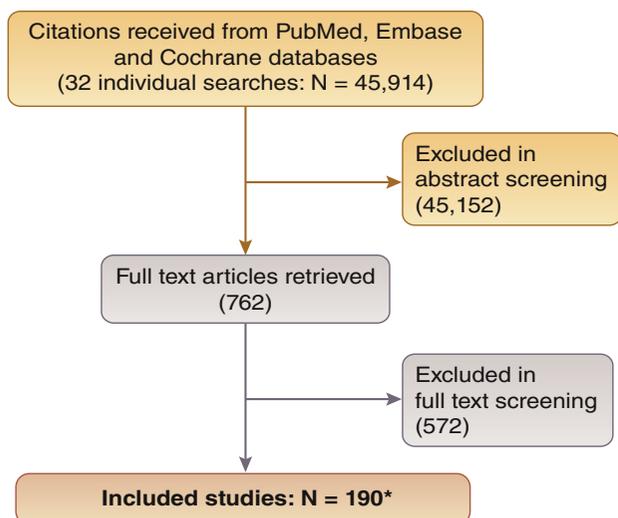


FIGURE 1. Search yield. \*See Table 3 for enumeration by topic.

representativeness of the population, and adjustment for different lengths of follow-up.<sup>7</sup> Based on these characteristics an overall assessment was made whether the study was of good, fair, or poor quality (Table 4).

Each reported outcome was then evaluated and given an individual grade depending on the quality of reporting and methodological issues specific to that outcome. However, the quality grade of an individual outcome could not exceed the quality grade for the overall study.

**Grading the quality of evidence and the strength of a guideline recommendation**

A structured approach, based on ‘Grades of Recommendation, Assessment, Development and Evaluation’ (GRADE)<sup>8-10</sup> and facilitated by the use of evidence profiles was used to grade the quality of the overall evidence and the strength of recommendations. For each topic, the discussion on grading of the quality of the

**TABLE 3.**  
Work products for the guideline

Topics	Topics Searched	Citations Screened	Included Studies, n	Summary Tables / Evidence Profiles
1. Access to Transplantation	Txp vs. WtL	1832	8	+
2. Age as a factor	Pre-emptive	*	*	+
	*	*	*	*
3. Pediatric issues	†		†	†
4. Psychosocial assessment	Psychosocial	449	2	+
5. Adherence issues	Nonadherence	1137	1	+
6. Tobacco use	Tobacco Cess'n	407	0	-
7. Obesity and related surgical issues	Bariatric	2838	0	-
8. Diabetes	Testing	738	7	+
9. Cause of ESKD	Recurrence	2285	86	+
	Recur Tx	231	0	-
10. Infection	TB Tx	925	4	+
	Nephrectomy	1528	2	+
	HIV	1138	7	+
	HBV	622	3	+
	TB screen/Vac	1319	5	+
11. Malignancy	Cancer Tx	1001	2	+
	Prostatectomy	440	2	+
	Screening	699	4	+
12. Pulmonary disease	Chest CT	673	0	-
13. Cardiac disease	Revasc	1144	2	+
	Echo	2824	6	+
14. Peripheral artery disease	PAD	1400	0	-
15. Neurologic disease	ADPKD	364	4	+
	Carotid Doppler	988	1	+
16. GI and liver disease	-		0	-
17. Hematologic disorders	Thrombophilia	546	6	+
	Dual antiPlt	3028	0	-
	Gammopathies	419	12	+
18. Bone and mineral metabolism	PTx	1371	0	-
19. HLA testing	Crossmatch	1342	0	-
Predictors of outcomes*	Registries	3248	26	+

ADPKD, autosomal dominant polycystic kidney disease; antiPlt, antiplatelet drugs; Cess'n, cessation; CT, computed tomography; Echo, echocardiography; ESKD, end-stage kidney disease; GI, gastrointestinal; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HLA, human leukocyte antigens; PAD, peripheral artery disease; PTx, parathyroidectomy; Recur, recurrence; Revasc, (cardiac) revascularization; TB, tuberculosis; Tx, treatment; Txp, (kidney) transplant; Vac, vaccination (all vaccinations); WtL, waitlist.

\* Topics were covered by searches for registry studies.

† Covered within other topic searches and tables.

**TABLE 4.****Classification of study quality**

<b>Good quality</b>	Low risk of bias and no obvious reporting errors; complete reporting of data. Must be prospective. If study of intervention, must be RCT.
<b>Fair quality</b>	Moderate risk of bias, but problems with study or paper are unlikely to cause major bias. If study of intervention, must be prospective.
<b>Poor quality</b>	High risk of bias or cannot rule out possible significant biases. Poor methods, incomplete data, reporting errors. Prospective or retrospective.

RCT, randomized controlled trial

**TABLE 5.****GRADE system for grading quality of evidence**

<b>Step 1: Starting grade for quality of evidence based on study design</b>	<b>Step 2: Reduce grade</b>	<b>Step 3: Raise grade</b>	<b>Final grade for quality of evidence and definition</b>
Randomized trials = High	<i>Study quality</i> –1 level if serious limitations –2 levels if very serious limitations	<i>Strength of association</i> +1 level if strong <sup>a</sup> , no plausible confounders +2 levels if very strong <sup>b</sup> , no major threats to validity	<b>High</b> = Further research is unlikely to change confidence in the estimate of the effect
Observational study = Low	<i>Consistency</i> –1 level if important inconsistency	<i>Other</i> +1 level if evidence of a dose–response gradient	<b>Moderate</b> = Further research is likely to have an important impact on confidence in the estimate of effect, and may change the estimate
Any other evidence = Very Low	<i>Directness</i> –1 level if some uncertainty –2 levels if major uncertainty	+1 level if all residual plausible confounders would have reduced the observed effect	<b>Low</b> = Further research is very likely to have an important impact on confidence in the estimate, and may change the estimate
	<i>Other</i> –1 level if sparse or imprecise data <sup>c</sup> –1 level if high probability of reporting bias		<b>Very Low</b> = Any estimate of effect is very uncertain

GRADE, Grading of Recommendations Assessment, Development and Evaluation.

<sup>a</sup> Strong evidence of association is defined as “significant relative risk of >2 (<0.5)” based on consistent evidence from two or more observational studies, with no plausible confounders.<sup>b</sup> Very strong evidence of association is defined as “significant relative risk of >5 (<0.2)” based on direct evidence with no major threats to validity.<sup>c</sup> Sparse if there is only one study or if total *N* <500. Imprecise if there is a low event rate (0 or 1 event) in either arm or confidence interval spanning a range >1.Adapted by permission from Uhlig K, Macleod A, Craig J *et al.*<sup>10</sup>

evidence was led by the ERT, and the discussion regarding the strength of the recommendations was led by the Work Group Co-Chairs. The “strength of a recommendation” indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm. The “quality of a body of evidence” refers to the extent to which our confidence in an estimate of effect is sufficient to support a particular recommendation.<sup>9</sup>

**Grading the quality of evidence for each outcome across studies.** Following GRADE, the quality of a body of evidence pertaining to a particular outcome of interest was initially categorized on the basis of study design. For each outcome, the potential grade for the quality of evidence for each intervention–outcome pair started at “high” but was then lowered if there were serious limitations to the methodological quality of the aggregate of studies, if there were important inconsistencies in the results across studies, if there was uncertainty about the directness of evidence including limited applicability of the findings to the population of interest, if the data were imprecise (a low event rate [0 or 1 event] in either arm or a confidence interval [CI] spanning a range both <0.5 and >2) or sparse (only 1 study or total *N* < 500), or if there was thought to

be a high likelihood of bias. The final grade for the quality of the evidence for an intervention–outcome pair could be one of the following four grades: “High”, “Moderate”, “Low” or “Very Low” (Table 5).

**Grading the overall quality of evidence.** The quality of the overall body of evidence was then determined on the basis of the quality grades for all outcomes of interest, taking into account explicit judgments about the relative importance of each outcome. The resulting four final categories for the quality of overall evidence were: “A”, “B”, “C” or “D” (Table 6).

**Assessment of the net health benefit across all important clinical outcomes.** The net health benefit was determined on the basis of the anticipated balance of benefits and harms across all clinically important outcomes (Table 7). The assessment of net benefit also involved the judgment of the Work Group and the ERT.

**Developing the recommendations.** Draft recommendation statements were developed by the Work Group Co-Chairs and Work Group members. The health benefits, side effects, and risks associated with each recommendation were considered when formulating the guideline, as well as information on patient preferences when available.

**TABLE 6.**  
Final grade for overall quality of evidence

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

**TABLE 7.**  
Balance of benefits and harms

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

- For statistically significant benefit or harm, report as “benefit [or harm] of intervention”.
- For non–statistically significant benefit or harm, report as “possible benefit [or harm] of intervention”.
- In instances where studies are inconsistent, report as “possible benefit [or harm] of intervention”.
- “No difference” can only be reported if a study is not imprecise.
- “Insufficient evidence” is reported if imprecision is a factor.

Recommendation statements were revised in a multi-step process during face-to-face meetings and by subsequent drafts by email. All Work Group members provided feedback on initial and final drafts of the recommendation. A draft was then distributed for external public review and subsequently revised by the Work Group Co-Chairs and members based on this open feedback. Approval from all Work Group members must be received before publication of the final guideline.

**Grading the strength of the recommendations.** The strength of a recommendation is graded as level 1 or level 2. Table 8 shows the KDIGO nomenclature for grading the strength of a recommendation and the implications of each level for patients, clinicians, and policy makers. Recommendations can be for or against doing something. Each recommendation includes an explicit link between the quality of the available evidence and the strength of that recommendation. However, Table 9 shows that the strength of a recommendation is determined not only by

the quality of the evidence but also by other, often complex judgments regarding the size of the net medical benefit (potential risks vs benefit), values, and preferences, and costs. Formal decision analyses including cost analysis were not conducted.

**Ungraded statements.** This category was designed to allow the Work Group to issue general advice. Typically an ungraded statement meets the following criteria: it provides guidance based on common sense; it provides reminders of the obvious; and it is not sufficiently specific to allow for application of evidence to the issue and therefore it is not based on systematic evidence review. As such, ungraded statements may be considered to be relatively strong recommendations; they should not be interpreted as weak recommendations based on limited or poor evidence. Common examples include recommendations about frequency of testing, referral to specialists, and routine medical care. We strove to minimize the use of ungraded recommendations.

This grading scheme, with two levels for the strength of a recommendation together with four levels of grading the quality of the evidence, as well as the option of an ungraded statement for general guidance, was adopted by the KDIGO Board in December 2008. The Work Group took on the primary role of writing the recommendations and rationale statements and retained final responsibility for the content of the guideline statements and the accompanying narrative. The ERT reviewed draft recommendations and grades for consistency with the conclusions of the evidence review.

**Format for guideline recommendations.** Each topic section contains one or more specific recommendations. Within each recommendation, the strength of recommendation is indicated as level 1 or level 2 and the quality of

**TABLE 8.**  
KDIGO nomenclature and description for grading recommendations

Grade*	Implications		
	Patients	Clinicians	Policy
<b>Level 1</b> “We recommend”	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
<b>Level 2</b> “We suggest”	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

\*The additional category “Not Graded” is used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. Ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

the supporting evidence is shown as A, B, C, or D. The recommendation statements and grades are followed by the rationale text summarizing the key points of the evidence base and the judgments supporting the recommendation.

In relevant sections, considerations of the guideline statements in international settings and suggested audit criteria are also provided where applicable. Important key points and research recommendations suggesting future research

**TABLE 9.****Determinants of strength of recommendation**

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the more likely a level 1 recommendation is warranted. The narrower the gradient, the more likely a level 2 recommendation is warranted.
Quality of the evidence	The higher the quality of evidence, the more likely a level 1 recommendation is warranted.
Values and preferences	The more variability in values and preferences, or the more uncertainty in values and preferences, the more likely a level 2 recommendation is warranted. Values and preferences were obtained from the literature where possible or were assessed in the judgment of the Work Group when robust evidence was not identified.
Costs (resource allocation)	The higher the costs of an intervention—that is, the more resources consumed—the less likely a level 1 recommendation is warranted.

**TABLE 10.****The Conference on Guideline Standardization (COGS) checklist for reporting clinical practice guidelines**

Topic	Topic Description	How Topic Addressed
<b>1. Overview material</b>	Provide a structured abstract that includes the guideline's release date, status (original, revised, updated), and print and electronic sources.	Abstract and Executive Summary.
<b>2. Focus</b>	Describe the primary disease/condition and intervention/service/technology that the guideline addresses. Indicate any alternative preventative, diagnostic or therapeutic interventions that were considered during development.	ESKD, candidates for kidney transplantation. Interventions and treatments to assess candidacy and prepare candidates for transplantation.
<b>3. Goal</b>	Describe the goal that following the guideline is expected to achieve, including the rationale for development of a guideline on this topic.	This CPG is intended to assist the practitioner caring for patients with CKD who are potential candidates for transplantation, with the particular goals of minimizing graft loss and death while optimizing patients' quality of life.
<b>4. User/setting</b>	Describe the intended users of the guideline (eg, provider types, patients) and the settings in which the guideline is intended to be used.	Target audience is practicing nephrologists and other health care providers for adults and children with ESKD who are potential candidates for transplantation
<b>5. Target population</b>	Describe the patient population eligible for guideline recommendations and list any exclusion criteria.	Adults and children with ESKD who are potential candidates for transplantation
<b>6. Developer</b>	Identify the organization(s) responsible for guideline development and the names/credentials/potential conflicts of interest of individuals involved in the guideline's development.	Organization: KDIGO Names/credentials/potential conflicts of interest of Work Group members involved in the guideline's development are disclosed in the <i>Appendix: Biographic and Disclosure Information</i> .
<b>7. Funding source/sponsor</b>	Identify the funding source/sponsor and describe its role in developing and/or reporting the guideline. Disclose potential conflict of interest.	This guideline is funded by KDIGO.
<b>8. Evidence collection</b>	Describe the methods used to search the scientific literature, including the range of dates and databases searched, and criteria applied to filter the retrieved evidence.	Topics were triaged either to a) systematic review, b) systematic search followed by narrative summary, or c) narrative summary. For systematic reviews, we searched PubMed, EMBASE, Cochrane Central Registry for trials, and Cochrane database of systematic reviews. Screening criteria for this and other topics are outlined in the <i>Methods for Guideline Development</i> section. The search was updated through August 2017, with an additional search conducted in May 2019 and supplemented by articles identified by Work Group members through September 2019. We also searched for pertinent existing guidelines and systematic reviews.

*Continued next page*

**TABLE 10. (Continued)**

Topic	Topic Description	How Topic Addressed
<b>9. Recommendation grading criteria</b>	Describe the criteria used to rate the quality of evidence that supports the recommendations and the system for describing the strength of the recommendations. Recommendation strength communicates the importance of adherence to a recommendation and is based on both the quality of the evidence and the magnitude of anticipated benefits and harms.	Quality of individual studies was graded in a three-tiered grading system (see Table 4). Quality of evidence and strength of recommendations were graded following the GRADE approach (Tables 5, 6 and 8). The Work Group could provide general guidance in the form of ungraded statements.
<b>10. Method for synthesizing evidence</b>	Describe how evidence was used to create recommendations, eg, evidence tables, meta-analysis, decision analysis.	For systematic review topics, summary tables and evidence profiles were generated. For recommendations on interventions, the steps outlined by GRADE were followed.
<b>11. Prerelease review</b>	Describe how the guideline developer reviewed and/or tested the guidelines prior to release.	The guideline has undergone external public review in October 2018. Public review comments were compiled and fed back to the Work Group, which considered comments in its revision of the guideline.
<b>12. Update plan</b>	State whether or not there is a plan to update the guideline and, if applicable, an expiration date for this version of the guideline.	Following the publication of this guideline, requirement for updating will be assessed on a regular basis to determine if new evidence will lead to changes to the recommendations or may modify information provided herein.
<b>13. Definitions</b>	Define unfamiliar terms and those critical to correct application of the guideline that might be subject to misinterpretation.	See Abbreviations and Acronyms.
<b>14. Recommendations and rationale</b>	State the recommended action precisely and the specific circumstances under which to perform it. Justify each recommendation by describing the linkage between the recommendation and its supporting evidence. Indicate the quality of evidence and the recommendation strength, based on the criteria described in Topic 9.	Each guideline section contains recommendations for the management of potential kidney transplantation candidates. Each recommendation builds on a supporting rationale with evidence tables if available. The strength of the recommendation and the quality of evidence are provided in parenthesis within each recommendation.
<b>15. Potential benefits and harms</b>	Describe anticipated benefits and potential risks associated with implementation of guideline recommendations.	The benefits and harm for each comparison of interventions are provided in summary tables and summarized in evidence profiles. The estimated balance between potential benefits and harm was considered when formulating the recommendations.
<b>16. Patient preferences</b>	Describe the role of patient preferences when a recommendation involves a substantial element of personal choice or values.	Recommendations that are level 2 or "discretionary," indicating a greater need to help each patient arrive at a management decision consistent with her or his values and preferences.
<b>17. Algorithm</b>	Provide (when appropriate) a graphical description of the stages and decisions in clinical care described by the guideline.	See Figures 2 and 3.
<b>18. Implementation considerations</b>	Describe anticipated barriers to application of the recommendations. Provide reference to any auxiliary documents for providers or patients that are intended to facilitate implementation. Suggest review criteria for measuring changes in care when the guideline is implemented.	These recommendations are global. Local versions of the guideline are anticipated to facilitate implementation and appropriate care. Review criteria were not suggested because implementation with prioritization and development of review criteria have to proceed locally. Most recommendations are discretionary, requiring substantial discussion among stakeholders before they can be adopted as review criteria. The decision whether to convert any recommendations to review criteria will vary globally. Research recommendations were also outlined to address current gaps in the evidence base.

to resolve current uncertainties are also outlined at the conclusion of each section.

### Review of guideline development process

Several tools and checklists have been developed to assess the quality of the methodological process for systematic review and guideline development. These include the Appraisal of Guidelines for Research and Evaluation (AGREE 2) criteria, the Conference on Guideline Standardization (COGS) checklist,<sup>11</sup> and the National Academy of Medicine's (formerly known as Institute of Medicine) *Standards for Systematic Reviews and Clinical Practice Guidelines We Can Trust*.<sup>4,5</sup> Table 10 shows the criteria which correspond to the COGS checklist and how each one is addressed in this guideline. Similarly, Supplemental Appendix B demonstrates the level of concurrence with which this guideline corresponds to the National Academy of Medicine standards for systematic reviews and guidelines.<sup>4,5</sup>

## SECTION 1: ACCESS TO TRANSPLANTATION

1.1: We recommend that all patients with chronic kidney disease (CKD) G4-G5 (glomerular filtration rate [GFR] < 30 ml/min/1.73 m<sup>2</sup>) who are expected to reach end-stage kidney disease [ESKD] (excluding those listed in Rec 1.1.3) be informed of, educated about, and *considered* for kidney transplantation regardless of socioeconomic status, sex, gender identity, or race/ethnicity (1D).

1.1.1: Refer potential kidney transplant candidates for evaluation at least 6 to 12 months before anticipated dialysis initiation to facilitate identification/work-up of living donors and plan for possible pre-emptive transplantation (Not Graded).

1.1.2: Refer potential candidates already on dialysis when medically stable and kidney failure deemed irreversible (Not Graded).

1.1.3: We recommend not referring patients for kidney alone transplant evaluation with the following conditions (1D):

- Multiple myeloma (Rec 9.13.1.1), light chain deposition disease or heavy chain deposition disease (Recs 9.13.2.1, 9.13.2.2 and 9.13.2.3) unless they have received a potentially curative treatment regimen and are in stable remission;
- AL amyloidosis with significant extrarenal involvement (Recs 9.13.3.1 and 13.8);
- Decompensated cirrhosis (consider for combined liver-kidney transplant; Recs 10.5.2.4.2, 16.7.2);
- Severe irreversible obstructive or restrictive lung disease (Rec 12.5);
- Severe uncorrectable and symptomatic cardiac disease that is deemed by a cardiologist to preclude transplantation (Rec 13.7);
- Progressive central neurodegenerative disease (Rec 15.4).

1.1.3.1: Document the reason(s) for not referring patients for transplant evaluation (Not Graded).

1.1.3.2: Inform patients about the reason(s) for not referring for transplant evaluation (Not Graded).

1.1.4 We recommend *delaying* transplant evaluation in patients with the following conditions until properly managed (1D):

- An unstable psychiatric disorder that affects decision-making or puts the candidate at an unacceptable level of post-transplant risk (Rec 4.2);
- Ongoing substance use disorder that affects decision-making or puts the candidate at an unacceptable level of post-transplant risk (Rec 4.3);
- Ongoing, health-compromising nonadherent behavior despite education and adherence-based counseling (Rec 5.4);
- Active infection (excluding hepatitis C virus infection) that is not properly treated (Rec 10.1.1);
- Active malignancy except for those with indolent and low-grade cancers such as prostate cancer (Gleason score ≤ 6), and incidentally detected renal tumors (≤ 1 cm in maximum diameter) (Rec 11.2.1);
- Active symptomatic cardiac disease (eg, angina, arrhythmia, heart failure, valvular heart disease) that has not been evaluated by a cardiologist (Rec 13.2);
- Active symptomatic peripheral arterial disease (Rec 14.5);
- Recent stroke or transient ischemic attack (Rec 15.1);
- Active symptomatic: peptic ulcer disease (Rec 16.2.2), diverticulitis (Rec 16.3.1), acute pancreatitis (Rec 16.4.1), gallstone/gallbladder disease (16.5.1), inflammatory bowel disease (Rec 16.6.1);
- Acute hepatitis (Rec 16.7.2);
- Severe hyperparathyroidism (Rec 18.2).

1.2: Use a multidisciplinary team, which includes at a minimum a transplant physician, transplant surgeon and a health care professional experienced in the psychosocial aspects of transplantation, to evaluate and decide about suitability for kidney transplantation (Not Graded).

1.3: Approve patients for kidney transplantation that have an estimated survival which is acceptable according to national standards (Not Graded).

1.3.1: Inform patients of their option to seek a second opinion from another transplant center if they are declined (Not Graded).

1.4: We recommend pre-emptive transplantation with a living kidney donor as the preferred treatment for transplant-eligible CKD patients (1A).

1.4.1: We recommend pre-emptive transplantation (living or deceased donor) in adults when the estimated glomerular filtration rate (eGFR) is < 10 ml/min/1.73 m<sup>2</sup> or earlier with symptoms (1D).

1.4.2: We recommend pre-emptive transplantation (living or deceased donor) in children when the eGFR is < 15 ml/min/1.73 m<sup>2</sup> or earlier with symptoms (1D).

## BACKGROUND

For suitable candidates, kidney transplantation is the preferred form of kidney replacement therapy because it improves survival and quality of life and is less costly

than dialysis.<sup>2,12–15</sup> Therefore, all patients with advanced chronic kidney disease (CKD) should be informed about options for kidney replacement therapy, including transplantation. In most industrialized countries the majority of patients with end-stage kidney disease (ESKD) are older patients with many comorbidities. In most regions less than 30% of prevalent dialysis patients are on the transplant waitlist but there is considerable variability.<sup>16,17</sup> Given that demand for transplantable kidneys exceeds supply, it is reasonable to match patient survival with anticipated graft survival in order to avoid futility and maximize utility. In fact, such an algorithm has been implemented for deceased donor kidney transplantation in some regions of the world.<sup>18,19</sup> Therefore, a reasonable estimated life expectancy, according to national standards, should be considered a prerequisite in order to proceed with transplant evaluation. The situation is different in living donor kidney transplantation. In this scenario, there is no waiting-time, surgery is planned and ‘borderline’ recipients can be optimized pre-transplantation. The decision to proceed in such cases requires an open discussion with both the donor and recipient regarding anticipated outcomes.

## RATIONALE

- Kidney transplantation improves survival and quality of life and is less costly compared to dialysis.
- Patients with advanced CKD who are expected to reach ESKD have the right to be informed of all available treatment options, including transplantation.
- Demand for transplantable kidneys exceeds supply and thus candidacy for deceased donor transplantation needs careful evaluation.
- Initiation of the transplant evaluation process depends on the patient’s subjective well-being, underlying kidney disease and rate of glomerular filtration rate (GFR) loss; number and severity of comorbid conditions; and the anticipated need for specialized testing (eg, coronary angiography).
- Depending on the patient and region, the transplant evaluation process may take weeks to several months to complete.
- Pre-emptive transplantation is the preferred treatment option but requires sufficient time to ensure a complete evaluation, and in many regions is restricted to those with a suitable living donor.
- The timing of pre-emptive living donor transplantation needs individual decision making depending on patient’s symptoms and estimated GFR (eGFR).
- Candidacy assessment is to some extent subjective; those declined should have the right to seek a second opinion.

## Access to transplantation

Patients with progressive CKD (eg, CKD G4-G5) who are expected to reach ESKD should be informed about all available treatment options. This also includes the option of conservative management in cases with limited life expectancy or severe comorbidities. All patients have the right to be informed of all treatment options available, including transplantation, within their local health context and such discussions should occur regardless of the patient’s socioeconomic status, sex, age, gender identity, or race/ethnicity. Data demonstrate that on average, transplantation achieves superior medical outcomes (i.e.,

survival and quality of life) at lower cost as compared to dialysis, and transplantation is therefore considered to be the economically dominant and medically desirable therapy (Summary Tables: Kidney transplantation vs wait-listing; Evidence Profiles: Kidney transplantation vs wait-listing, Pre-emptive transplantation);<sup>2</sup> This does not mean that all CKD patients should be *referred* for transplant evaluation. Rather, patients should receive appropriate information to facilitate a discussion regarding transplantation. Indeed, some factors such as progressive dementia, severe, uncorrectable cardiac dysfunction or certain cancers are common reasons for patients not to be considered for transplant evaluation.

Not all patients who may benefit from transplantation will actually receive a kidney transplant due to the shortage of donor organs. Some regions have limited access to deceased donor kidney transplants based on anticipated survival.<sup>20–23</sup> The threshold or estimated survival needed for transplant candidacy is not consistent,<sup>20–23</sup> however prediction models have been created to guide clinicians.<sup>24–26</sup> These tools, while not perfect, can be used to inform decision-making regarding eligibility for deceased donor transplantation. One of these prediction models<sup>24</sup> has been adopted for use in New Zealand.<sup>20</sup> The United Kingdom (UK) Renal Association guidelines on transplant eligibility state that patient survival must not be compromised by transplantation<sup>23</sup> and that graft survival should not be limited by premature death (maximum benefit obtained from a limited resource).<sup>23</sup> These statements imply that clinical judgment, although subjective, is needed to ensure that appropriate candidates are referred for transplantation while those not likely to benefit should not proceed with evaluation.

Given the difficult decisions regarding candidacy in some patients, it is advisable to use a multidisciplinary team to evaluate and decide about suitability for transplantation. Since some comorbid conditions are only relative contraindications and can improve over time, a re-evaluation of patients initially denied may be advisable. Similarly, since much of this decision making is subjective in nature, patients should be informed of their option to seek a second opinion from another transplant center if they are declined.

There are many potential predictors of post-transplantation outcomes for patients undergoing evaluation for kidney transplantation candidacy. In the following sections we discuss many of the factors separately. Numerous registry studies have been analyzed to evaluate whether a host of risk factors may be predictors of post-transplantation outcomes. The registry studies are described in Summary Tables: Registry studies; Evidence Profiles: Pre-transplant predictors summarize the evidence regarding pre-transplantation predictors of post-transplantation mortality, graft loss, and other outcomes.

Potential candidates should begin the evaluation process at least 6 to 12 months before the anticipated start of kidney replacement therapy. Earlier evaluation may render some of the diagnostic tests outdated while a delay might lead to an incomplete work-up and miss the opportunity for pre-emptive transplantation. When a live donor is available or where pre-emptive deceased donor transplantation is possible, cases should proceed when the eGFR is  $<10\text{ ml/min/1.73 m}^2$  (10 to 15 ml/min/1.73 m<sup>2</sup> in pediatrics). Optimal timing, however, depends on factors other

than GFR such as the pace of renal decline, presence of symptoms and living donor preferences.

### What prior guidelines recommend

Prior guidelines from Kidney Health Australia-Caring for Australasians with Renal Impairment (KHA-CARI) do not specifically address the topic of access to transplantation.<sup>27</sup> In the 2013 update, the KHA-CARI guidelines focused on the evaluation of pediatric patients and those with specific comorbidities (cardiovascular disease [CVD], diabetes mellitus [DM], viral infections, malignancies, obesity). The American Society of Transplantation (AST) evaluation guideline does not have specific recommendations on access to kidney transplantation.<sup>28</sup> The Canadian Society of Transplantation (CST), however, has published consensus guidelines on eligibility for kidney transplantation in 2005.<sup>29</sup> Similar to our current KDIGO guideline, the CST guideline strongly recommends (Grade A) to consider all ESKD patients without absolute contraindication for kidney transplantation. The European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA) endorsed the 2009 KDIGO guidelines on management of the kidney transplant recipient but no specific statements are given regarding access or eligibility for kidney transplantation.<sup>30,31</sup> The UK Renal Association guidelines have a detailed section on access to transplantation with several specific recommendations, some of which are similar to this current guideline.<sup>23</sup> Important recommendations include a statement about equity of access to transplant regardless of gender or ethnicity; that all patients predicted to have an increased life expectancy with transplant should be evaluated; all transplant programs should have written criteria for transplant eligibility; and that patients should be active on the waitlist within six months of their anticipated dialysis start date.<sup>23</sup>

### RESEARCH RECOMMENDATIONS

- Randomized controlled trials (RCTs) should be conducted on early versus late pre-emptive transplantation to determine whether important clinical outcomes are improved with earlier transplantation after accounting for lead-time bias.
- RCTs should be conducted on prediction-model guided evaluation process versus usual care to determine if the proportion of appropriate candidates referred would increase with a reduction in inappropriate referrals and improvement in post-transplant survival.

### RELEVANT SUPPLEMENTAL MATERIAL

Summary table: Kidney transplantation vs waitlisting

Summary table: Kidney transplantation vs waitlisting (quality assessment)

Evidence profile: Kidney transplantation vs waitlisting

Evidence profile: Effect of pre-emptive transplantation on post-transplant outcomes

Summary table of registry studies: Categorical outcomes

Summary table of registry studies: Quality assessment

Evidence profile: Pre-transplant predictors of post-transplant mortality

Evidence profile: Pre-transplant predictors of graft loss

Evidence profile: Pre-transplant predictors of post-transplant outcomes other than death and graft loss

### SECTION 2: 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).

### RATIONALE

- In adjusted analyses, kidney transplantation is associated with greater survival compared to similar patients on the waitlist – this is also true for elderly patients.
- This survival advantage is maintained for elderly patients that receive advanced age donor kidneys, expanded-criteria donor (ECD) kidneys or high kidney donor profile index (KDPI) kidneys.<sup>32</sup>
- Estimated biological age together with several other risk factors for mortality should be taken into account when deciding about transplantation.

Patients aged 65 years and older represent the fastest growing group on the US waitlist with the numbers increasing from 12.9% in 2003 to 21.2% of the waitlist in 2014.<sup>33</sup> This trend, although encouraging, fails to highlight the overall low rate of elderly patients waitlisted or transplanted. For instance, less than 5% of dialysis patients > 65 years are on the waiting list in the UK and only 10% are transplanted in the first 5 years.<sup>34</sup> The elderly population brings with them a unique set of problems, including frailty, cognitive impairment, and comorbidities less commonly seen in the other age groups.<sup>35</sup> All these factors have been associated with morbidity and mortality after transplantation,<sup>36–39</sup> although the trend has improved.<sup>40</sup>

Despite these issues, a number of studies have shown improvement in overall life expectancy (mortality risk 40–60% lower) for those who have received a transplant compared to similar waitlisted patients who have remained on dialysis.<sup>41–51</sup> This survival advantage persists despite a significantly higher incidence of early mortality in some reports.<sup>40,41,45,46,52</sup> A number of European and American studies<sup>53–72</sup> have confirmed that transplantation in advanced age patients is associated with prolonged graft survival, since patient survival is often the limiting factor.<sup>53,55–59,62–64,66,67,69,70,73</sup> On the contrary, other studies have shown higher mortality and worse death-censored graft survival in older recipients using ECD kidneys.<sup>34,54,59,61,68,71,74</sup>

Most elderly patients listed for transplantation will receive an ECD kidney, often from an older donor. Consequently, it is important to clarify if there is a survival advantage in using these kidneys compared to remaining on dialysis.<sup>41,42,44–50,52,75,76</sup> In an attempt to minimize confounding factors, a paired-matched analysis has recently been published, comparing 823 recipients from donors over 65 years and counterparts listed with the same comorbidity.<sup>42</sup> The risk for death was 2.66-fold higher in the dialysis group.<sup>42</sup> In another analysis, the outcomes using donors ≥ 75 years were examined. Even using these

extreme aged kidneys, the survival benefit was clear with a 60% reduction in mortality for those transplanted compared to the patients remaining on dialysis.<sup>47</sup>

### What prior guidelines recommend

The CST eligibility guidelines state that advanced age *per se* is not a contraindication to kidney transplantation (Grade B level of evidence).<sup>29</sup> The UK Renal Association guideline recommends that age is not a contraindication to transplantation but recognizes that age-related comorbidity is an important limiting factor (1B level of evidence).<sup>23</sup> The AST,<sup>28</sup> ERA-EDTA<sup>77</sup> and KHA-CARI<sup>27</sup> evaluation guidelines do not have specific recommendations regarding age and access to kidney transplantation.

## RESEARCH RECOMMENDATIONS

- Tools for predicting the outcomes of transplantation for older candidates, and older candidates with multimorbidity in particular, should be investigated.
- Prospective studies to evaluate the utility of formally measuring frailty as part of the transplant evaluation process should be conducted.

## SECTION 3: PEDIATRIC ISSUES

- 3.1: We suggest performing a neurocognitive assessment in pediatric candidates who experienced end-stage kidney disease before the age of 5 years (2D).
- 3.2: We suggest performing an academic assessment in pediatric candidates of school age who are experiencing academic difficulties (2D).

## RATIONALE

Neurocognitive assessment evaluates all aspects of cognitive function including global intelligence, language, problem-solving, visual-spatial perception, attention, memory, processing speed, motor function, emotion, and executive functions. This is distinguished from academic assessment, which evaluates academic performance in relation to expected performance based on age and on neurocognitive abilities. Neither neurocognitive nor academic assessments should be used to determine transplant eligibility. As noted in Recommendation 15.5.1, individuals should not be excluded from kidney transplantation because of non-progressive intellectual, developmental, or cognitive disability. Neurocognitive and academic assessments are suggested for the following reasons:

- Abnormalities in cognitive function and academic performance are common in pediatric kidney transplant recipients, but may be unrecognized without formal testing.
- Identification of cognitive and/or academic deficits will facilitate specialized services if needed.
- Planning of transition to adult care and expectations for self-care may be modified by results of cognitive assessment.

Children with CKD are at high risk for abnormal neurodevelopment due to a combination of factors including the impact of uremic toxins on the developing brain,

anemia, malnutrition, hypertension, and impaired interactions with the environment due to illness and frequent medical procedures.<sup>78</sup> Cognitive deficits result in impaired academic performance and may also influence self-care abilities. While the intelligence of the majority of pediatric kidney transplant recipients is in the average range, a greater than expected proportion are in the impaired, borderline, or low average range compared with healthy children.<sup>79</sup> Memory deficits have been reported consistently in the pediatric CKD population; attention problems are also common.<sup>78,80</sup> However, cognitive deficits may be unrecognized; the proportion of pediatric kidney transplant recipients receiving special educational services is lower than expected given the level of cognitive impairment.<sup>80</sup> Academic performance may be lower than expected for age for many reasons including frequent illnesses and school absences, chronic fatigue, and cognitive developmental delays and dysfunction.

Assessment of cognitive and academic function will help set appropriate expectations for patients, parents, and educational professionals, and will guide provision of appropriate services, including accommodations and support.<sup>79</sup> Furthermore, cognitive assessment may uncover deficits in executive functions (eg, planning, organization, problem-solving) that could influence the patient's ability to engage in self-care behaviors such as medication adherence.<sup>79</sup>

The specific cognitive deficits identified in children with CKD and kidney transplants vary somewhat across studies. There are several potential reasons for these inconsistencies, including changes in the severity of deficits over time due to improvements in care, heterogeneity of the populations studied, small sample sizes, and inclusion or exclusion of children with comorbid neurological conditions. Children with moderate to severe CKD pre-transplant have consistently shown poorer cognitive function than healthy children or sibling controls.<sup>78,81</sup> There is some evidence that cognitive function improves following kidney transplant.<sup>81-83</sup> Kidney transplant recipients have better cognitive function than children with moderate to severe CKD pre-transplant,<sup>78,81,82</sup> but still show deficits compared with healthy children.<sup>80,84</sup> Improvements in attention and memory following transplant were observed in one longitudinal study.<sup>83</sup> Younger age at onset of ESKD, longer duration of dialysis, and older age at transplant were associated with poorer cognitive function.<sup>80,84</sup>

Neurocognitive and academic performance assessment must be done by a qualified psychologist. Results are effort-dependent; assessment tools may not be available in all languages and some may be difficult to interpret in children from non-Western cultural backgrounds. No studies have examined the impact of pre-transplant neurocognitive and/or academic performance assessment on long-term outcomes. Therefore, the value of such assessments in improving academic, occupational, quality of life or self-care (and therefore graft) outcomes is unknown.

### What prior guidelines recommend

To our knowledge, no prior guidelines addressed the issue of neurocognitive or academic assessment in pediatric candidates.

## RESEARCH RECOMMENDATION

- Studies are needed to assess the frequency with which pre-transplant neurocognitive and academic assessments lead to implementation of specialized education programs, educational accommodations or modifications in self-care training or expectations, as well as whether pre-transplant assessments lead to improved educational, vocational and graft outcomes. Economic analyses or cost-benefit studies would also be helpful, especially in resource-limited regions.

## SECTION 4: 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).

## RATIONALE

The psychosocial assessment of potential kidney transplant candidates typically occurs within a multidisciplinary context. It provides an opportunity to assess the patient's psychological, behavioral health, and social network strengths and limitations that may facilitate or hinder adaptation to the complexities and challenges of chronic illness, transplantation, lifestyle modifications, and long-term survivorship. Moreover, a comprehensive psychosocial assessment allows for identification of factors that may adversely impact the success of transplantation and for targeted interventions to be implemented, thereby enhancing the likelihood of a favorable outcome for the patient.

Published guidelines, consensus statements, transplant center protocols, regulatory requirements, and

clinical practice articles representing several countries were reviewed for content pertaining to the psychosocial assessment.<sup>27,28,77,85-93</sup> While most guidelines stress the relative importance of a psychosocial assessment, we concluded that there is wide variability in practice with respect to this component of the transplant evaluation process. Psychosocial evaluation is mandatory in some regions, at the discretion of transplant centers in other regions, or not performed in some parts of the world due to lack of qualified mental health professionals. Additionally, even when a psychosocial assessment is performed as part of the transplant evaluation, there is no empirical evidence on who should conduct the assessment, how the assessment should be conducted, what factors are most essential to evaluate, and how to handle psychosocial issues that are uncovered during the assessment.<sup>85-87</sup> Recommendations regarding these elements of the psychosocial assessment are based on expert opinion. Evidence is limited and generally weak regarding the predictive role of pre-transplant psychosocial factors on post-transplant outcomes. Consequently, recommendations put forth regarding the psychosocial assessment, like prior guidelines, are based largely on expert opinion.

### Should all candidates have a psychosocial assessment?

Our suggestion is consistent with prior guidelines, regulations in some countries, and expert opinion, which describe the psychosocial assessment as an important and essential part of the evaluation of each potential transplant candidate.<sup>27,28,77,85-92</sup> However, we recognize that in certain regions of the world, there may be limited or no qualified health care professionals available to conduct such assessments on behalf of the transplant program.

### Who should perform the psychosocial assessment?

The psychosocial assessment should be conducted by a qualified health care professional. The type of health care professional (eg, social worker, psychologist, psychiatrist, psychiatric nurse practitioner) may vary from center to center and region to region; however, the health care professional should be knowledgeable of and experienced in the psychosocial aspects of transplantation.

### How should the psychosocial assessment be performed?

There is considerable variability in how psychosocial assessments are performed across transplant programs and regions. The different formats of the psychosocial assessment and their relationship to post-transplant outcomes have not been the focus of clinical investigation. However, consistent with sound clinical practice, the psychosocial assessment should be conducted face-to-face with the transplant candidate. In addition to conducting an interview, it may be important in some instances to obtain collateral or corroborating information from one or more members of the patient's identified social network who will provide caregiving assistance throughout the transplant process. In rare instances, it may not be possible to conduct a face-to-face interview assessment of the patient (eg, medically incapacitated and unable to participate reliably in interview), thus requiring the clinician to rely

heavily on collateral sources (eg, family member, primary care physician) for information to complete the psychosocial assessment.

The psychosocial elements considered essential to examine in a transplant candidate also vary considerably based on availability of qualified mental health professionals, cultural factors, regulatory requirements, different health care systems, and other factors. Elements of the psychosocial assessment should include: a mental status examination; cognitive evaluation to ensure valid decision-making capacity and ability to provide informed consent for transplantation; understanding of the transplant process; motivation for transplantation; expectations of the outcomes (including graft/patient survival, symptom relief, and quality of life); ability and willingness to form a collaborative relationship with the transplant team; past and current psychiatric/psychological disorders; past and current substance use (eg, alcohol, tobacco, drugs); past and current adherence to recommendations regarding medical treatment and lifestyle modifications; social history (eg, education, occupation, financial resources, important relationships, living circumstances); cultural factors relevant to chronic illness and transplantation; and availability and stability of the social network as it pertains to meeting any caregiving needs of the patient. Assessment of these elements may allow the clinician to make an informed conceptualization of the patient's relative personal strengths and limitations that may be relevant to favorable psychosocial adjustment throughout the transplant continuum of care.<sup>85–87,93–95</sup>

Clinician rating scales (eg, Psychosocial Assessment of Candidates for Transplantation, Stanford Integrated Psychosocial Assessment for Transplant, Transplant Evaluation Rating Scale, INTERMED, Psychosocial Assessment Tool, Psychosocial Transplant Evaluation Scale) may be used to supplement the psychosocial assessment. These instruments aid in the identification of patient strengths and limitations as they pertain to psychosocial readiness for transplantation.<sup>96–103</sup> However, we suggest that such tools not be used in isolation to determine candidacy for transplantation. There is insufficient evidence regarding their validity and reliability, and they may have limited applicability beyond the US.

### What psychosocial criteria preclude listing for transplantation?

In our evidence review, we found limited and generally weak evidence regarding the utility of specific psychosocial elements in predicting post-transplant outcomes (psychosocial or medical) (Summary Table and Evidence Profile: Psychosocial). While some prior reports and guidelines suggest that certain psychiatric conditions, severe developmental disorders, substance use, lack of social support, and a history of nonadherence may be contraindications to transplantation, the literature was very inconsistent about the presence of these factors pre-transplant and the association with poor post-transplant outcomes. Similarly, the absence of these psychosocial risk factors was not consistently associated with favorable post-transplant outcomes.<sup>87,94,95</sup> A history of affective disturbances such as anxiety or depression is not uncommon among transplant candidates.<sup>104–108</sup> While there is evidence that these affective disorders may be associated with graft function and mortality, such distress

that occurs early post-transplant is more strongly associated with mortality than depression and anxiety that was present prior to transplantation.<sup>105,109–114</sup> Therefore, we recommend that these affective conditions not necessarily exclude transplantation. Rather, identifying the presence of these factors provides the transplant center with an opportunity to recommend or provide appropriate treatment or additional support to remove these potential barriers and to optimize outcomes.

While the primary goal of the psychosocial assessment is to identify areas necessitating additional support or intervention, some conditions may interfere with a patient's ability to engage in self-care activities at a level necessary to achieve favorable transplant outcomes. Substance use disorder – which may include alcohol and/or drugs – has been found to be an independent risk factor for medication nonadherence and associated graft failure.<sup>115–118</sup> However, the definition of substance abuse or dependency, the duration and frequency of use, and the abstinence duration prior to transplantation have been variably applied in the literature. As such, there is weak evidence regarding which patients, if any, with a history of substance abuse should be precluded from transplantation. Moreover, while much has been written about the relationship between alcohol abuse and outcomes, very little is known about the association between drug use, abuse, or dependency (eg, marijuana, cocaine, prescription drugs) and post-transplant psychosocial and medical outcomes. Patients with recent or current substance use disorder should be further evaluated by a substance abuse specialist and, as appropriate, offered or referred for counseling or treatment. Given the high relapse rate both in and beyond the transplant population, written policies regarding abstinence expectations, toxicology screening, and how relapses will be managed by the transplant program while the patient is on the waiting list are advisable.<sup>119</sup> We recommend that patients with ongoing substance use disorder (as defined in the Diagnostic and Statistical Manual of Mental Disorders)<sup>120</sup> despite appropriate treatment, that adversely impacts decision-making or increases the level of post-transplant risk that is higher than acceptable to the transplant program not be accepted for transplantation.

An available and stable support system that provides patients with both instrumental and practical assistance throughout the transplant process is often considered an integral component of the evaluation process.<sup>28,91,92</sup> While the presence of a caregiver is based on sound clinical judgment, there is little evidence suggesting that the absence of social support is an absolute contraindication to transplantation.<sup>121</sup> However, in light of the complexities of progressive kidney failure, its treatment, and the associated demands of post-transplant recovery and rehabilitation, we recommend that patients who are unable to engage independently in self-care activities have an identified support system in place prior to transplantation.

### What prior guidelines recommend

Prior guidelines from the CST and the AST suggest or recommend a psychosocial evaluation of all transplant candidates,<sup>28,29</sup> while other guidelines are either silent about the need for such evaluation (KHA-CARI; Transplantation Society of Australia and New Zealand [TSANZ]) or fall

short of suggesting psychosocial assessment for all transplant candidates (ERA-EDTA).<sup>27,88,90</sup>

The CST and AST guidelines indicate that mental illness alone is not a contraindication to transplantation and that patients with psychiatric or psychological disorders should be referred for treatment.<sup>28,29</sup> The ERA-EDTA states that transplant candidates with a history of suicide attempt and psychosis are “poor candidates,” while the KHA-CARI and TSANZ guidelines are silent on evaluation and/or selection of candidates with a psychiatric or psychological disorder.<sup>27,88,90</sup>

All prior guidelines from the CST, AST, ERA-EDTA, KHA-CARI, and TSANZ considered ongoing or active substance abuse to be a contraindication to transplantation.<sup>27–29,88,90</sup> The CST and AST guidelines further suggested delaying transplantation until patients with a history of substance abuse have received appropriate treatment and achieved a minimum abstinence period of six months.<sup>28,29</sup>

The CST, AST, ERA-EDTA, and KHA-CARI guidelines are silent about the role of social support in determining transplant eligibility.<sup>27–29,88</sup> The TSANZ guidelines suggest that patients with cognitive or neuropsychiatric deficits may not be appropriate transplant candidates if they do not have a caregiver to facilitate post-transplant medication adherence.<sup>90</sup>

## RESEARCH RECOMMENDATIONS

- RCTs are needed to examine the effectiveness of different evaluation strategies designed to reliably identify psychosocial risk factors predictive of post-transplant outcomes.
- Multicenter prospective studies are needed to assess the validity and reliability of existing and emerging clinician rating scales for identifying psychosocial risk factors during the evaluation process.
- Multicenter prospective studies and psychosocial risk-prediction modeling are needed to isolate the unique contribution of psychosocial factors on different post-transplant outcomes (eg, psychosocial functioning, nonadherence, rehospitalization rates, complications, healthcare utilization, graft survival, patient survival).
- RCTs are needed to test interventions given during the pre-transplant period that will reduce the risk of poor post-transplant psychosocial and medical outcomes.

## RELEVANT SUPPLEMENTAL MATERIAL

Summary table: Psychosocial

Summary table: Psychosocial (quality assessment)

Evidence profile: Psychosocial testing

## SECTION 5: ADHERENCE

- 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 nonadherence be considered for transplantation unless there is ongoing, health-compromising non-adherent behavior (*1D*).

## RATIONALE

Non-adherence is defined as “deviation from the prescribed medication regimen sufficient to adversely influence the regimen’s intended effect.”<sup>122</sup> Although the exact degree of deviation required to result in a poor outcome is unknown, even minor deviations have been linked to inferior outcomes among kidney transplant recipients.<sup>123</sup> Although some have suggested that a history of poor adherence should exclude patients from transplant candidacy, our ability to predict future adherence behavior from past behavior is imperfect. Furthermore, not all adherence behaviors are equivalent; poor adherence in one domain (eg, dietary and fluid restriction) does not necessarily predict poor adherence in another (eg, medication adherence). In addition, adherence may change over time, particularly among developing adolescents and young adults. The recommendations provided are based on the following:

- Poor adherence to immunosuppressive medication is one of the most important factors limiting graft survival.
- Identification of patients at high risk for post-transplant non-adherence may allow more intensive monitoring and intervention to promote better adherence.
- Identification of patients’ barriers to adherence before transplant may permit pre-transplant intervention to address these barriers.
- Pre-transplant nonadherence modestly predicts post-transplant nonadherence, but not all adherence behaviors are equivalent; evidence that nonadherence to dialysis treatments or dietary restrictions predicts post-transplant medication nonadherence is lacking.
- Adherence behavior may change over time.
- Denying patients who admit non-adherence a chance for another transplant will ‘punish honesty’ and may lead to more covert non-adherence and undermine the therapeutic relationship

### Pre-transplant adherence assessment

Medication non-adherence is estimated to be responsible for at least 15% of graft failures and about 50% of late acute rejections.<sup>124</sup> Solid organ transplant recipients who reported pre-transplant non-adherence have been shown to have a 3.1 to 7.9 times higher likelihood of post-transplant non-adherence than those who did not report nonadherence.<sup>121,125</sup> However, these may represent overestimates of the ability of pre-transplant non-adherence to predict post-transplant non-adherence. Patients willing to report pre-transplant nonadherence may also be more likely to report post-transplant nonadherence.

Important stakeholders, including members of the general community, patients, and transplant healthcare professionals have expressed the view that adherence behavior should be considered in organ allocation decisions.<sup>126–128</sup> However, very few transplant centers have an objective

protocol in place to assess pre-transplant adherence. A survey of 79 US transplant centers found that only 51% of respondents had any knowledge of a protocol to evaluate pre-transplant adherence, and of these, only 10% used a standardized assessment questionnaire.<sup>129</sup> The most commonly used means of assessing pre-transplant adherence was the number of missed hemodialysis sessions. However, it is not known if missed hemodialysis sessions predicts poor medication adherence post-transplant; transportation problems were reported as the most frequent reason for missing hemodialysis sessions.<sup>129</sup> In contrast, the reason for medication non-adherence post-transplant most frequently cited by survey respondents was an inability to pay for medications (73%). When assessing pre-transplant adherence, it is important to consider the likelihood that non-adherence in one domain of treatment will predict non-adherence in another. For example, failure to adhere to dietary and fluid restrictions (i.e., to NOT do something) may be a poor predictor of a patient's ability to take medication on a strict schedule (i.e., to DO something). Furthermore, the complexity and burden of tasks required for self-care pre-transplant (eg, dietary and fluid restrictions, regular dialysis treatments, erythropoiesis stimulating agent injections, phosphate binders, numerous other medications three or more times per day) may be overwhelming compared with the tasks post-transplant.

Pre-transplant adherence assessment should include not only evaluation of the patient's adherence to treatment, but assessment of personal barriers to medication adherence, and identification of risk factors for poor adherence post-transplant. Such a comprehensive assessment will permit identification of high risk patients for more intensive monitoring and potential interventions, and will allow care providers to address adherence barriers before problems arise.

### **Adherence as a criterion for transplant**

Although pre-transplant non-adherence is a risk factor for post-transplant non-adherence,<sup>121,125</sup> concordance is not perfect. A study of 924 kidney transplant recipients found 30% to have self-reported non-adherence pre-transplant. The proportion reporting non-adherence at 6 months post-transplant was only 10%, and at 3 years post-transplant was 20%.<sup>125</sup> However, survival bias may have resulted in underestimation of the prevalence of non-adherence as non-adherent patients are likely to lose their grafts before adherent patients and therefore be less likely to contribute to the prevalence of non-adherence over time. Whether the patients exhibiting non-adherence post-transplant had also been non-adherent pre-transplant was not reported. It must also be recognized that accurate adherence assessment is difficult; many patients with suboptimal adherence may not be detected. It would be difficult to base such a critical decision regarding access to transplantation on a questionable measure such as perceived adherence. Furthermore, poor adherence does not universally lead to poor outcomes (Summary Table and Evidence Profile: Nonadherence). Patients with excellent human leukocyte antigen (HLA) matching may tolerate some non-adherence, and have shown outcomes similar to those of adherent patients with poorer HLA matching.<sup>130</sup>

Although we advise that pre-transplant non-adherence should not disqualify patients from transplant candidacy, we do not suggest that pre-transplant non-adherence be

ignored. The preparation for and timing of transplantation should be carefully considered for patients at high risk for post-transplant non-adherence. Transplantation before adherence barriers are addressed, or before there is some evidence of willingness to adhere to treatment may not be in the patient's best interest. Post-transplant non-adherence will likely increase the risk of sensitization, limiting options for another transplant should one be needed. Non-adherence post-transplant may also lead to repeated and intensive immunosuppression to treat rejection, increasing the risks of infectious and malignant complications. Patients should be informed of the substantial risks associated with post-transplant non-adherence, including limited opportunity for another transplant due to sensitization. Preparation for transplant should include efforts to identify and address each patient's personal barriers to adherence.

### **RE-TRANSPLANT FOLLOWING GRAFT LOSS DUE TO NON-ADHERENCE**

Greater controversy surrounds the question of whether a patient who has lost a graft to non-adherence should be offered another transplant. The general community, patients, and transplant healthcare professionals often react strongly to non-adherent behavior, considering non-adherent individuals less deserving of an organ than adherent individuals.<sup>126–128</sup> The scarcity of organs, along with the poorer outcomes observed following re-transplantation, has been cited as justification for denying repeat transplants to patients who lost a graft to non-adherence.<sup>124</sup> A strict utilitarian approach would exclude patients with prior graft loss due to non-adherence from re-transplantation, directing organs preferentially to low risk patients with the longest potential graft survival. A comparison of 35 patients re-transplanted after graft loss following overt non-adherence with 552 patients re-transplanted without non-adherence showed a trend towards poorer graft and patient survival for the non-adherent group.<sup>131</sup> Although survival differences were not statistically significant, study power was limited. Such differences, if true, would support excluding non-adherent patients from re-transplant under utilitarianism. However, strict utilitarianism is not applied to other decisions regarding transplant candidacy. For example, patients at high risk of disease recurrence (such as focal segmental glomerulosclerosis [FSGS]), or at high immunologic risk, are routinely accepted for transplantation. If we are to be consistent in our decisions, strict utilitarianism cannot be applied to the non-adherent patients.

The difficulty in accurately identifying non-adherence also makes the exclusion from re-transplantation problematic. Only when a patient admits non-adherence can it be confirmed. An open dialogue between patients and healthcare professionals is critical to high quality care and is important to promoting good adherence. If patients fear that honesty about non-adherence will reduce their opportunities for re-transplantation, they may be less likely to report it.

In a study of 114 kidney transplant recipients who lost a graft to non-adherence, adolescent issues and financial problems were the most common reasons given for non-adherence; 29% were pediatric recipients, the majority of whom lost their grafts during adolescence or early young adulthood.<sup>131</sup> Interestingly, pediatric recipients showed a lower rate of non-adherence after re-transplantation

than adult recipients (38% vs 55%).<sup>131</sup> These data show that behavior change is possible. Indeed, among pediatric recipients, behavior change is expected as a part of normal neurodevelopment. Neuroscientists hypothesize that the risk-taking behavior common among adolescents and young adults may reflect relatively rapid development of the limbic system (associated with reward-seeking and emotion) paired with slow maturation of the prefrontal cortex (associated with impulse control, planning, and organization).<sup>132</sup> Brain development continues well into the twenties.<sup>133,134</sup> The coincident decrease in graft failure risk after the age of about 25 years may reflect better adherence associated with brain maturity.<sup>135</sup>

Excluding patients who have lost a graft to non-adherence from re-transplant may particularly discriminate against pediatric recipients. Not only do pediatric recipients likely have a higher risk of non-adherence when they reach adolescence than other age groups – possibly due to brain immaturity – but they also require graft function for many more years than older recipients. Denying an individual who lost a graft to non-adherence during adolescence any hope of re-transplant effectively condemns him or her to a dramatically shortened life expectancy and an inferior quality of life. Furthermore, such an approach would necessitate prolonged high-cost dialysis, rather than relatively economical transplant.

Proceeding with re-transplantation for a patient who has lost a graft to non-adherence should be undertaken carefully. A protocol for selective retransplantation was proposed in 2009 (Figure 2).<sup>131</sup> Although there is no evidence that this protocol results in better outcomes than would be seen without the protocol, the approach is reasonable and has the potential to be beneficial.

### What prior guidelines recommend

Prior guidelines from KHA-CARI,<sup>27</sup> AST,<sup>28</sup> CST,<sup>29</sup> and ERA-EDTA<sup>88</sup> all suggested a pre-transplant assessment aimed at identifying risk factors for nonadherence in order to target high-risk patients for adherence education and counselling. KHA-CARI guidelines specifically discussed adherence only in relation to pediatric patients, and did not recommend delaying transplant due to nonadherence.<sup>27</sup> The AST guidelines, which discussed adherence for both adult and pediatric candidates, suggested considering delaying transplant for patients who continue to demonstrate poor adherence despite intervention.<sup>28</sup> The CST guidelines were more specific, recommending that transplantation be delayed until adherence has been demonstrated for at least 6 months.<sup>29</sup> Although the ERA-EDTA guidelines stated that those with a history of poor adherence are poor candidates for transplant, the guidelines recommended against excluding those with a past history of nonadherence from repeat transplantation.<sup>88</sup>

### RESEARCH RECOMMENDATIONS

- Studies examining trajectories of adherence from pre- to post-transplant would be helpful in understanding the true value of pre-transplant non-adherence in predicting post-transplant non-adherence.

- Clinical trials are needed to test the value of pre-transplant adherence evaluation and selective re-transplant protocols, such as the one shown above, in improving clinical outcomes for those transplanted following graft failure due to non-adherence.

### RELEVANT SUPPLEMENTAL MATERIAL

Summary table: Nonadherence

Summary table: Nonadherence (quality assessment)

Evidence profile: Nonadherence

### SECTION 6: TOBACCO

- 6.1: Assess past and present use of tobacco products by candidates at transplant evaluation and while on the waiting list (*Not Graded*).
- 6.2: We recommend counseling all candidates to avoid tobacco products before and indefinitely after transplantation (*1B*).
- 6.3: We recommend offering a tobacco cessation program to candidates who are using tobacco products (*1B*).
- 6.4: We recommend that candidates abstain from tobacco use, at a minimum 1 month prior to wait-listing or living donor transplantation (*1B*).
- 6.5: We suggest chest computed tomography (CT) for current or former heavy tobacco users ( $\geq 30$  pack-years) as per local guidelines to screen for occult lung cancer (*2C*).

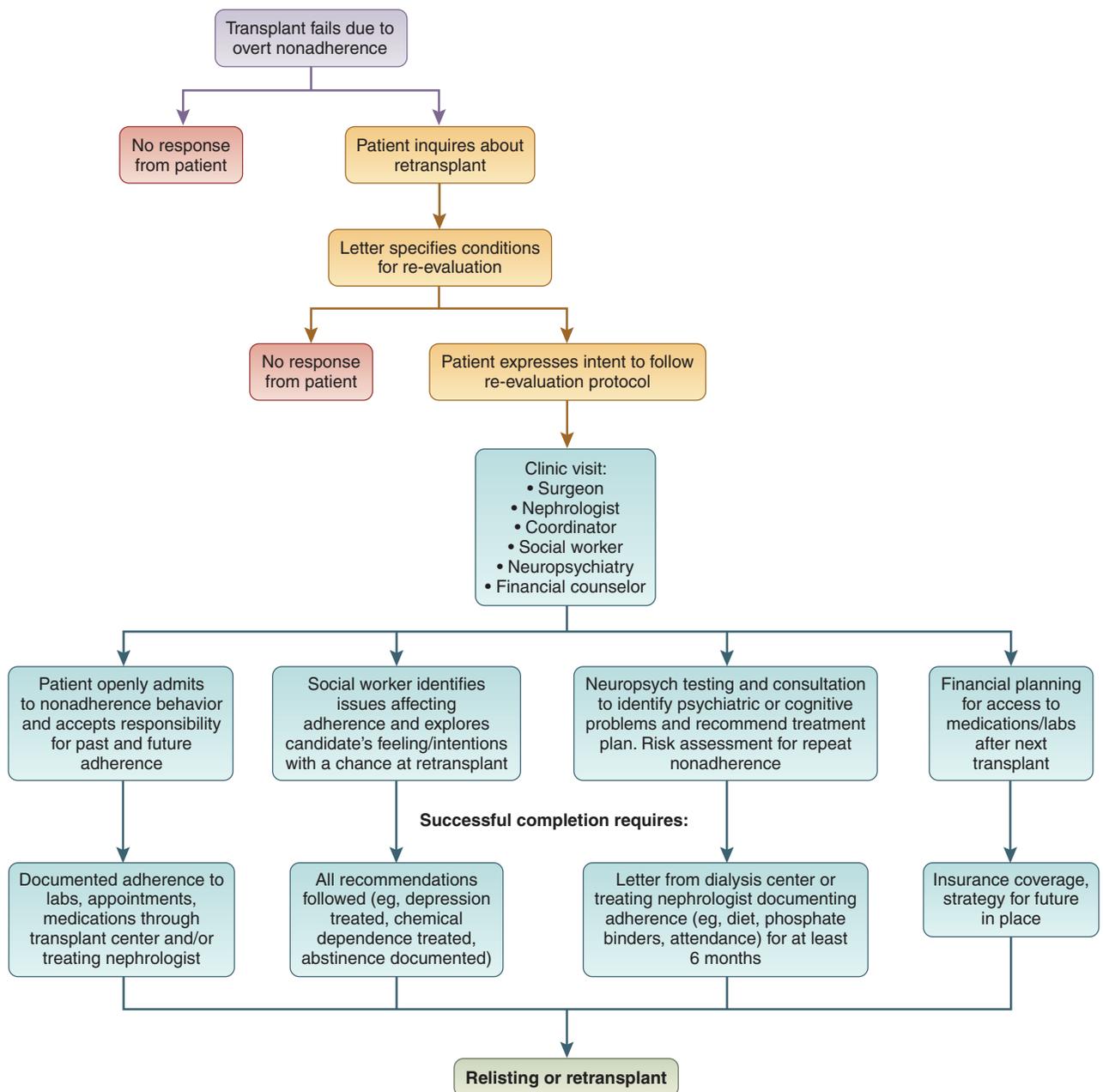
### BACKGROUND

Smoking after transplantation is associated with poor outcomes in both the short and long term after kidney transplantation.

### RATIONALE

- There is high quality evidence that smokers have an increased risk of perioperative respiratory complications.
- There is high quality evidence that people who smoke have an increased risk of CVD, non-skin malignancy, and death after kidney transplantation compared to non-smokers.
- There is high quality evidence that smoking cessation programs are more likely to result in patients stopping smoking compared to no intervention.
- There is moderate quality evidence that an annual low-dose computed tomography (CT) scan of the chest versus a chest x-ray for 3 consecutive years reduces the risk of death from lung cancer and all-cause mortality in patients in the general population who have at least a 30 pack-year history of smoking.

Current smokers have an increased risk of perioperative respiratory complications with the risk depending on several factors including duration of smoking, the presence of respiratory symptoms and a history of chronic lung disease. Recent evidence has suggested that smoking



**FIGURE 2.** Reevaluation protocol after graft loss to nonadherence. Reproduced with permission.<sup>131</sup>

discontinuation as recently as 4 weeks prior to surgery can decrease post-operative complications.<sup>136</sup>

In the long-term there is an increased risk of CVD, non-skin malignancies and death. A recent systematic review examined 43 studies of kidney transplant recipients<sup>137</sup> and reported that younger individuals, males and those with a lower body mass index (BMI) were more likely to smoke. There was an increased risk of new CVD occurring after transplantation (odds ratio [OR] 1.41, 95% CI: 1.02-1.95;  $P = 0.036$ ) in smokers compared with non-smokers. Additionally there was a more than two-fold risk of non-skin malignancies in smokers compared with non-smokers (OR 2.58, 95% CI: 1.26-5.29;  $P = 0.01$ ) and a significantly shorter survival time (OR 0.59, 95% CI: 0.44-0.79;  $P < 0.001$ ) while patient mortality was significantly higher in smokers (OR 1.74, 95% CI: 1.21-2.48;  $P = 0.003$ ). Other studies have shown similar results with an increase

in malignancy and death in kidney transplant recipients who smoke in addition to reduced graft survival.<sup>138,139</sup>

Smoking cessation programs should be offered to patients who are current smokers. There is high quality evidence in the general population demonstrating efficacy of smoking cessation measures compared with no intervention.<sup>140,141</sup>

Due to the increased mortality associated with smoking after transplantation, smoking may be considered an additional risk factor that along with other comorbidities, may preclude transplantation suitability.

The National Lung Screening Trial was a large RCT in which current and former smokers were randomized to annual screening for three years with either low-dose CT scans or a chest x-ray.<sup>142</sup> 53,454 individuals aged between 55 – 74 who had a history of cigarette smoking of at least 30 pack-years, and, if former smokers,

had quit within the previous 15 years, were randomized to undergo 3 annual screenings with either CT or chest x-ray. Compared with a plain chest x-ray, CT reduced the risk of death from lung cancer by 20% and the overall risk of death by 6.7%.

However, there were a number of important issues raised in the study. Firstly there were a large number of false positive tests in the CT screening arm with around a quarter of patients having a positive finding on one of the CT scans – of these 96.4% were false positives. Hence screening did lead to increased follow up investigations with potential complications arising from these. Additionally individuals in this study were otherwise healthy and did not have kidney failure.

Screening is recommended for high-risk smokers by a number of organizations including the American Association of Thoracic Surgery, American Cancer Society, American College of Chest Physicians/American Society of Clinical Oncology, the Canadian Task Force on the Periodic Health examination, the National Comprehensive Cancer Network and the US Preventative Services Task Force.

### What prior guidelines recommend

The Work Group agrees with the European Renal Best Practice, UK Renal Association, AST, KHA-CARI and Canadian guidelines,<sup>23,27–29,143</sup> all of which recommend smoking cessation prior to transplantation and recommend the offering of a smoking cessation program to current smokers. Canadian guidelines also argue that patients who continue to smoke may be eligible for kidney transplantation with full informed consent regarding their increased risk.<sup>29</sup>

## RESEARCH RECOMMENDATION

- Further studies should examine the costs and benefits of screening for lung cancer in candidates.

## SECTION 7: SURGICAL ISSUES INCLUDING 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).

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

7.3: We suggest that candidates be assessed for medical conditions that inhibit wound healing, including obesity, undernutrition, tobacco use, and prior abdominal surgeries, to inform risks of delayed wound healing and hernia formation (2B).

7.4: Candidates should not be excluded from consideration for kidney transplantation because of their need

for anticoagulation, antiplatelet therapy or a history of heparin-induced thrombocytopenia (HIT) (Not Graded).

7.4.1: Single antiplatelet agents (eg, aspirin, clopidogrel, ticagrelor) can be continued while waiting for deceased donor transplant (Not Graded).

7.4.2: Delay transplantation for the mandated period of treatment with dual antiplatelet therapy (eg, aspirin plus clopidogrel) when the risk of stopping medication (eg, stent thrombosis) or operating while on treatment (eg, surgical bleeding) exceeds the anticipated benefit of transplantation (Not Graded).

7.4.2.1: Antiplatelet agents (except aspirin) should be stopped 5 days prior to living donor transplantation (unless cessation is contraindicated) and during the perioperative period for deceased donor transplantation (Not Graded).

7.4.3: Do not transplant patients on direct-acting oral anticoagulants (DOACs; eg, apixaban, rivaroxaban) except when there is specific expertise using DOACs perioperatively and access to DOAC reversal agents (Not Graded).

7.4.3.1: Switch to an alternative anticoagulant (eg, warfarin) prior to waitlisting or living donor transplantation if recommended by a thrombosis expert/hematologist or if there is no expertise using DOACs perioperatively or access to DOAC reversal agents (Not Graded).

7.4.4: Use non-heparin based agents for perioperative anticoagulation in candidates with a history of HIT (Not Graded).

7.5: Assess vascular anatomy and patency for patients with significant peripheral arterial disease (Section 14), prior transplant procedures, venous dialysis catheters, pelvic surgery, or deep venous thrombosis (Not Graded).

7.6: Evaluate native kidney size in patients with polycystic kidney disease (Not Graded).

7.6.1: We suggest staged or simultaneous native nephrectomy and transplantation for candidates with polycystic kidney disease that is symptomatic (eg, recurrent pain, recurrent infection), a suspicion of malignancy, or if the patient has insufficient room for a transplant (2D).

7.7: Refer to a urologist experienced in transplant issues for patients at increased risk for or those with a history of urologic malignancy, recurrent urinary tract infections, dysfunctional voiding, prior bladder augmentation/division, an ileal conduit, significant structural anomalies of the kidneys or urinary tract, or nephrolithiasis (Not Graded).

7.7.1: We suggest cystoscopy to screen for bladder carcinoma in candidates at increased risk, such as those with high-level exposure to cyclophosphamide or heavy smoking ( $\geq 30$  pack-years) (2D).

7.7.2: We suggest that pre-transplant unilateral or bilateral nephrectomy be considered for pediatric candidates with high urine volumes ( $> 2.5$  ml/kg/hour) or heavy proteinuria associated with hypoalbuminemia (2D).

## RATIONALE

### Definitions

- BMI is defined as weight in kilograms squared divided by the height in meters. Obesity is defined as a BMI  $\geq 30 \text{ kg/m}^2$  and can be subdivided into classes I (BMI 30-34.9), II (BMI 35-39.9) and III ( $\geq 40 \text{ kg/m}^2$ ).
- Waist-to-hip ratio is defined as the ratio of the circumference of the waist to that of the hips. Waist-to-hip ratios  $> 0.85$  for women or  $> 0.9$  for men is considered obese by the World Health Organization.
- Frailty is characterized by a loss of function in 5 domains: (1) shrinkage (unintentional weight loss and sarcopenia), (2) muscular weakness, (3) exhaustion and lack of endurance, (4) slow gait, and (5) physical inactivity (refer to Frailty Index [FI]<sup>144,145</sup>).

### Obesity

Obesity is highly prevalent across high-income countries and increasingly so across low- and low-middle income countries. In the US, nearly 70% of the adult population is overweight or obese, while 6.7% have class III obesity (BMI  $\geq 40$ ).<sup>146</sup> Obesity in the context of metabolic syndrome is a strong risk factor for the development of ESKD. In the Reason for Geographic and Racial Differences in Stroke (REGARDS) study which prospectively evaluated 30,239 black and white adults in the US, the overall incidence of obesity (BMI  $\geq 30 \text{ kg/m}^2$ ) was 38%, of whom 66% had metabolic syndrome. In the presence of metabolic syndrome, obesity increased the risk of ESKD twofold. However, there was no independent association of obesity and ESKD in the absence of metabolic syndrome. Despite the clear association of obesity with peripheral vascular disease, coronary artery disease, and steatohepatitis, obesity is often associated with a lower risk of death among patients receiving maintenance dialysis.<sup>147,148</sup>

The impact of obesity on kidney transplant outcomes is complex. When compared to remaining on dialysis, obese patients who undergo kidney transplant experience prolonged survival.<sup>149,150</sup> Among obese patients, Gill *et al.* demonstrated a 48% reduction in mortality after transplantation compared to remaining on dialysis. However, a recent meta-analysis including more than 200,000 recipients comparing outcomes in obese and non-obese recipients, demonstrated that obesity (BMI  $> 30 \text{ kg/m}^2$ ) conveys an increased risk of death (relative risk [RR] 1.52), delayed graft function (RR 1.52), acute rejection (RR 1.17), wound infection (RR 3.13), dehiscence (RR 4.85), and prolonged hospital stay (2.31 days). Consequently, the Work Group recommends assessment of all candidates for obesity using either BMI or waist-to-hip criteria. Obesity is a relative contraindication to kidney transplantation. Patients found to be obese or particularly those with class II or class III obesity (BMI  $\geq 35 \text{ kg/m}^2$ ) should be considered for intervention such as dietary counseling or bariatric surgery. The Work Group did not establish a firm BMI cutoff, but encourages each transplant program to consider their own resources and skills in caring for this population. For example, early experience with robotically assisted transplantation has demonstrated improved outcomes among obese patients.<sup>151</sup> Pre-transplant panniculectomy may be useful in reducing BMI and improving wound outcomes

following transplant.<sup>152</sup> Transplantation in patients with a BMI  $\geq 40 \text{ kg/m}^2$  should be approached with caution; patients need to understand the increased risk of post-operative complications in this situation.

### Frailty

Frailty is a constellation of symptoms resulting in reduced physiological reserve which progresses with aging and chronic disease. In the ESKD population, the incidence of frailty in a European cohort increased from 27.5% in patients aged  $< 65$  to 43.6% in patients  $> 65$  as identified using the FI.<sup>144,145</sup> Similar rates have been documented in the US using the FI. Frailty was 3.3 times more frequent in women and appears to increase over time among patients on dialysis. Higher FI has been associated with greater risks of mortality, morbidity, and hospitalization among ESKD patients.<sup>153</sup>

Recent prospective studies have evaluated the independent impact of frailty on kidney transplant outcomes. Patients determined to be frail at the time of transplant have greater rates of delayed graft function, longer length of stay, and a greater incidence of risk adjusted graft loss and mortality.<sup>154</sup> Furthermore, frailty appears to increase immediately after transplant, returning to baseline values after 3 months. Assessment of frailty at the time of listing is crucial to assess physiologic reserve and the potential for perioperative complications. However, frailty alone should not be a contraindication to transplantation as average survival after transplantation is superior to long-term dialysis. The Work Group believes that patients with significant frailty should be referred for rehabilitation and conditioning prior to transplantation, although evidence to support this strategy is currently not available. Frail patients should also be counselled regarding the risk of significant complications including perioperative mortality.

### Wound healing and hernia management

All kidney transplant procedures have a risk of wound complications including infection and hernia formation due, in part, to the impact of immunosuppressive medications on wound healing. Comorbid conditions that increase this risk include diabetes, polycystic kidney disease, prior surgical procedures (including transplantation or hernia repairs), and tobacco use. The reported incidence of incisional hernia is approximately 7% at 10 years, and is increased 2-fold in patients who are active or former smokers.<sup>155-157</sup> Technical factors that increase the rate of hernia include closure of the myofascial wall in one layer, the development of a lymphocele, need for re-exploration, or the development of a wound infection. Patients with risk factors for hernia formation should be advised of the potential need for surgical repair after transplant and tobacco cessation should be strongly advised.

Wound healing is also affected by the development of superficial and deep tissue infections. Risk factors for post-transplant wound infections include obesity, diabetes, peripheral vascular disease, rheumatologic conditions (including lupus), and prior narcotic use disorder. Significant wound infections occur in approximately 15% of kidney transplant recipients. Perioperative antibiotics and chlorhexidine-based skin preparation should be administered as per surgical guidelines.

## Collagen vascular disease/Ehlers-Danlos Syndrome

Collagen vascular diseases are an uncommon spectrum of disease that affect the formation and cross linking of collagen. Collagen vascular diseases contribute to transplant morbidity including an elevated risk of hernia formation.<sup>158</sup> A history of collagen vascular diseases may be a contraindication to transplant in patients with other risks for poor wound healing. Ehlers-Danlos Syndrome (EDS), specifically, is the result of abnormal fibrillary collagen formation due to inherited deficiencies in collagen-processing enzymes, dominant negative effects of mutant collagen  $\alpha$ -chains, and haploinsufficiency. Type IV or vascular type EDS is an autosomal dominant defect in type III collagen synthesis. Affected individuals have an increased risk of arterial and hollow organ rupture, arterial dissection, and aneurysm formation resulting in an average life expectancy of less than 50 years. While endovascular techniques have been used to prevent exsanguination, these arteries frequently fail to hold sutures, making vascular anastomoses quite treacherous. Alternative surgical techniques can be considered including the use of pledgetted sutures, fibrin glue, and end-to-end anastomosis with the internal iliac artery rather than end-to-side to the common or external iliac. However, any vascular surgery in this population carries a high risk of morbidity and mortality. Pre-transplant diagnosis, discussion of risks and surgical planning are advised in determining candidacy and approach to transplantation.

## Anticoagulation

Patients with ESKD are frequently exposed to anticoagulants during dialysis treatment, as treatment for comorbid conditions including atrial fibrillation, ischemic heart disease, peripheral arterial disease, prior thromboembolism and other pro-thrombotic states. Among dialysis patients, 11.6% develop atrial fibrillation and many are placed on warfarin despite a lack of data confirming clinical benefit in the ESKD population.<sup>159,160</sup> Given long waiting times and a high rate of comorbidities, the proportion of ESKD patients taking anticoagulation and antiplatelet agents is likely to increase.

The Work Group does not believe that the use of warfarin, dipyridamole, or aspirin should be considered as a contraindication to proceeding with listing for or receiving a kidney transplant. In the case of living donor transplant, most clinicians recommend stopping warfarin for a period of 5 days, dipyridamole for 7 days, and continuing aspirin throughout the transplant period. For deceased donor transplantation, anticoagulation can be reversed successfully with prothrombin complex concentrate, fresh frozen plasma, vitamin K, and platelet transfusions prior to transplant or after reperfusion of the kidney. However, transplantation of patients receiving warfarin (OR 8.2,  $P < 0.001$ ) or antiplatelet therapy (OR 2.9,  $P = 0.001$ ) markedly increases the likelihood of receiving a blood transfusion when compared to patients on no therapy.<sup>161</sup> The impact of newer direct-acting oral anticoagulants (DOACs) on transplant outcomes has yet to be reported. Unlike warfarin-based therapy, they cannot be readily reversed with prothrombin complex concentrate or fresh frozen plasma. Unless there is specific expertise using DOACs perioperatively and access to DOAC reversal

agents, these agents should be avoided in patients awaiting deceased donor transplantation. It is recommended that DOACs be stopped at least 48-72 hours prior to elective surgery, particularly in patients with kidney failure.<sup>162</sup>

The development of heparin-induced thrombocytopenia (HIT) is the result of immunization against soluble heparin/platelet complexes which bind to protein platelet factor 4. There are only six published case reports of HIT in kidney transplantation, mostly demonstrating graft loss. In patients with established HIT, the use of heparin-free anticoagulation (eg, argatroban, hirudin) as a bridge to warfarin is recommended. In addition, in studies of other solid organ transplant recipients, the use of heparin during organ recovery did not appear to precipitate HIT recurrence in patients who were free from heparin for at least 100 days.

## Surgical planning

Kidney transplantation requires completion of vascular anastomoses to provide appropriate arterial inflow and venous outflow. The kidney transplant is traditionally placed in the iliac fossa, which is extra-peritoneal, reducing risk of intra-abdominal infection and facilitating ureteral reconstruction given the shorter ureter and risk of ischemia due to a poor ureteral blood supply. Arterial inflow is generally obtained from the iliac artery (external, common, internal) and venous outflow provided into the iliac vein. Alternative placement includes use of the distal aorta and vena cava, portal venous drainage, and an orthotopic transplant with recipient nephrectomy.<sup>163</sup> Significant peripheral vascular disease should be assessed and the surgical plan adjusted as described in Section 14. Patients with extensive past surgical interventions or vascular procedures should be evaluated with cross-sectional imaging prior to listing.

Appropriate pre-transplant anatomic evaluation is crucial to identify the optimal location for vascular anastomoses and plan for the recipient's incision. In the case of prior kidney transplant, the optimal approach is generally to avoid previously violated tissue planes and not performing transplant nephrectomies if possible. For the initial re-transplant procedure, this can be accomplished using the contralateral iliac fossa. Subsequent kidney transplant can be performed using a midline incision mobilizing the right colon, and using the distal aorta and inferior vena cava. Alternatively, the superior mesenteric vein can be used for drainage.

Prolonged exposure to hemodialysis has led to the exhaustion of upper extremity vascular access options for a growing population of ESKD patients. In these cases, lower extremity options for access, such as arteriovenous fistulas, arteriovenous grafts, and central venous catheters have been used.<sup>164</sup> Ipsilateral lower extremity arteriovenous fistula and arteriovenous graft may contribute to venous hypertension and potential graft dysfunction, but do not pose a contraindication to transplantation. In the case of hemodynamically significant venous hypertension, the arteriovenous graft/fistula should be ligated after the transplant procedure. Ipsilateral central venous catheters have a high incidence of femoral and iliac venous thrombosis and infection. Patients with a history of dialysis access procedures in the lower extremity should have perioperative imaging to confirm venous patency. Imaging options

include CT with intravenous contrast, magnetic resonance imaging with time-of-flight sequences, vascular Doppler ultrasonography, or venography. Transplantation using an iliac vein with an indwelling central venous catheter is generally contraindicated, especially without pre-operative imaging confirming patency of the vein.

Patients with polycystic kidney disease should undergo a non-contrast CT scan of the abdomen and pelvis to determine if they would benefit from simultaneous or staged native nephrectomy. The indications for pre-transplant nephrectomy include bleeding, recurrent infection, renal mass precluding safe transplant into the iliac fossa, suspicion of renal cell carcinoma, and constraint syndrome resulting in poor oral intake and pain. The options for surgical interventions include pre-transplant bilateral laparoscopic nephrectomy, simultaneous bilateral nephrectomy/transplant, or post-transplant nephrectomy (open or laparoscopic). Each approach can be performed safely, suggesting that patient symptomatology, kidney size and local surgical expertise should dictate the timing and type of this procedure.<sup>165–167</sup>

### Native nephrectomy for pediatric candidates

High urine output is relatively common among children with ESKD because many of the conditions leading to ESKD involve significant tubular dysfunction (eg, renal hypoplasia, nephronophthisis, cystinosis). These high urine volumes from the native kidneys may persist following transplantation making fluid management challenging. Infants and very young children in particular may have difficulty maintaining adequate perfusion of an adult donor kidney – which may result in a drop in GFR and accelerated fibrosis.<sup>168,169</sup> Polyuria increases the risk of volume depletion in the recipient. Some have advocated unilateral or bilateral native nephrectomy prior to transplant, or at the time of transplant, to facilitate maintenance of adequate volume status and improve perfusion of the graft.<sup>169,170</sup>

Heavy proteinuria has also been proposed as an indication for native nephrectomy pre-transplant due to the associated increased risk of graft thrombosis among patients losing anti-thrombotic factors in the urine.<sup>169,171,172</sup> Pre-transplant nephrectomy for patients with nephrotic syndrome and persistent hypoalbuminemia may allow recovery of normal levels of anticoagulation factors prior to the transplant.<sup>169</sup>

### What prior guidelines recommend

The AST guidelines suggest that a BMI  $\geq 30$  kg/m<sup>2</sup> should not be considered an absolute contraindication, though weight loss is recommended.<sup>28</sup> The CST reviewed additional data from the US Renal Data System. While stopping short of declaring a high BMI as an absolute contraindication, the CST states, the increased risk of death post-transplant first becomes significant when BMI is 34–36 kg/m<sup>2</sup>.<sup>29</sup> The relative risk for mortality is even greater when BMI at transplant is above 36 kg/m<sup>2</sup>. These data suggest that transplantation at this level of BMI may be associated with unacceptably higher risk and will need careful consideration. The CST further recommends monitored weight loss programs and consideration of bariatric surgical options to achieve a BMI  $< 30$  kg/m<sup>2</sup>.<sup>29</sup> The ERA-EDTA reports similar conclusions – they suggest that there is no clear evidence that denying obese patients

transplant is in the best interest of the patient regardless of the the reduction in post-transplant outcomes.<sup>143</sup> They suggest dietary modification and do not endorse pharmacologic or surgical weight loss interventions. Finally, the KHA-CARI guidelines<sup>27</sup> suggest that a BMI  $< 40$  kg/m<sup>2</sup> not be considered a contraindication to transplant, provided the patient's comorbid conditions are not prohibitive. In patients with a BMI  $> 40$  kg/m<sup>2</sup>, the guideline appears to question the benefit of transplant compared to dialysis, given the risk of complications and graft loss.

## RESEARCH RECOMMENDATIONS

- Studies, ideally RCTs, should examine the impact of pre-transplant rehabilitation on post-operative outcomes for frail patients who present for pre-transplant assessment.
- Studies should investigate the impact of pre-transplant bariatric surgery (eg, sleeve gastrectomy) on outcomes after kidney transplantation.

## SECTION 8: DIABETES

8.1: We recommend that candidates with type 1 or type 2 diabetes mellitus (DM) be considered for kidney transplantation (1B).

8.1.1: We suggest candidates with ESKD and type 1 DM be considered for simultaneous pancreas-kidney transplantation in regions where this procedure is available (2A).

8.2: We suggest testing for abnormal glucose metabolism by oral glucose tolerance test in candidates who are not known to have diabetes (2A).

## RATIONALE

Diabetic nephropathy is the most common cause of ESKD globally. Candidates with type 1 and type 2 DM are, however, less likely to be listed for transplantation and less likely to be transplanted than people with ESKD from causes such as glomerulonephritis and polycystic kidney disease, due to the higher prevalence of comorbidities among those with diabetes.<sup>173</sup> Inferior patient and kidney survival rates for those with diabetes have been evident for many years, attributed to a higher burden of vascular, surgical and infective complications. Several single-center studies have reported substantial improvement in recent eras,<sup>174,175</sup> however this was not matched in a recent registry analysis from Australia.<sup>176</sup> Nonetheless, survival after kidney transplantation is superior to remaining on dialysis for the majority of those candidates with ESKD due to diabetes.<sup>15</sup> Therefore, diabetes *per se* should not be seen as a contraindication to transplantation, but rather an indication to closely evaluate and manage associated complications. For assessment of comorbidities commonly present in people with diabetes, please refer to the following sections of this Guideline on cardiac (section 13), vascular (section 14), obesity (section 7), wound healing (section 7) and frailty (sections 2 and 7) evaluations.

People with ESKD and type 1 DM may benefit more from simultaneous pancreas-kidney transplantation over kidney-alone transplantation. Discussion of the merits of simultaneous pancreas-kidney transplantation are beyond

the scope of this guideline, however referral to and evaluation by a center with expertise in simultaneous pancreas-kidney transplantation is warranted where available.

New-onset diabetes after transplantation (NODAT) is a common complication of kidney transplantation, occurring in 10-40% of recipients.<sup>177</sup> NODAT is associated with reduced survival after kidney transplantation, principally due to an increase in cardiovascular mortality, and an increase in comorbidity.<sup>177,178</sup> Pre-transplant assessment of the risk of a candidate developing NODAT is therefore indicated to enable implementation of strategies to reduce risk, such as steroid minimization, choice of cyclosporine over tacrolimus or early post-transplant use of insulin, and to inform the candidate and their medical team of this risk.<sup>179-181</sup> In addition to recognized risk factors for the development of NODAT, including obesity, family history of diabetes and older age, demonstration of impaired glucose tolerance is strongly predictive.<sup>182-185</sup>

Screening for undiagnosed DM and impaired glucose tolerance may be performed by fasting blood glucose, glycated hemoglobin (HbA<sub>1c</sub>), or oral glucose tolerance test. Fasting blood glucose is an insensitive test for DM among ESKD patients and for the diagnosis of NODAT,<sup>186,187</sup> however, elevated fasting blood glucose has been advocated as an indication for oral glucose tolerance test during candidate assessment. Performance characteristics of HbA<sub>1c</sub> for the diagnosis of DM or the prediction of NODAT development have not been formally assessed in transplant candidates, however the altered performance of HbA<sub>1c</sub> in advanced kidney disease and the poor sensitivity of HbA<sub>1c</sub> for NODAT imply the utility of this test is likely to be reduced in ESKD as compared to the general population.<sup>187-189</sup> The use of oral glucose tolerance test to predict risk of NODAT has been assessed in several studies of moderate to good quality, which have found moderate to good performance characteristics for the prediction of NODAT (Summary Table and Evidence Profile: DM testing).<sup>182-185</sup> Caillard *et al.* reported a cumulative incidence of NODAT of 50% (n = 11) among candidates with impaired glucose tolerance as compared to 20% (n = 20) candidates with normal glucose tolerance, as determined by pre-transplant oral glucose tolerance test. In that study, impaired glucose tolerance, older recipient age and autosomal dominant polycystic kidney disease (ADPKD) as cause of ESKD were significantly predictive of NODAT in a multivariate model. Thus use of oral glucose tolerance test may be considered the gold standard for demonstration of pre-transplant glucose metabolic status and prediction of NODAT, despite the cost, inconvenience and potential for day-to-day variability of this test.<sup>182</sup>

### What prior guidelines recommend

We concur with existing guidelines in their general recommendation that diabetes should not on its own preclude a patient from kidney transplant candidacy. Most guidelines recommend screening for cardiovascular disease prior to and regularly after listing for transplantation – here we have not addressed this requirement specifically in the section on diabetes, but captured it within Section 13 on Cardiac Disease. We have been more circumspect as to the role of screening asymptomatic patients both before and after listing for transplantation, and discuss the evidence available and required to enable firm recommendations to be made. Both the AST and KHA-CARI guidelines

recommend assessing ischemic heart disease risk factors including diabetes.<sup>27,28</sup> Given recent evidence, we have suggested screening for diabetes and impaired glucose tolerance by oral glucose tolerance test to enable assessment of risk of diabetes after transplant and to inform management choices. We have made this a “suggestion,” acknowledging the practical and economic limitations involved.

### RESEARCH RECOMMENDATION

- RCTs should be conducted to determine the impact of various interventions, including choice of immunosuppression, on development of NODAT for those found to have impaired glucose tolerance by pre-transplant oral glucose tolerance test.

### RELEVANT SUPPLEMENTAL MATERIAL

Summary table: DM testing

Summary table: DM testing (quality assessment)

Evidence profile: Glucose tolerance testing pre-transplantation

## SECTION 9: CAUSE OF END-STAGE KIDNEY DISEASE (ESKD)

### 9.1 Cause of ESKD and kidney transplantation

9.1.1: We recommend that the cause of ESKD in candidates be determined, where possible, to inform risks and management after kidney transplantation (1A).

9.1.2: Advise candidates about the disease-specific risk of recurrence and resultant risk of graft loss (*Not Graded*).

### RATIONALE

Many causes of ESKD can recur after transplantation and affect the survival of the transplant and the patient. Primary disease can recur in up to 20% of transplants and has been reported as the cause of graft loss in 8.4% of grafts 10 years after transplantation, representing the third most common cause of graft loss.<sup>190 191</sup> Despite the risk of recurrence, transplantation is the treatment of choice in eligible patients. However, patients should be made aware of the risk of recurrence of the primary disease and the implication this would have for transplant survival. There is a significant proportion of patients for whom the cause of ESKD is not known. One recent registry analysis suggests the risk of recurrence in such patients is low.<sup>192</sup>

### 9.2 Focal segmental glomerulosclerosis (FSGS)

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).

## RATIONALE

There is a significant risk of recurrence of primary FSGS after transplantation, reported in 10-56% of transplants (average 30%).<sup>193-196</sup> When disease recurs, graft loss attributed to recurrence is reported in 30-50% of cases. Therefore, in candidates with primary FSGS, approximately 10-20% of grafts will be lost due to recurrent disease, with a reported RR for graft loss of 2.03 (95% CI: 1.19-3.44;  $p = 0.009$ ) compared to other glomerular diseases.<sup>190</sup> In the ANZDATA (Australia and New Zealand Dialysis and Transplant) data, 5-year graft survival was 52% in patients with recurrent FSGS compared to 83% in patients without recurrent disease.<sup>197</sup>

Factors associated with recurrence of FSGS include: young age, non-white ethnicity, living donor transplant, mesangial hypercellularity, rapid progression to ESKD, high levels of pre-transplant proteinuria and recurrence of FSGS in a previous graft.<sup>194,196,197</sup> However, clinical assessment of recurrence risk lacks specificity. Soluble urokinase plasminogen activator receptors have been proposed as a biomarker of recurrence, but this has not been confirmed in other studies.<sup>198,199</sup>

Despite living donation being an independent risk factor for disease recurrence, allograft survival is generally equivalent to or superior to deceased donor grafts.<sup>197</sup> Living donation is therefore not contraindicated. Registry data suggest that outcome is better in zero mismatched grafts.<sup>200</sup>

Most reports suggest that genetic forms of the disease have a lower rate of recurrence although recurrence has been reported.<sup>201-203</sup> The low rate of recurrence reported by most authors would suggest that genetic screening is indicated to inform risk prior to transplantation in younger patients with a history of steroid resistant nephrotic syndrome.

The risk of recurrence in candidates who have previously lost a transplant due to recurrent disease is high, in the order of 80%.<sup>193</sup> The benefits of re-transplantation with likely recurrence compared with long-term, maintenance dialysis should be considered on a case-by-case basis.

Plasma exchange is frequently used to treat recurrent disease. Case reports and case series have suggested efficacy of pre-transplant rituximab<sup>194,195</sup> or plasma exchange<sup>196,204</sup> to prevent FSGS recurrence, however the absence of RCTs and the presence of negative case reports<sup>196,205</sup> demonstrate uncertainty (Summary Table: Recurrence FSGS and Evidence Profile: Treatments to prevent kidney disease recurrence). Thus neither therapy can be recommended at this stage.<sup>194</sup>

### 9.3 Membranous nephropathy (MN)

- 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).

## RATIONALE

There is a significant risk of recurrent primary membranous nephropathy (MN) following transplantation. The reported rate of recurrence is between 10-50%.<sup>206-208</sup> This wide range of reported recurrence rate is due to different follow-up periods and reporting of clinical recurrence versus histological recurrence on 'for cause' or protocol biopsy.

The effect of recurrent primary MN on allograft outcome is unclear with reports of worse or equivalent outcomes in patients with recurrent primary MN.<sup>207,209</sup> This difference may reflect whether disease is detected on protocol or 'for cause' biopsy and the use of newer treatment strategies. It is clear that recurrent primary MN can lead to graft failure and when it does recur, 50% of death-censored graft losses have been attributed to recurrent disease.<sup>207</sup>

Our understanding of the pathogenesis of primary MN has advanced significantly since the identification of autoantibodies to the phospholipase A2 receptor (PLA2R). Approximately 70% of patients with primary MN have anti-PLA2R antibodies. Patients who are anti-PLA2R antibody positive have a higher risk of recurrence (60-83%) compared to those patients who are antibody negative (28-53%).<sup>207,210,211</sup> Insufficient data are available to understand the relevance to transplantation of other autoantibodies. Heavy proteinuria prior to transplantation is also a risk factor for recurrence.<sup>207</sup>

There is accumulating evidence for the use of anti-CD20 therapy for the treatment of recurrent primary MN. Complete or partial clinical remission has been reported in 80% of cases treated with rituximab.<sup>207,208,212</sup> There is currently insufficient data to determine whether the presence of anti-PLA2R antibodies is predictive of the response to anti-CD20 treatment. Alkylating agents have also been used to treat recurrent primary MN similar to the treatment of native kidney disease. However, there is no evidence at present for the pre-emptive treatment of candidates with either rituximab or alkylating agents to prevent recurrent primary MN.

### 9.4 IgA nephropathy (IgAN)

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

## RATIONALE

There is significant variability in the reported rate of recurrence of IgA nephropathy (IgAN) after transplantation.

This relates to the criteria for biopsy (protocol or for cause) and the duration of follow-up. Clinical recurrence occurs in approximately 30% of cases.<sup>213</sup> Histological recurrence is more common and probably occurs in > 50% of cases, with this percentage increasing the longer the period between transplantation and biopsy.<sup>193,214</sup>

Generally the outcome of transplantation for those with IgAN is equivalent to or better than other primary diagnoses.<sup>213,215</sup> However, despite good outcome overall in patients with IgAN, recurrence is associated with a higher risk of allograft failure.<sup>216</sup> Early recurrence of IgAN is unusual but this may be more common in younger candidates with rapidly progressive, crescentic disease in their native kidneys.<sup>217</sup>

### 9.5 IgA vasculitis

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

## RATIONALE

A primary diagnosis of IgA vasculitis, previously referred to as Henoch-Schönlein purpura, is associated with a similar death-censored graft survival compared to other diagnoses.<sup>218</sup> The risk of recurrence is lower than for IgAN with a rate of recurrence of 11.5% at 10 years reported in a multicenter European study.<sup>218</sup> The proportion of graft losses attributed to recurrent disease was 7.5-13.6% in the European series and United Network for Organ Sharing (UNOS) database study.<sup>218,219</sup>

### 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).

## RATIONALE

Recent progress in our understanding of the pathogenesis of membranoproliferative glomerulonephritis (MPGN) has led to a revision of the classification depending on the presence of immunoglobulin containing immune complexes (IC-MPGN) or dominant C3 (C3G). The assessment of the candidates and the risk of recurrent disease is dependent on the type of MPGN and therefore studies that do not differentiate between the different types of MPGN have to be interpreted with caution. Overall the rate of recurrence is high and recurrence is associated with inferior graft outcomes.<sup>191,220,221</sup>

Using protocol biopsies, Lorenz and colleagues reported a risk of recurrent IC-MPGN of 41%, with a higher risk in those patients with monoclonal IgG deposition.<sup>220,222</sup> Recurrence of MPGN with monoclonal deposition is associated with a poor graft prognosis. Only a minority of patients will have a detectable paraprotein (30%) and there is a low risk of progression to multiple myeloma. The risk of recurrent disease in cases with polyclonal IgG deposition, including secondary cryoglobulinemia, is lower provided the underlying cause is adequately treated.

C3 glomerulopathy (C3G) is divided into two diseases depending primarily on appearances under electron microscopy: dense deposit disease (DDD) and C3 glomerulonephritis (C3GN). The rate of recurrence of both subtypes of C3G is high, 70% in C3GN<sup>223-225</sup> and 50-100% in DDD.<sup>223,225</sup>

Recurrence of C3G has a negative impact on transplant survival. A study using data from the North American Pediatric Renal Transplant Cooperative Study reported a 5-year graft survival of only 50% in patients with a primary diagnosis of DDD compared with 74% for the database as a whole.<sup>226</sup> This 5-year survival is consistent with other reports in the literature.<sup>226,227</sup> When DDD recurs, the proportion of graft losses attributable to recurrence is > 50%.<sup>227</sup> A similar 5-year allograft survival is reported for patients with C3GN.<sup>223</sup> Nevertheless, in patients with either C3GN or DDD 5-year survival of > 50% are expected, therefore transplantation is a realistic option for this patient cohort despite the risk of recurrence.

The cause of C3G should be determined when testing is available as it may affect future treatment in case of recurrence. Insufficient data are available to comment on whether the cause of complement dysregulation (genetic or acquired) predicts risk of recurrence. Several factors have been reported to predict a higher risk of recurrence and poor outcome including low complement (C3 and C4) levels at the time of transplant in some<sup>220,228</sup> but not all reports,<sup>226,229</sup> young age, heavy proteinuria and crescentic primary disease.<sup>226</sup>

### 9.7 Lupus nephritis (LN)

9.7.1: We recommend not excluding candidates with LN from kidney transplantation; however,

the risk of recurrence should be considered and discussed with the candidate (1B).

- 9.7.2: We recommend that lupus activity should be clinically quiescent on no or minimal immunosuppression prior to transplantation (1D).
- 9.7.3: We recommend evaluation for secondary antiphospholipid antibodies prior to transplantation to inform perioperative management (1C).

## RATIONALE

The reported incidence of systemic lupus erythematosus recurrence after transplantation varies widely, ranging from 2.5-54%, depending on whether clinical or biopsy recurrence is reported.<sup>230-233</sup> A retrospective analysis of the UNOS database suggested a low rate of clinical recurrence, affecting 2.4% of patients.<sup>234</sup> This is in contrast to a recurrence rate of 54% in one study where surveillance biopsies were performed.<sup>235</sup> Clinically relevant recurrence is likely to be in the range reported from registry data (< 5%).

From the UNOS data, the risk of graft failure is increased in patients who develop recurrence, four fold higher than patients without recurrence.<sup>234</sup> However, only 7% of graft losses were attributed to recurrent disease. Although some studies have suggested that transplant outcome is worse in patients with LN,<sup>236</sup> most studies report a low rate of graft loss due to recurrent LN and equivalent transplant survival in patients with LN compared to patients with other primary diseases.<sup>230,232,233,237,238</sup>

The UNOS data suggest that black race, female gender and young age increase the risk of recurrence.<sup>234</sup> Similar risk factors are identified in other reports.

There are cases of successful transplantation in patients with serologically active lupus. However, the risk of recurrence is higher in patients with clinical or serological disease activity at the time of transplantation.<sup>239,240</sup> Therefore, it is generally accepted that disease should be quiescent, or at least stable, on no or minimal immunosuppression prior to transplantation. There is no relationship between time on dialysis before transplantation and risk of recurrence.<sup>230</sup> Although a period on dialysis prior to transplantation has been suggested to reduce recurrence risk, there is insufficient evidence to support this.<sup>241</sup>

A proportion of patients with LN exhibit features of antiphospholipid syndrome (APS). Because of the implications of APS in kidney transplantation (see Section 9.8), we suggest that kidney transplant recipients with a primary diagnosis of LN be screened for the presence of antiphospholipid antibodies (APLAs).

### 9.8 Antiphospholipid syndrome (APS)

- 9.8.1: We recommend not excluding candidates with APS from kidney transplantation; however, the risks of post-transplant thrombosis and perioperative anticoagulant therapies should be considered and discussed with the candidate (1B).
- 9.8.2: We suggest that APS should be clinically quiescent prior to transplantation (2D).
- 9.8.3: Continue anticoagulation (eg, aspirin, warfarin) at the time of activation on the transplant waitlist (*Not Graded*).

## RATIONALE

Primary or secondary APS (most commonly in association with systemic lupus erythematosus) can cause intrarenal vascular disease and thrombotic microangiopathy, ultimately leading to ESKD. A diagnosis of APS is associated with arterial and venous thrombosis and bleeding at the time of transplant, recurrence of nephropathy or casta-trophic APS. Consequently the presence of APS is associated with worse allograft and patient survival, particularly in patients who have high level of pre-transplant antibodies.<sup>242</sup> However, the relevance of isolated positive antibody tests, particularly anti-cardiolipin, in the absence of clinical features of APS, is less clear as anti-cardiolipin antibodies can be found in up to one-third of dialysis patients. Although there are some reports that the presence of anti-phospholipid antibodies increase the risk of early graft loss,<sup>243</sup> other studies have not identified an increased thrombotic risk.<sup>244</sup>

### 9.9 Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis

- 9.9.1: We recommend not excluding candidates with ANCA-associated vasculitis from kidney transplantation; however, the risk of recurrence should be considered and discussed with the candidate (1B).
- 9.9.2: We suggest that ANCA-vasculitis should be clinically quiescent prior to transplantation (2D).

## RATIONALE

The reported rate of relapse for ANCA-associated vasculitis varies from 9-36.8%<sup>245,246</sup> with a pooled analysis of reported cases finding that recurrence in the graft occurred in 17% of those transplanted.<sup>246</sup> The variation may be explained by the different treatment regimens used to treat primary disease and the criteria used for diagnosis of recurrence. A more recent study, with patients on modern immunosuppression, reported a lower rate of recurrence (8.6%).<sup>247</sup> The only relapses that occurred were extrarenal and no detrimental effect on graft function was identified.

Both allograft and patient survival is good in recipients with a primary diagnosis of ANCA-associated vasculitis, with 10-year patient and death-censored graft survival of 87% and 70-84%, respectively.<sup>245,248,249</sup>

The risk of relapse is not influenced by the pattern of original disease (granulomatosis with polyangiitis or microscopic polyarteritis) or ANCA type.<sup>246</sup> ANCA positivity at the time of transplant did not increase risk of allograft loss,<sup>246,249</sup> but high titer antibodies at the time of transplant may be associated with early recurrence.<sup>250</sup> There is some evidence that the risk of relapse is increased if transplantation is performed within 1 year of clinical remission and therefore a period of 1 year of clinical remission prior to transplantation has been recommended in previous guidelines.<sup>29,249</sup>

### 9.10 Anti-glomerular basement membrane (anti-GBM) disease

- 9.10.1: We recommend not excluding candidates with anti-GBM disease from kidney transplantation (1B).

- 9.10.2: We recommend that anti-GBM antibody titers be measured in candidates and that transplantation is only performed when antibodies are undetectable (1D).

## RATIONALE

The exact rate of anti-glomerular basement membrane (anti-GBM) disease recurrence after transplantation is not known but is estimated to be < 10% and is more likely if anti-GBM antibodies are detectable at the time of transplantation.<sup>251</sup> Therefore, to reduce the risk of recurrence, we suggest that serological remission be confirmed. Although 9-12 months of serological remission prior to transplantation has been suggested, there is insufficient evidence to recommend this.<sup>252</sup>

### 9.11 Hemolytic uremic syndrome (HUS)

- 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).

## RATIONALE

Hemolytic uremic syndrome (HUS) is most commonly due to infection with a Shiga-toxin producing *E. coli* (STEC-HUS, 90% of cases). STEC-HUS is a self-limiting illness that only rarely results in ESKD, although lesser degrees of CKD are common. STEC-HUS recurs very rarely after transplantation (0-1%) and therefore this diagnosis is not a contraindication to transplantation.<sup>253</sup> The low rate of ESKD in patients with STEC-HUS raises the possibility of an alternative diagnosis when ESKD occurs, particularly an atypical, complement-mediated form of the disease. In this situation, consideration should be given to testing for of a genetic or acquired defect in complement regulation.<sup>254</sup>

When presumed STEC-HUS has recurred after transplantation, again an alternative diagnosis such as atypical hemolytic uremic syndrome (aHUS) should be considered. Alberti *et al.* described genetic defects in complement

regulation in 2 patients with recurrent HUS, despite evidence of STEC infection during the initial presentation.<sup>254</sup>

Unlike STEC-HUS, the renal prognosis of aHUS is poor with 50% of patients developing ESKD.<sup>255</sup> The risk of recurrence and subsequent graft loss is high. Patients with a pathological variant of Complement Factor H (CFH), Complement Factor I (CFI), C3, Complement Factor B (CFB) or high titer anti-CFH autoantibodies have an 80-90% risk of recurrence and, without treatment with a complement inhibitor, most grafts are lost following recurrence.<sup>256,257</sup> Patients with a variant Membrane Cofactor Protein or low titer of historical anti-CFH antibodies can be considered for transplantation as the recurrence risk is low.<sup>256,257</sup> Candidates in whom no cause of aHUS is identified are at an intermediate risk of recurrent disease.<sup>258</sup>

Candidates at risk of recurrent aHUS should be counseled about the pre-emptive use of a complement inhibitor or the need to start treatment if aHUS occurs post-transplant (Summary Table: Recurrence aHUS and evidence profile: Treatments to prevent kidney disease recurrence).<sup>259</sup> Transplant candidates with a genetic defect in proteins primarily synthesized in the liver (CFH, CFI, C3 and CFB) could be considered for combined liver and kidney transplantation.<sup>260</sup>

### 9.12 Systemic sclerosis

- 9.12.1: We recommend not excluding candidates with systemic sclerosis from kidney transplantation in the absence of severe pulmonary, gastrointestinal, or other life-threatening extrarenal disease (1C).

## RATIONALE

Transplantation should be considered for candidates with systemic sclerosis as a cause of ESKD provided that the severity of extrarenal manifestation of the disease does not preclude transplantation. UNOS database studies suggested that although transplantation improved the outcome of patients with systemic sclerosis, survival was less favorable than for other kidney transplant candidates (68% 1-year graft survival).<sup>261,262</sup> More recently a French Registry study reported the outcome of 36 transplants in 34 patients with a primary diagnosis of systemic sclerosis. Patient survival was 82.5% at 5 years, with death-censored graft survival of 92.8% at 5 years.<sup>263</sup> There were 3 cases of renal crisis, and cardiac and gastrointestinal disease worsened in 45% and 26% of patients, respectively.

### 9.13 Plasma cell dyscrasias (PCDs)

Please consult Section 17.6 Hematologic Disorders for recommendations related to monoclonal gammopathy of undetermined significance (MGUS)

#### 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).

## RATIONALE

Renal manifestations of plasma cell dyscrasias (PCDs) are common and are present in approximately 25% of cases at the time of presentation and in 50% of patients at some stage.<sup>264,265</sup> The most common renal manifestations of PCD are cast nephropathy, monoclonal immunoglobulin deposition disease (MIDD) and AL amyloidosis. In patients with PCD, these are found in 40-63%, 19-26% and 7-30%, respectively. Patient survival is dependent on the type of kidney disease present, with a median survival of 6, 48 and 22 months for cast nephropathy, MIDD and AL amyloidosis, respectively, and secondly on kidney function at presentation, with impaired function predicting a poor survival.

There have been advances in the treatment of PCD which have led to a significant improvement in remission rates and survival. Hence, older reports should be interpreted with caution.

Multiple myeloma with cast nephropathy has been regarded as a contraindication to transplantation because of the high risk of recurrence and poor survival due to the underlying multiple myeloma.<sup>89</sup> However, there are a number of case series and reports describing short and medium term survival after kidney transplantation in patients with multiple myeloma.<sup>266</sup> In a series of nine patients with multiple myeloma who received a kidney transplant, patients survived between 14 and 114 months, though this is a report from 1996 prior to the introduction of new treatment strategies.<sup>267</sup> Three patients died of recurrent disease

and 3 from sepsis. No graft was lost due to recurrent cast nephropathy. The ERA-EDTA registry identified 35 cases of patients with multiple myeloma undergoing transplantation with a median survival of 9.6 years.<sup>268</sup> There is no information about disease or patient characteristics, but this is likely to represent a highly selected group of patients. There is no evidence to inform the wait time between induction of multiple myeloma remission and transplantation. A multidisciplinary approach to transplant candidate with multiple myeloma, involving hematologists and nephrologists, is advised.

Successful outcomes have been reported after HLA matched, combined kidney and stem cell transplantation. In a series of 7 cases reported in 2011, 4 remained disease free after 4 years.<sup>269</sup> Given the difficulties in finding well-matched donors, an emerging strategy has been treatment with chemotherapy and stem cell transplant to obtain stable remission followed by kidney transplantation.<sup>270</sup>

Light chain deposition disease (LCDD) is the most common form of MIDD and has been considered as a contraindication to transplant.<sup>88</sup> LCDD occurs in association with monoclonal gammopathy of undetermined significance (MGUS, 20%) or multiple myeloma (60%) and, as with cast nephropathy, poor outcomes have been reported after kidney transplantation. In a series reported by Leung *et al.*, 7 patients with LCDD received a transplant with a median allograft survival of 37 months. LCDD recurred in 5 patients, 4 of whom died.<sup>271</sup>

Light and heavy chain deposition disease (LHCDD) is the second most common form of MIDD, representing 10% of cases, but is still rare. As with LCDD, underlying multiple myeloma is common, present in about 50% of cases. Heavy chain deposition disease (HCDD) is very rare with a review in 2013 identifying only 37 cases in the literature. Therefore, there is limited experience of kidney transplantation in this patient group. Renal prognosis is poor, with case reports of response to corticosteroids and chemotherapy. The proportion of patients with multiple myeloma is lower than with LCDD (20%). Of two patients who received a kidney transplant, one developed recurrent disease.<sup>272</sup>

An updated series of 255 patients with MIDD, which includes patients with LCDD, HCDD and LHCDD, has recently been published.<sup>273</sup> Patients received a variety of treatments including bortezomib and high dose melphalan followed by autologous stem cell transplantation. Twenty-three patients received a kidney transplant. Consistent with previous literature, graft survival was poor in those who did not receive appropriate treatment pre-transplant. However, there was a subset of 14 patients who received a kidney transplant after achieving a hematological response. Disease recurrence occurred in 4 patients but only one sustained graft loss after 5 years. Therefore, in select patients who have achieved a remission, kidney transplantation appears to be a viable treatment option for patients with MIDD.

There have been a few series of patients with AL amyloidosis reporting kidney allograft survival in 41 patients from 18 to 72 months without evidence of disease recurrence. These patients had received treatment for their PCD consisting of chemotherapy with or without autologous stem cell transplant and had maintained good functional status without significant extrarenal amyloid deposition. A study from the UK National Amyloidosis Centre reported

outcome of 25 patients with AL amyloidosis who received a kidney transplant. Median patient survival was 7.3 years and median graft survival was 5.8 years. No graft was lost due to recurrent AL amyloidosis. Survival was improved if there was at least a partial response to treatment aimed at suppression of the precursor fibril load (median survival 8.9 vs 5.2 years in those patients with no response).

A recent paper from the US analyzed 49 patients who underwent kidney transplantation with AL amyloidosis.<sup>274</sup> Eighty percent had received a stem cell transplant and were in stable remission before kidney transplantation. Although 33% had evidence of cardiac involvement, none of the patients had “clinically significant” amyloid heart disease. Unfortunately, the degree of cardiac involvement was not detailed further and anyone with “advanced” organ involvement was excluded. Median patient survival from kidney transplantation was 10.5 years with even better survival for those with a complete hematological response pre-transplant. The authors also found that those patients transplanted in the most recent era had a significant improvement in survival. The authors concluded that carefully selected patients with amyloidosis can have good outcomes following kidney transplantation.<sup>274</sup>

Other manifestations of monoclonal deposition are considered in the sections on MPGN and fibrillary glomerulonephritis.

#### 9.14 AA amyloidosis

- 9.14.1: We recommend not excluding candidates with AA amyloidosis from kidney transplantation after adequate treatment of the underlying cause and in the absence of severe extrarenal organ involvement (1D).

#### RATIONALE

There are conflicting data on the outcome of kidney transplantation in candidates with a primary diagnosis of AA amyloidosis, with both equivalent and inferior graft and patient survival reported.<sup>275,276</sup> A multicenter study reported inferior 10-year patient survival for AA amyloid versus non-amyloid ESKD (62% vs 83%) but equivalent death-censored graft survival, suggesting an effect of extrarenal manifestations of AA amyloidosis on patient survival.<sup>277</sup>

#### 9.15 Fibrillary/immunotactoid glomerulonephritis

- 9.15.1: We recommend not excluding candidates with fibrillary or immunotactoid glomerulonephritis from kidney transplantation; however, the risk of recurrence should be considered and discussed with the candidate (1D).

#### RATIONALE

Fibrillary and immunotactoid glomerulonephritis can recur after transplantation.<sup>278</sup> A case series reported recurrence of fibrillary glomerulonephritis in 43% of cases, and this was more common in patients with a monoclonal gammopathy.<sup>279,280</sup> Fibrillary glomerulonephritis with a monoclonal gammopathy is associated with a high risk of allograft loss suggesting that treatment of the underlying PCD is required prior to kidney transplantation.<sup>280</sup> A

recent registry analysis found that patients with fibrillary glomerulonephritis had similar long term graft survival to other causes of ESKD.<sup>281</sup> Although only four patients with immunotactoid glomerulonephritis were transplanted, there was 100% renal-allograft survival at 3.66 years.<sup>281</sup>

#### 9.16 Hyperoxaluria (oxalosis), primary and secondary

- 9.16.1: We suggest that candidates with primary hyperoxaluria type 1 be considered for combined or sequential liver-kidney transplantation (2C).
- 9.16.2: We suggest genetic testing to identify the cause of primary hyperoxaluria to inform treatment decisions (2C).
- 9.16.3: We suggest not excluding candidates with correctable hyperoxaluria—pyridoxine-responsive or secondary—from kidney transplantation alone; however, the risk of recurrence should be considered and discussed with the candidate (2D).
- 9.16.4: We recommend the use of strategies to lower total body oxalate burden prior to transplantation in patients with hyperoxaluria, including intensive dialysis, diet modification, and pyridoxine treatment as appropriate on a case-by-case basis (1D).

#### RATIONALE

Primary hyperoxaluria causes kidney injury due to crystal deposition in the kidneys, and this can lead to ESKD. As kidney disease progresses, oxalate production exceeds excretion and tissue accumulation occurs. This continues while on dialysis, which does not remove sufficient oxalate to prevent accumulation. After transplantation, in primary hyperoxaluria the kidney is exposed to both new oxalate produced in the liver and tissue oxalate that is mobilized on restoration of kidney function, and this may cause early graft failure.

A study of the outcome of kidney transplantation in patients with primary hyperoxaluria published in 1990 from the European Dialysis and Transplant Association registry reported a 3-year graft survival of 23% from living donors and 17% from deceased donors.<sup>282</sup> More recently a publication from the International Primary Hyperoxaluria Registry reported a 5-year survival of 45%.<sup>283</sup>

Liver transplantation will reverse the metabolic abnormality responsible for primary hyperoxaluria type 1. Less is known about the benefit in other types. Combined liver-kidney transplantation offers superior death-censored graft survival compared with kidney transplant alone.<sup>283,284</sup> Although the metabolic defect is corrected, high oxalate levels may persist after transplantation due to mobilization of tissues stores.<sup>285</sup> Sequential liver and kidney transplantation can be performed in order to minimize oxalate accumulation in the transplanted kidney and may be considered.<sup>286</sup> If this is not possible, strategies to reduce oxalate burden, including intensive dialysis and a low oxalate diet, should be started early, even with a GFR above 20 ml/min/1.73 m<sup>2</sup>.<sup>282</sup> Current early-phase trials of small interfering RNA (siRNA) strategies to prevent excess oxalate accumulation in people with primary hyperoxaluria type 1 have shown positive results. If more definitive trials are successful and the compound is made available, initiation prior to transplantation may greatly reduce the risk of recurrence for such patients in the future.<sup>287,288</sup>

### 9.17 Cystinosis

9.17.1: We recommend not excluding candidates with cystinosis from kidney transplantation in the absence of severe extrarenal manifestations (1C).

#### RATIONALE

Cystinosis does not recur in the kidney allograft and transplantation represents the best treatment for patients with cystinosis and ESKD, provided that extrarenal manifestations do not represent an unacceptable risk.<sup>289</sup>

### 9.18 Fabry disease

9.18.1: We recommend not excluding candidates with Fabry disease from kidney transplantation in the absence of severe cardiac or other systemic extrarenal organ involvement (1C).

#### RATIONALE

Fabry disease does not recur after transplantation.<sup>290</sup> Reports suggest that allograft and patient survival is good after transplantation in patients with Fabry disease, although perhaps worse than in patients with other primary diseases due to extrarenal disease.<sup>290–292</sup> Therefore kidney transplantation is an option for most transplant candidates with Fabry disease. In some patients the severity of cardiac or cerebrovascular disease may preclude transplantation.

### 9.19 Sickle cell disease

9.19.1: We recommend not excluding candidates with sickle cell disease from kidney transplantation in the absence of active, severe extrarenal sickle cell disease (1C).

#### RATIONALE

Sickle cell disease can recur in the allograft but currently there are insufficient data to determine the rate of recurrence.<sup>293</sup> Earlier reports suggested poor allograft survival in patients with sickle cell disease, but more recent studies report similar graft and patient survival compared to patients with normal hemoglobin genotype.<sup>294</sup> A review of US Renal Data System reported that transplant survival was similar at 1 year in patients with a primary diagnosis of sickle cell disease compared to black patients with other primary diagnoses.<sup>295</sup> However, longer-term patient and allograft survival was inferior in sickle cell patients, with a RR of 1.60 for graft failure and 2.95 for death. Although mortality is higher in sickle cell patients after transplant, it is lower than in sickle cell patients who remain on dialysis. There are insufficient data available to predict the effect of bone marrow transplantation on outcomes after kidney transplantation.

### 9.20 Sarcoidosis

9.20.1: We recommend not excluding candidates with renal sarcoidosis from kidney transplantation in the absence of severe extrarenal disease (1C).

#### RATIONALE

Sarcoidosis can recur in the kidney allograft. There are case reports and one series of 18 kidney transplant candidates with sarcoidosis, 10 of whom had renal sarcoid diagnosed prior to transplantation. Sarcoidosis recurred in the grafts of 3 of the 10 patients who had renal sarcoid in their native kidneys.<sup>296,297</sup> Graft loss was not seen in patients with recurrent renal sarcoid but kidney function was inferior.

### 9.21 Alport syndrome

9.21.1: We recommend not excluding candidates with Alport syndrome from kidney transplantation (1C).

#### RATIONALE

The outcome of transplantation is equivalent to or better in patients with Alport syndrome compared to other causes of ESKD. The development of post-transplant anti-GBM disease has been recognized and occurs in 3–5% of recipients and candidates should be aware of this potential outcome. It is more likely to occur in patients with large gene deletions. This outcome was not seen in a recent report of 51 patients with Alport syndrome undergoing kidney transplant, suggesting that modern immunosuppressive regimens may be protective against this occurrence.<sup>298</sup>

#### What prior guidelines recommend

We are in agreement with other guidelines that there are only a limited number of diseases causing ESKD that are a contraindication to transplantation. There have been changes in the classification of some disease, for example MPGN, and the current guidelines reflect these changes and therefore differ from previous guidelines. There have also been advances in the diagnostics which allow more accurate assessment of the risk of recurrence, eg, antibody status in membranous nephropathy. These tests are not included in previously published guidelines but will be addressed in the forthcoming KDIGO glomerulonephritis guideline update. Advancing in treatments have also changed how some diseases are considered with respect to recurrence risk. Atypical HUS with certain causative mutations had been considered a contraindication to transplantation.<sup>299</sup> The availability of complement inhibitors now allows kidney-only transplantation for these patients. However, it is important to recognize that new treatments may not be universally available. Similarly, multiple myeloma and other plasma cell dyscrasias are considered absolute contraindications to transplantation in some guidelines<sup>27,29</sup> but the availability of curative treatments allows successful kidney transplantation for a subgroup of patients.

#### RESEARCH RECOMMENDATIONS

- Studies should evaluate the efficacy of pre- and post-transplant interventions to prevent or treat post-transplant FSGS recurrence.
- Studies should evaluate the efficacy of pre-transplant rituximab to prevent recurrence of MN, including effect on anti-PLA2R positive and negative candidates.

- RCTs should compare pre-transplant complement inhibition versus post-transplant therapy only on the presence of aHUS recurrence.
- Further studies should assess the impact of new treatments for PCD on kidney transplant outcomes.
- The ability of pre- and post-transplant siRNA administration to prevent post-transplant recurrent oxalosis in people with primary hyperoxaluria type 1 should be examined.

## RELEVANT SUPPLEMENTAL MATERIAL

Summary table: Recurrence aHUS

Summary table: Recurrence FSGS

Evidence profile: Treatments to prevent kidney disease recurrence

## SECTION 10: INFECTIONS

### 10.1 Active infections

- 10.1.1: We recommend that kidney transplantation be delayed until active infections (bacterial, fungal, viral [except hepatitis C], parasitic) are treated (1C).

### RATIONALE

Patients awaiting kidney transplantation are at risk for a variety of infectious diseases due to underlying immunologic abnormalities from CKD, diabetes, and the process of dialysis itself. All infections should be treated with the goal to cure. Clinical and radiologic improvement should occur before transplantation. Microbiologic eradication should be documented in situations where cultures can be obtained. Any active infection at the time of transplant surgery can increase the risk of sepsis and wound infection. In addition, the infection can also become more difficult to resolve due to post-transplant immunosuppression. Ideally, the patient should complete the full course of therapy for an active infection prior to transplantation. Although not ideal, transplantation can be considered prior to completion of the course of therapy as long as clinical improvement has occurred, cultures have become negative and the patient will continue on the antimicrobials post-transplant.

Common infections in dialysis patients include central venous catheter-related, soft tissue and bloodstream infections. These infections are usually caused by *Staphylococcus aureus* or coagulase-negative Staphylococci although Gram-negative organisms and fungi can also be isolated. Infection source, such as catheters, should be removed especially in the case of bloodstream infections from *Staphylococcus aureus*, *Candida* spp., *Pseudomonas* spp., and other multidrug resistant Gram-negative bacteria where antimicrobial options are limited.<sup>300</sup> Infection of the peritoneal dialysis catheter can also occur and lead to the development of peritonitis. Culture negativity, a decrease in peritoneal dialysis fluid leukocyte count as well as clinical improvement should be documented before transplantation. In some cases, infection of the peritoneal dialysis catheter can recur or become chronic. In such cases, infection is not possible to completely cure and transplantation with simultaneous removal of the catheter is the best

treatment option. Skin and soft tissue infections in diabetic patients may develop in candidates and are often polymicrobial. In chronic infections or ulcers, an atypical organism (eg, Mycobacterium) or an underlying osteomyelitis should be considered and excluded. Surgical management may be necessary for severe cases prior to transplantation. In the ideal situation, an ulcer should not be actively infected and healing should be complete or nearing completion prior to transplantation.

### 10.2 Colonization

- 10.2.1: Follow local protocols for detection and management of colonization with drug-resistant organisms (Not Graded).
- 10.2.2: We recommend not excluding patients from kidney transplantation with asymptomatic bacterial, parasitic or fungal colonization (1C).

### RATIONALE

Transplant candidates may harbor drug-resistant microbes. Knowledge of colonization with specific organisms can help in management and selection of antimicrobials for peri- and post-operative infections. Many healthcare facilities have implemented screening practices to detect and manage colonization with drug resistant organisms such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, carbapenem-resistant enterobacteriaceae, etc. Although active screening for multidrug resistant organisms (MDROs) is not required for transplantation, candidates may test positive during routine screening or have a prior history of MDRO infection. In such cases, consideration can be given to modification of perioperative and post-transplant prophylaxis to cover the organisms found during screening. Transplant candidates may have a history of fungal, parasitic or bacterial colonization. Colonization without evidence of infection is not a contraindication for transplant. However, there is greater risk of progression to infection and strategies to mitigate progression such as antimicrobial prophylaxis should be considered at the time of transplant.

### 10.3 Specific Infections

#### 10.3.1 Urinary tract infections (UTIs)

10.3.1.1: We recommend treating symptomatic UTIs prior to kidney transplantation (1B).

10.3.1.2: We suggest not routinely performing prophylactic nephrectomy for recurrent pyelonephritis or cyst infections (2D).

### RATIONALE

For transplant candidates with recurrent urinary tract infections (UTIs), anatomic abnormalities need to be ruled out. In the specific case of polycystic kidney disease, recurrent UTIs with the same organism may be indicative of a renal cyst infection. One study reported on 73 polycystic kidney disease patients, 30 of whom underwent pre-transplant nephrectomy while 43 did not. Complications, especially cyst infections, were more frequent in those without nephrectomy although the overall rate was not

significantly different.<sup>301</sup> Some experts suggest native nephrectomy at the time of transplant in patients with a history of cyst infection although this has not shown to reduce post-transplant UTI or to reduce the risk of graft loss (Summary Table and Evidence Profile: Nephrectomy).<sup>302</sup> In select situations, patients with chronic pyelonephritis have also undergone nephrectomy prior to transplantation with significant post-operative complications.<sup>303,304</sup> One study that determined the effect of bilateral nephrectomy in patients with vesicoureteral reflux showed no significant difference in the rates of UTIs at 3 years in those with or without nephrectomy.<sup>305</sup>

### 10.3.2 Tuberculosis (TB)

- 10.3.2.1: We suggest complete treatment of active TB prior to kidney transplantation, as per World Health Organization or local guidelines (2C).
- 10.3.2.2: We recommend screening for latent TB at the time of candidate evaluation in low TB prevalence areas with a chest radiograph along with a purified protein derivative (PPD) skin test or interferon-gamma release assay (1C).
- 10.3.2.3: We suggest starting treatment of latent TB prior to or immediately following kidney transplantation in low TB prevalence areas (2C).
- 10.3.2.4: We suggest screening for latent TB at the time of candidate evaluation as per local guidelines in intermediate and high TB prevalence areas with post-transplantation vigilance for active TB (2C).

## RATIONALE

One specific infection that may occur in persons with CKD is active tuberculosis (TB), especially in persons living in endemic areas. Therapy for active TB involves a multidrug regimen for at least 6 months with longer durations for more complex disease.<sup>306,307</sup> Overall, multidrug resistant TB makes up approximately 2-5% of cases; however, in some areas, resistance rates to the primary anti-tuberculous drugs may exceed 20%.<sup>307</sup> The World Health Organization recommends at least 20 months of treatment for multidrug resistant TB. In a meta-analysis, cure rates for multidrug resistant-TB were only 65%.<sup>308</sup> Ideally, therapy for TB should be completed prior to transplantation. However, studies have shown that transplantation can successfully occur after 3-6 months of therapy for active TB with completion of therapy in the post-transplant setting (Summary Table and Evidence Profile: TB treatment).<sup>309-312</sup> At a minimum, the patient should be documented as culture-negative, and have clinical as well as radiologic improvement. In some situations, it may not be feasible to wait for therapy completion before transplantation (eg, lack of access to dialysis); in such cases, the benefit of transplantation should be weighed against the risk of recurrent TB or non-completion of therapy.

Latent TB is a significant worldwide problem and it is estimated that 1 in 4 people are infected. Post-transplant, there is a 20-55 fold increase in the risk of TB reactivation

compared to the general population. In many non-endemic countries (< 20 cases per 100,000 population annually), public health measures such as contact tracing and ensuring completion of therapy are used to control transmission of TB. Therefore, many guidelines recommend screening and subsequent treatment for latent TB. Screening can be performed using either purified protein derivative (PPD) skin test or an interferon-gamma release assay as well as a chest radiograph.<sup>313</sup> One study showed that a positive PPD test and previously healed TB on chest radiograph were significant risk factors for post-transplant TB.<sup>314</sup> Where TB screening is performed, it should be repeated annually if there is ongoing risk of exposure while awaiting transplantation. If the patient is determined to have latent TB, there are several treatment regimens that can be used.<sup>309,315,316</sup> There is no consensus as to the duration of treatment that needs to be completed prior to transplantation; however, it is reasonable that once the patient is clinically tolerating the therapy, transplantation can be performed. Since the majority of reactivation occurs within the first year post-transplant, therapy for latent TB should be instituted no later than 1-2 weeks post-transplant if it was not started in the pre-transplant period.<sup>317,318</sup>

While TB screening in low prevalence countries is generally performed, the same may not be feasible in intermediate or high prevalence countries where there is a high rate of positivity and resistance to first-line anti-tuberculous agents. Therefore, in TB-endemic regions, screening strategies or universal therapy for latent TB may not prevent post-transplant TB since there is risk for ongoing exposure. In such situations, local screening guidelines should be followed (Summary Table and Evidence Profile: TB testing). At a minimum, a chest radiograph should be performed to rule out active TB and the clinician should remain vigilant for the development of post-transplant TB.

### 10.4 Screening for periodontal disease

- 10.4.1: We suggest dental evaluation, as per local general population guidelines, to screen for dental/periodontal disease prior to kidney transplantation (2C).

## RATIONALE

Dental screening is important prior to transplant in order to screen for and prevent post-transplant oral infections.<sup>319-321</sup> Although not mandated prior to transplantation, a dental evaluation may be especially important in diabetics who appear to have a greater risk of periodontal disease.

### 10.5 Screening for viral infections (see Table 11)

#### 10.5.1 Human immunodeficiency virus (HIV)

- 10.5.1.1: We recommend screening all patients for HIV infection, using HIV serology (1A).
- 10.5.1.2: We recommend not excluding patients with controlled HIV infection from kidney transplantation (1C).
- 10.5.1.3: Kidney transplant candidates with HIV should be managed in a

**TABLE 11.****Recommendations for initial and follow-up screening of viral and non-viral pathogens in kidney transplant candidates.**

Pathogen	Test	Repeat testing
<b>Viral infections</b>		
HIV	IgG	If negative, repeat annually and at time of transplant
HCV	IgG	If negative, repeat annually and at time of transplant
HBV	Anti-HBs, Anti-HBc, HBsAg	If negative, repeat annually and at time of transplant
CMV	IgG	If negative, repeat at time of transplant
EBV	VCA IgG or EBNA IgG	If negative, repeat at time of transplant
HSV	IgG	If negative, repeat at time of transplant
VZV	IgG	If negative, repeat at time of transplant and 4 weeks post-vaccination
Measles, Mumps, Rubella	IgG	If negative, repeat at time of transplant and 4 weeks post-vaccination
HTLV	IgG	None unless ongoing risk of exposure
<b>Non-Viral infections</b>		
Syphilis	IgG with confirmatory testing if IgG positive	None
Strongyloides	IgG	None
Chagas disease	IgG	None
Tuberculosis (in low prevalence areas)	Tuberculin skin test or Interferon-gamma release assay (IGRA)	Annually if ongoing risk of exposure
Malaria	Blood smear if clinically indicated	None

Anti-HBc, hepatitis B core antibody; Anti-HBs, hepatitis B surface antibody; CMV, cytomegalovirus; EBNA, EBV nuclear antigen; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; HTLV, human T-lymphotropic virus; IgG, immunoglobulin G; VCA, viral capsid antigen; VZV, varicella zoster virus.

center with experience in this area  
(*Not Graded*).

### 10.5.2 Hepatitis C virus (HCV) [This section is adapted from 2018 KDIGO HCV Guideline]

10.5.2.1: We recommend screening all patients for HCV infection (1A). (*KDIGO HCV Guideline Recommendation 1.1.4*)

10.5.2.2: We recommend using an immunoassay followed by nucleic acid testing (NAT) if immunoassay is positive (1A). (*KDIGO HCV Guideline Recommendation 1.1.1.1*)

10.5.2.3: We recommend kidney transplantation as the best therapeutic option for patients with CKD G5 irrespective of presence of HCV infection (1A). (*KDIGO HCV Guideline Recommendation 4.1.1*)

10.5.2.4: We suggest that all candidates with HCV infection be evaluated for severity of liver disease and presence of portal hypertension (if indicated) prior to acceptance for kidney transplantation (Figure 3) (2D). (*KDIGO HCV Guideline Recommendation 4.1.2*)

10.5.2.4.1: We recommend that patients with HCV and compensated cirrhosis (without portal hypertension) undergo isolated kidney transplantation (1B). (*KDIGO HCV Guideline Recommendation 4.1.2.1*)

10.5.2.4.2: We recommend referring patients with HCV and

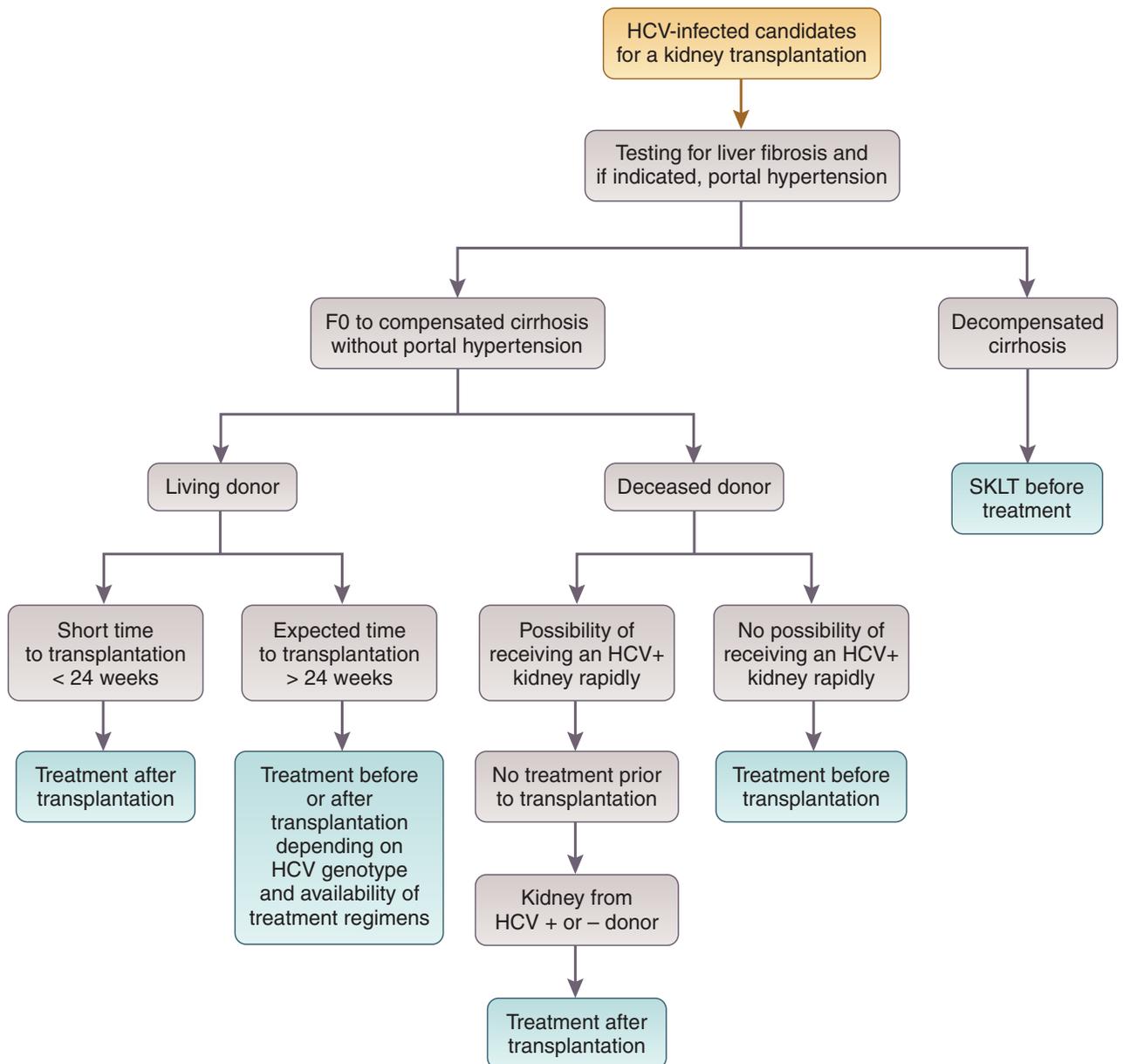
decompensated cirrhosis for combined liver-kidney transplantation (1B) and deferring HCV treatment until after transplantation (1D). (*KDIGO HCV Guideline Recommendation 4.1.2.2*)

10.5.2.5: Timing of HCV treatment in relation to kidney transplantation (before vs. after) should be based on donor type (living vs. deceased donor), waitlist times by donor type, center-specific policies governing the use of kidneys from HCV-infected deceased donors, HCV genotype, and severity of liver fibrosis (*Not Graded*). (*KDIGO HCV Guideline Recommendation 4.1.3*)

10.5.2.5.1: We recommend that all patients with HCV who are candidates for kidney transplantation be considered for direct-acting antiviral (DAA) therapy, either before or after transplantation (1A). (*KDIGO HCV Guideline Recommendation 4.1.3.1*)

10.5.2.5.2: We suggest that candidates with HCV with a living kidney donor can be considered for treatment before or after transplantation according to HCV genotype and anticipated timing of transplantation (2B). (*KDIGO HCV Guideline Recommendation 4.1.3.2*)

10.5.2.5.3: We suggest that if receiving a kidney from an HCV-positive



**FIGURE 3.** Algorithm for the evaluation of kidney transplant candidates with HCV. Reproduced from KDIGO 2018 Clinical Practice Guideline on the Prevention, Diagnosis, Evaluation and Treatment of Hepatitis C in CKD.<sup>329</sup> F0, no fibrosis; HCV, hepatitis C virus; SKLT, simultaneous kidney-liver transplantation.

donor improves the chances for transplantation, the HCV NAT-positive patient can undergo transplantation with an HCV-positive kidney and be treated for HCV infection after transplantation (2B). (KDIGO HCV Guideline Recommendation 4.1.3.3)

### 10.5.3 Hepatitis B virus (HBV) [See Section 10.7 for related recommendations on HBV vaccinations]

10.5.3.1: We recommend screening for HBV infection with HBsAg, anti-HBs, and anti-HBc (1A).

10.5.3.2: We recommend screening with HBV DNA for patients with a positive HBsAg or anti-HBc (1A).

10.5.3.3: We recommend that patients from hepatitis D virus (HDV) endemic areas be screened with HDV serology if they are positive for HBsAg or anti-HBc (1A).

10.5.3.4: We recommend that HBsAg positive and/or HBV DNA positive candidates be referred to a specialist with expertise in the management of liver disease and HBV infection to determine appropriate antiviral treatment (1D).

10.5.3.4.1: We recommend that HBsAg positive and/or HBV DNA positive candidates undergo isolated kidney transplantation if they do not have decompensated cirrhosis and

- are stable on antiviral therapy after specialist evaluation (1B).
- 10.5.3.5: We recommend not excluding anti-HBc antibody positive (HBsAg negative) patients from kidney transplantation (1C).
- 10.5.3.5.1: We recommend that anti-HBc antibody positive (HBsAg negative) patients not receive antiviral prophylaxis given that the risk of reactivation is low (1D).
- 10.5.3.5.2: We suggest that anti-HBc antibody positive (HBsAg negative) patients have a plan in place for post-transplant monitoring of HBsAg and HBV DNA for a minimum of 1-year post-transplantation (2C).
- 10.5.4 Cytomegalovirus (CMV)**
- 10.5.4.1: We recommend screening for CMV with CMV IgG (1C).
- 10.5.5 Epstein-Barr virus (EBV)**
- 10.5.5.1: We recommend screening for EBV with EBV viral capsid antigen (VCA) IgG and/or EBV nuclear antigen (EBNA) IgG (1C).
- 10.5.6 Herpes simplex virus (HSV)**
- 10.5.6.1: We suggest screening for HSV with HSV IgG (2C).
- 10.5.7 Varicella-zoster virus (VZV)**
- 10.5.7.1: We recommend screening for VZV with VZV IgG (1C).
- 10.5.7.1.1: We recommend varicella immunization for VZV seronegative candidates at least 4 weeks prior to transplantation (1C).
- 10.5.8 Measles, mumps, and rubella (MMR)**
- 10.5.8.1: We suggest screening for MMR using IgG serology (2C).
- 10.5.8.1.1: We suggest MMR immunization for MMR seronegative candidates at least 4 weeks prior to transplantation (2C).
- 10.5.9 BK virus**
- 10.5.9.1: We recommend not screening for BK virus infection in candidates (1C).
- 10.5.9.1.1: We recommend not excluding patients for repeat transplantation if a previous graft was lost due to BK nephropathy (1C).
- 10.5.10 Human T-cell lymphotropic virus (HTLV)**
- 10.5.10.1: We recommend screening for HTLV 1/2 with IgG serology in candidates from endemic areas as per World Health Organization (1C).

post-transplant prophylaxis and pre-emptive strategies to mitigate infections (Table 11). Standard serologic testing is generally available for the following viruses: HIV, HCV, HBV, CMV, EBV, HSV, VZV, MMR, and HTLV. These serologies should be performed at the time the candidate is evaluated. Assays with sufficient sensitivity for testing in candidates should be used. If negative at initial screening, serology for HIV, HCV, and HBV should be repeated annually while on the waitlist and at the time of transplantation. For other viruses such as CMV, EBV, HSV, MMR, and VZV, if initial serology is negative, then testing should be repeated at the time of transplantation (Table 11).

## RATIONALE

If the candidate is HIV positive, this does not preclude transplantation (Summary Table and Evidence Profile: HIV).<sup>322–326</sup> However, the patient will need further testing for viral load, T-cell counts and viral resistance to determine an appropriate immunosuppressive regimen and post-transplant anti-retrovirals. HIV positive transplant candidates should be considered if: (a) CD4+ T-cell count is  $\geq 200/\mu\text{l}$  and stable for the past 3 months; (b) the viral load is undetectable; (c) no opportunistic infections in the past 6 months; (d) compliant with antiretroviral regimen; (e) no cognitive impairment; (f) no history of progressive multifocal leukoencephalopathy and (g) no history of central nervous system lymphoma.<sup>327</sup> Re-transplantation has been performed in HIV positive candidates but has been associated with an increased risk of death and graft loss.<sup>328</sup> Evaluation of HIV positive transplant candidates should be done in collaboration with an HIV specialist. Ideally, the candidate should be stabilized on an anti-retroviral regimen that minimizes risks of drug-drug interactions post-transplant.

If the candidate is HCV seropositive, this does not preclude transplantation. However, HCV RNA and liver imaging should be performed to rule out hepatocellular carcinoma. The patient should be assessed for chronic liver disease and treatment with direct-acting antivirals (DAAs) to eradicate HCV should be considered (Figure 3). Please consult the 2018 KDIGO HCV guideline for further details.<sup>329</sup>

The prevalence of HBV infections ranges from 0–7% of patients on hemodialysis.<sup>330,331</sup> A positive hepatitis B serology (hepatitis B surface antigen [HBsAg] and/or antibody to hepatitis B core antigen [anti-HBc]) does not preclude transplantation but does require further evaluation. Positivity of HBsAg denotes actively replicating virus and this should be further quantified using HBV DNA. In such cases, the patient should be assessed for chronic liver disease. Liver imaging should be performed to rule out hepatocellular carcinoma and expert consultation should be sought to determine antiviral therapy prior to transplantation (Summary Table and Evidence Profile: HBV treatment). Positivity of hepatitis B core antibody (anti-HBc) with a negative HBsAg is evidence of prior infection. Active replication should be ruled out with HBV DNA testing. Patients with isolated anti-HBc positivity (with or without a positive antibody to hepatitis B surface antigen [anti-HBs]) can undergo transplantation. There is a small risk of reactivation (< 5%) post-transplant and monitoring

## BACKGROUND

Viral infections are one of the most common opportunistic infections post-transplant. Therefore, pre-transplant risk stratification using viral serology can help to define

of HBsAg and HBV DNA is required at regular intervals up to one year post-transplant.<sup>332,333</sup> Since hepatitis D virus (HDV) can co-infect those with HBV, and HDV is endemic in Asia and Africa, transplant candidates from these regions who have serologic evidence of HBV infection should also have HDV serology performed.

If the candidate is CMV seronegative and receives a CMV seropositive donor kidney, this puts the patient at high risk for primary CMV infection. Another high risk group for CMV reactivation is the CMV seropositive recipient who receives anti-lymphocyte globulin. In such cases, a prophylactic or pre-emptive approach to preventing CMV is required.<sup>334</sup> Transplant candidates who are CMV negative should have serology repeated at the time of transplantation.

Transplant candidates are at risk for primary herpesvirus infection or reactivation of latent herpesviruses. Screening is therefore important in order to risk stratify and make decisions for post-transplant prevention. If the candidate is EBV seronegative and receives an EBV seropositive donor kidney, this increases the risk of primary EBV infection and post-transplant lymphoproliferative disease.<sup>335</sup> If the candidate is VZV seronegative, varicella immunization is recommended. Since varicella vaccine is live-attenuated, the candidate should defer transplant for at least 4 weeks after immunization. Immunization should not occur pre-transplantation if patient is immunosuppressed for another indication (eg, treatment of underlying kidney disease with steroids). If the candidate is HSV seropositive and corticosteroids are used, there is increased risk of local and disseminated HSV infection. There may also be risk for primary infection in HSV seronegative recipients of seropositive donors and antiviral prophylaxis may be indicated. HSV seropositivity should not be assumed as prevalence varies widely by geography and is falling in some regions.<sup>336</sup>

If the candidate is MMR seronegative, consideration should be given to MMR immunization prior to kidney transplant (Summary Table and Evidence Profile: Vaccines, vaccination, respectively). Those born after the introduction of MMR vaccine in their region may be seronegative since circulation of wild-type virus decreased. Since MMR vaccine is live-attenuated, the candidate should defer transplant for at least 4 weeks after immunization. Similarly, live virus immunization should not occur pre-transplantation if patient is immunosuppressed for another indication (eg, treatment of underlying kidney disease with steroids).

It is unknown whether BK viremia or viruria pre-transplant affects graft outcomes post-transplant.<sup>337,338</sup> There are also limited data on graft nephrectomy and the risk of subsequent BK nephropathy. In one study, 7 of 10 patients that underwent retransplantation for BK virus-associated nephropathy had nephroureterectomy of the first graft; only one patient had recurrent BK virus-associated nephropathy (Summary Table and Evidence Profile: Nephrectomy).<sup>339</sup> Another report suggested no benefit of transplant nephrectomy in the setting of retransplantation following BK nephropathy.<sup>340</sup>

HTLV is endemic in many parts of the world including the Caribbean, Japan and South America. If the candidate is HTLV seropositive, this does not preclude transplantation. However, the patient should be counseled as to the increased risk of HTLV-associated disease post-transplant

such as T-cell leukemia and myelopathy/spastic paraparesis.<sup>341,342</sup> In addition, there should be a high-index of suspicion for these conditions post-transplant.

Although the above recommendations describe established viruses in the population, the clinician should be cognizant of emerging viral infections such as new respiratory viruses (eg, new coronaviruses), arboviruses (eg, Zika, Chikungunya virus) and hemorrhagic fever viruses (eg, Ebola), their incubation periods and disease manifestations. Transplant candidates with symptomatic disease from these viruses should await resolution.

## 10.6 Screening for non-viral infections

### 10.6.1 Syphilis

10.6.1.1: We recommend screening for syphilis (*Treponema pallidum*) with serology at the time of candidate evaluation and treatment prior to transplantation if infection is identified (1C).

### 10.6.2 Strongyloides

10.6.2.1: We suggest screening for strongyloidiasis with serology at the time of evaluation in candidates from endemic areas, and treatment prior to transplantation if infection is identified (2C).

### 10.6.3 Chagas disease

10.6.3.1: We recommend screening for Chagas disease with serology at the time of evaluation in candidates from endemic areas, and treatment prior to transplantation if infection is identified (1C).

### 10.6.4 Malaria

10.6.4.1: We recommend screening for malaria with a malaria blood smear at the time of evaluation in candidates who have recently travelled to endemic areas, and treatment prior to transplantation if infection is identified (1C).

## RATIONALE

Syphilis is often asymptomatic but could progress with cardiac and neurologic disease post-transplant. Therefore, serology should be routinely performed in patients awaiting transplantation and the patient treated if a confirmatory test for syphilis is positive. Lumbar puncture can be done if neurologic or ocular involvement is suspected. The ideal treatment is three doses of benzathine penicillin, each one week apart. In penicillin-allergic patients, ceftriaxone or doxycycline can be used.

Testing for endemic infections and tropical diseases should only be done in transplant candidates at risk. The worldwide distribution of endemic zones for various infections is readily available on the World Health Organization website (www.who.int). Strongyloides infection may be asymptomatic and lead to hyperinfection post-transplant. Therefore, screening for strongyloides is recommended in those who have lived in or travelled to strongyloides endemic areas.<sup>343</sup> Screening should be done using serology and seropositive patients should be treated prior to, or at the time of, transplantation with ivermectin. Malaria

testing should be performed if a transplant candidate has returned within the past month from a malaria endemic area and did not use malaria prophylaxis. For patients living in endemic areas, testing should be performed if clinical symptoms suggest disease. Chagas disease is endemic in Latin America and is caused by the protozoan parasite, *Trypanosoma cruzi*. This infection is transmitted by an insect vector and can establish clinical latency for decades. After kidney transplantation, reactivation generally occurs in the first year as asymptomatic parasitemia or fever with skin, heart or brain involvement.<sup>344,345</sup> Screening for Chagas disease is by serology. In the case of seropositivity, most experts recommend to monitor for reactivation post-transplant using polymerase chain reaction rather than treatment of the asymptomatic phase. The clinical utility for detection of endemic fungal infection in an otherwise asymptomatic transplant candidate is low as the serology-based tests lack sensitivity.<sup>346</sup> Please see Table 11 for a summary of screenings for non-viral infections.

## 10.7 Vaccinations

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).

10.7.3: We recommend that splenectomized candidates or those at increased risk for post-transplant splenectomy receive pre-transplant pneumococcal, hemophilus, and meningococcal vaccination (1B).

10.7.4: We recommend that candidates requiring complement inhibitors perioperatively or post-transplant undergo meningococcal vaccination (1B).

10.7.5: We suggest administering the following vaccines to candidates who, due to age, direct exposure, residence or travel to endemic areas, or other epidemiological risk factors, are at increased risk for the specific diseases:

- Rabies (2D)
- Tick-borne meningoencephalitis (2D)
- Japanese encephalitis (inactivated) (2D)
- Meningococcus (2D)
- *Salmonella typhi* (inactivated) (2D)
- Yellow fever (2D)

## RATIONALE

Vaccine preventable diseases are an important cause of morbidity after kidney transplantation. Vaccine

immunogenicity is generally reduced in both CKD and post-transplant settings. However, data suggest that some vaccines are more immunogenic when given pre-transplant rather than post-transplant. In addition, live-attenuated vaccines should only be given prior to transplantation. Therefore, assessment of vaccination status is an integral part of the pre-transplant evaluation. Childhood vaccinations should be updated as per local guidelines. Accelerated schedules can be used.<sup>347,348</sup>

Inactivated vaccines can be given pre- or post-transplantation (see KDIGO Care of Transplant Recipient guideline<sup>30</sup>). Vaccines should be updated as per local guidelines for diphtheria, polio, tetanus, pertussis, and *Hemophilus influenzae*. Transplant recipients have an increased risk for developing invasive pneumococcal disease. As such, kidney transplant candidates should receive the conjugated pneumococcal vaccine followed by the polysaccharide pneumococcal vaccine at least 8 weeks later.<sup>349</sup> Transplant candidates should receive the influenza vaccine annually while awaiting transplantation. Depending on availability, the MF59 adjuvanted or the high-dose influenza vaccine can be used in transplant candidates  $\geq 65$  years of age. HBV vaccine is recommended for those with CKD (Summary Table: HBV vaccination).<sup>350</sup> A 40  $\mu\text{g}$  preparation ('dialysis dose') should be used with a 3-dose interval.<sup>351,352</sup> Anti-HBs titer should be measured 4-6 weeks after series completion. Titers of anti-HBs should be checked at regular intervals as they may decline over time.<sup>353</sup> If titers have declined to  $< 10$  IU/ml, a repeat HBV vaccine series can be given. In endemic areas (www.who.int), hepatitis A vaccine should be given to all candidates before transplantation. Meningococcal conjugate vaccine should be given to children as per local guidelines. In adults, meningococcal conjugate vaccine should be given to those with risk factors including functional or anatomic asplenia, travelers to meningococcus endemic areas (eg, sub-Saharan Africa, travelers for Hajj) or those likely to require complement inhibitors perioperatively or post-transplant. In adults, two doses of quadrivalent vaccine at least 8 weeks apart can be given. In candidates who may receive eculizumab or other complement inhibitors, two doses of quadrivalent meningococcal vaccine (for serogroups A, C, Y, W-135) as well as meningococcal serogroup B vaccine should be administered. Human papillomavirus vaccine is also inactivated and can be given using the 3-dose schedule to males and females over age 9 years. A recombinant subunit inactivated vaccine is available to prevent herpes zoster and can be used in transplant candidates  $\geq 50$  years of age. In the general population, efficacy of this vaccine is  $> 97\%$  and it is recommended for those  $\geq 50$  years;<sup>354</sup> however, there are no specific data on its efficacy or effectiveness in those with CKD. Please refer to Table 12 for a summary of routine vaccinations for kidney transplant candidates.

For inactivated vaccines, no specific wait period is required pre-transplantation and candidates can remain active if on a deceased donor waitlist; however, at least two weeks is required for establishment of vaccine immunity. Nevertheless, due to lack of data, there are no recommendations for reimmunization if transplantation occurs within days after vaccination. Vaccine series that are not completed pre-transplant can be generally resumed

**TABLE 12.**  
**Summary of routine vaccinations for kidney transplant candidates**

Routine Vaccines	Dosing Guidelines*	Comment
<b>Inactive Vaccines</b>		
Diphtheria, Pertussis, Polio, Tetanus, HiB	Generally given in childhood; Ensure these are up-to-date	
Pneumococcal Vaccination: PCV13, PPV23	One dose of PCV13 followed by one dose of PPV23 with a minimum of 8-week interval in between	One booster of PPV23 five years from previous PPV23
Influenza	One dose annually	
Hepatitis B	Three doses at 0, 1, 6 months	Check anti-HBs titer Monitor annually and give booster dose if titers decline <10 IU/ml
Hepatitis A	Two doses at 0, 2 months	Check titers; If not immune, give vaccination again (i.e., repeat if no response to first series)
Human Papillomavirus	Three doses in both males and females if not previously given (ages 9 to 45)	No boosters
Meningococcal quadrivalent conjugate (Serogroups A,C,Y,W-135)	Two doses given 8 weeks apart; Indicated for travel to endemic areas, prior or planned splenectomy or planned use of eculizumab	Repeat one dose every five years in patients at risk
Meningococcal B vaccine	One dose if planned use of eculizumab	
Shingles (Herpes Zoster Subunit)	Two doses at 0, 2-6 months for those age ≥ 50 years and VZV IgG positive	Unknown if benefit in less than 50 years of age No boosters
<b>Live Vaccines</b>		
Measles, Mumps, Rubella	Two doses given 4 weeks apart. Considered immune after two doses regardless of seroconversion.	Check serology and provide vaccination if negative
Varicella	Two doses given 4 weeks apart. Considered immune after two doses regardless of seroconversion.	Check serology and provide vaccination if negative
Shingles (Herpes Zoster Live)**	One dose in those age ≥ 50 years and VZV IgG positive	Unknown if benefit in less than 50 years of age No boosters

\*Duration and doses are suggestive only as they may be variable in different regions. Please check your local guidelines.

\*\*The herpes zoster subunit inactivated vaccine is preferred over the herpes zoster live vaccine. If the herpes zoster live vaccine has already been administered, the transplant candidate can be reimmunized with the inactivated vaccine a minimum of one year after the live vaccine.

Anti-HBs, hepatitis B surface antibodies; HiB, hemophilus influenzae type b; IgG, immunoglobulin G; IU, international unit; PCV13, pneumococcal conjugate vaccine-13 valent; PPV23, pneumococcal polysaccharide vaccine-23 valent; VZV, varicella zoster virus.

post-transplant. Please refer to the KDIGO Care of the Transplant Recipient guideline for post-transplant guidance on vaccination.<sup>30</sup>

Live attenuated vaccines include MMR, varicella, herpes zoster, yellow fever, oral typhoid and oral polio vaccine. Transplant candidates who do not have documented immunity to MMR and have not previously received MMR vaccine should receive MMR vaccination since the vaccine is immunogenic and immunity is shown to be retained post-transplant.<sup>355</sup> Since viremia can occur after vaccination, transplantation should be delayed by at least 4 weeks. Varicella vaccine is indicated for persons who are VZV IgG negative.<sup>356</sup> Herpes zoster vaccine is effective for the prevention of shingles in those ≥ 50 years of age that are VZV IgG positive. Herpes zoster vaccine is beneficial in CKD and can reduce the risk of zoster by approximately 2-fold.<sup>357</sup> However, since this is a live-attenuated vaccine, a period of 4 weeks should elapse before transplantation occurs in order to clear the viremia. Limited data show that vaccine titers persist post-transplant although the duration of persistence is unclear. In general, the inactivated herpes zoster vaccine is preferred over the live zoster vaccine since its efficacy in the general population is higher than that of

live vaccine and candidates can remain active on the wait-list. Yellow fever vaccine is also a live-attenuated vaccine. For transplant candidates at increased risk of developing yellow fever, vaccination must be given at least 4 weeks before transplantation.

Transplant candidates should also receive specific travel vaccines if travel to endemic areas is anticipated. Based on exposure risk, transplant candidates can safely receive any travel vaccines including both inactivated and live vaccines. Further details on vaccination in transplant candidates can be found in this recent review from the American Society of Transplantation Infectious Diseases Community of Practice.<sup>358</sup>

### What prior guidelines recommend

Our KDIGO infection guidelines are largely consistent with the 2019 AST infectious diseases guidelines in regards to kidney transplant candidate screening and vaccinations.<sup>358,359</sup> Most prior guidelines recommend to delay transplantation in a candidate with an active infection. All guidelines also recommend screening for HIV, HCV, and HBV prior to transplantation.<sup>23,27,29,143,359</sup> HIV infection is not a contraindication for transplant in all previous

guidelines.<sup>23,27,29,143,359</sup> Only the AST<sup>360</sup> and CST<sup>29</sup> guidelines address screening for TB and recommend that all transplant candidates be screened and treated. In the current KDIGO guidelines, we recognize that treatment may not be feasible in TB-endemic countries performing kidney transplants and therefore make separate recommendations for regions with low and high TB prevalence. We address screening for geographically restricted infections (eg, strongyloides, Chagas disease, malaria) which are not addressed in most other guidelines. The AST,<sup>359</sup> CST,<sup>29</sup> and ERA-EDTA<sup>143</sup> guidelines address pre-transplant immunization to varying extents. The AST<sup>358</sup> recommends annual influenza vaccine, polysaccharide pneumococcal vaccine, and routine childhood immunizations whereas the CST guidelines<sup>29</sup> additionally recommend hepatitis B and varicella immunization. ERA-EDTA specifically addresses only pre-transplant varicella vaccination.<sup>143</sup> Our KDIGO guideline recommendations address pre-transplant screening and immunizations in a comprehensive manner. The AST<sup>361</sup> and CST<sup>29</sup> guidelines also make a recommendation to consider retransplantation of kidney transplant candidates with prior BK nephropathy but do not outline a consensus on pre-transplant nephrectomy prior to retransplantation for BK.

## RESEARCH RECOMMENDATIONS

- Studies should determine the post-transplant infection rates, morbidity, and mortality of transplant candidates colonized with MDROs.
- Studies should determine newer strategies to increase the immunogenicity of vaccines in transplant candidates including influenza, shingles, pneumococcal, and hepatitis B vaccines. With newer high-dose influenza vaccines and adjuvanted influenza vaccines, comparative trials can be performed with immunogenicity or efficacy as an endpoint. Similarly, inactivated shingles vaccine should be evaluated in this population.
- Studies should examine whether pre-transplant vaccinations affect the incidence of post-transplant disease, specifically where the disease outcome is measurable (eg, varicella zoster).
- Studies should examine whether it is ideal to treat HCV-positive transplant candidates pre- or post-transplant.

## RELEVANT SUPPLEMENTAL MATERIAL

Summary table: Nephrectomy  
 Summary table: Nephrectomy (quality assessment)  
 Evidence profile: Transplantation outcomes after pre-transplant nephrectomy for UTI or BK-associated nephropathy  
 Summary table: TB testing  
 Summary table: TB testing (quality assessment)  
 Evidence profile: TB testing  
 Summary table: TB treatment  
 Summary table: TB treatment (quality assessment)  
 Evidence profile: TB treatment, short vs. full course  
 Summary table: HBV vaccination  
 Summary table: HBV vaccination (quality assessment)  
 Summary table: HBV treatment  
 Summary table: HBV treatment (quality assessment)  
 Evidence profile: HBV treatment (lamivudine)

Summary table: HIV

Summary table: HIV (quality assessment)

Evidence profile: Transplantation outcomes in patients with HIV

Summary table: Vaccines measles

Summary table: Vaccines measles (quality assessment)

Evidence profile: Pre-transplant vaccination

## SECTION 11: MALIGNANCY

### 11.1 Cancer screening

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

11.1.1.1: We suggest chest imaging prior to transplantation in all candidates (2C). (Same as Rec 12.2)

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

11.1.2: Screen candidates at increased risk for renal cell carcinoma (eg  $\geq 3$  years dialysis, family history of renal cancer, acquired cystic disease or analgesic nephropathy) with ultrasonography (Not Graded).

11.1.3: We suggest cystoscopy to screen for bladder carcinoma in candidates at increased risk, such as those with high-level exposure to cyclophosphamide or heavy smoking ( $\geq 30$  pack-years) (2D).

11.1.4: We recommend screening for hepatocellular carcinoma in candidates with cirrhosis prior to transplantation using techniques (eg, ultrasound,  $\alpha$ -fetoprotein) and frequency as per local guidelines (1C).

11.1.5: We recommend screening for bowel cancer in candidates with inflammatory bowel disease as per local guidelines (1C).

### 11.2 Potential kidney transplant candidates with a 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  $\leq 6$ ), superficial non-melanoma skin cancer, and incidentally detected renal tumors ( $\leq 1$  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).

11.2.3: We recommend no waiting time for candidates with curatively treated (surgically or otherwise) non-metastatic basal cell and squamous cell carcinoma of the skin; melanoma *in situ*; small renal cell carcinoma ( $< 3$  cm); prostate cancer (Gleason score  $\leq 6$ ); carcinoma *in situ* (ductal carcinoma *in situ*, cervical, others); thyroid cancer (follicular/papillary  $< 2$  cm of low grade histology); and superficial bladder cancer (1C).

**TABLE 13.****Recommendations for cancer screening in the general population and potential transplant candidates**

Cancer	General population	Potential transplant candidates
<b>Breast</b>	<ul style="list-style-type: none"> <li>• Women ages 40 to 49 should have the choice to start annual breast cancer screening if they wish to do so</li> <li>• Biennial mammography is recommended for women age 50 and above</li> <li>• Screening should continue as long as woman is in good health and is expected to live 10 more years or longer<sup>362</sup></li> </ul>	<ul style="list-style-type: none"> <li>• As per general population<sup>363</sup></li> </ul>
<b>Colorectal</b>	<ul style="list-style-type: none"> <li>• Biennial fecal immunochemical testing (FIT) is recommended for all people age 50 years and above. Those with positive FIT should have full examination of the colon, preferably by colonoscopy</li> <li>• Flexible sigmoidoscopy (every 5 or 10 years) may also be considered for people age 50 years and above</li> <li>• Screening can be stopped for people who are older than 75 years or with life expectancy less than 10 years</li> </ul>	<ul style="list-style-type: none"> <li>• As per general population<sup>364,365</sup></li> </ul>
<b>Liver</b>	<ul style="list-style-type: none"> <li>• Annual liver ultrasound and alpha-fetoprotein screening for those with known cirrhosis</li> </ul>	<ul style="list-style-type: none"> <li>• As per general population (see Rec 11.1.4)</li> </ul>
<b>Cervical</b>	<ul style="list-style-type: none"> <li>• Papanicolaou (Pap) test is recommended for women starting at the age of 21 and screening should be done every 3 years. Alternately, screening using HPV testing should be done every 5 years up to age 65 years. Women older than 65 should talk to their doctors about whether or not they need to have regular cervical screening. The decision to stop is often based on a woman's history of having normal or negative Pap test results</li> <li>• Women who had a previous total hysterectomy (removal of the uterus, including the cervix) do not require routine Pap screen</li> </ul>	<ul style="list-style-type: none"> <li>• As per general population<sup>366</sup></li> </ul>
<b>Lung</b>	<ul style="list-style-type: none"> <li>• Routine screening for lung cancer using chest radiography and low-dose computed tomography (LDCT) <i>is not recommended</i> for average risk individuals</li> <li>• However, there is some evidence to suggest annual screening for people at high risk of lung cancer using LDCT. Individuals at high risk are adults aged 55 to 80 years who have a smoking history of at least 30 pack-years and currently smoke or have quit within the past 15 years<sup>367</sup></li> </ul>	<ul style="list-style-type: none"> <li>• LDCT of the chest may be recommended for individuals who are at high risk of lung cancer, including a prolonged heavy smoking history (see Rec 11.1.1.2)</li> </ul>
<b>Prostate</b>	<ul style="list-style-type: none"> <li>• Men between the ages of 55 to 69 can undergo periodic screening for prostate cancer using prostate specific antigen if they wish to do so after understanding risks and benefits</li> <li>• Clinicians should not screen men who do not express a preference for screening and screening should stop at the age of 70</li> </ul>	<ul style="list-style-type: none"> <li>• As per general population<sup>368</sup></li> </ul>
<b>Kidney</b>	<ul style="list-style-type: none"> <li>• Routine screening for renal cell cancer is not recommended for average risk individuals</li> </ul>	<ul style="list-style-type: none"> <li>• Ultrasonographic screening of the native kidneys may be recommended for individuals who have a family history of renal cancer, a personal history of acquired cystic disease, analgesic nephropathy, long-term smoking and/or prolonged waiting time on dialysis<sup>369</sup> (see Rec 11.1.2)</li> </ul>
<b>Bladder</b>	<ul style="list-style-type: none"> <li>• Routine screening for bladder cancer is not recommended for average risk individuals</li> </ul>	<ul style="list-style-type: none"> <li>• Urine cytology and cystoscopies may be recommended for individuals who had been previously exposed to chemotherapeutic agents such as cyclophosphamide, regular users of compound analgesics and for heavy smokers (<math>\geq 30</math> pack-year history) (see Rec 11.1.3)</li> </ul>

FIT, fecal immunochemical testing; HPV, human papillomavirus; LDCT, low-dose computed tomography.

11.2.3.1: For other cancers, we suggest following waiting time parameters as outlined in Table 14 (2D).

11.2.3.2: We suggest that the recommended waiting time from cancer to kidney transplantation begins upon completion of potentially curative treatment (2D).

11.2.4: Decisions about transplantation for candidates in remission from cancer should be made collaboratively with oncologists, transplant nephrologists, patients, and their caregivers (Not Graded).

11.2.4.1: For relevant cancers, supplement estimates of prognosis using genomic profiling, other

**TABLE 14.****Recommended waiting times between cancer remission and kidney transplantation<sup>91</sup>**

<b>Breast</b>	Early	At least 2 years
	Advanced	At least 5 years
<b>Colorectal</b>	Dukes A/B	At least 2 years
	Duke C	2-5 years
	Duke D	At least 5 years
	Invasive	At least 2 years
<b>Bladder</b>	Invasive	At least 2 years
<b>Kidney</b>	Incidentaloma (< 3 cm)	No waiting time
	Early	At least 2 years
<b>Uterine</b>	Large and invasive	At least 5 years
	Localized	At least 2 years
	Invasive	At least 5 years
<b>Cervical</b>	Localized	At least 2 years
	Invasive	At least 5 years
<b>Lung</b>	Localized	2-5 years
<b>Testicular</b>	Localized	At least 2 years
	Invasive	2-5 years
<b>Melanoma</b>	Localized	At least 5 years
	Invasive	Contraindicated
<b>Prostate</b>	Gleason ≤6	No waiting time
	Gleason 7	At least 2 years
	Gleason 8-10	At least 5 years
<b>Thyroid</b>	Papillary/Follicular/ Medullary	
	Stage 1	No waiting time
	Stage 2	At least 2 years
	Stage 3	At least 5 years
	Stage 4	Contraindicated
<b>Hodgkin Lymphoma</b>	Anaplastic	Contraindicated
	Localized	At least 2 years
	Regional	3-5 years
<b>Non-Hodgkin Lymphoma</b>	Distant	At least 5 years
	Localized	At least 2 years
	Regional	3-5 years
<b>Post-transplant lymphoproliferative disease</b>	Distant	At least 5 years
	Nodal	At least 2 years
	Extranodal and cerebral	At least 5 years

molecular genomic tests, and phenotyping in consultation with the patient's oncologist (*Not Graded*).

11.2.5: We recommend not excluding candidates with a history of metastatic cancer provided that potentially curative therapy has been administered and complete remission achieved; however, the risk of recurrence should be a major consideration and discussed with the candidate and their oncologist (*ID*).

### 11.3 Hematologic malignancy (see Sections 17.7, 17.8, and 17.9)

#### 11.3.1 Acute leukemia and high-grade lymphoma, including post-transplant lymphoproliferative disease

11.3.1.1: Avoid transplanting patients with leukemia or lymphoma until they have received curative therapy, achieved remission and remained cancer free for a period to be determined in consultation with

the patient, a hematologist/oncologist and the transplant program (*Not Graded*).

#### 11.3.2 Myelodysplasias, chronic leukemia and chronic/low-grade lymphoma

11.3.2.1: Decisions about kidney transplantation in patients with myelodysplasia should be made in collaboration with a hematologist (*Not Graded*).

11.3.2.2: Advise consultation with a hematologist with transplant experience in determining transplant candidacy since many lesions may be deemed to be at high risk of accelerated progression or transformation post-transplant (*Not Graded*).

11.3.3: Decisions about kidney transplantation in patients with a prior history of hematologic malignancy who are now in remission should be made in collaboration with a hematologist (*Not Graded*).

## RATIONALE

### Cancer screening

Cancer is common in patients with ESKD. Evidence from observational studies and registry data reported a 2-fold increase in overall cancer incidence among patients on dialysis, with kidney-related (such as urogenital cancers), endocrine-related malignancy such as thyroid cancer, and solid organ cancers such as colorectal cancer seen in excess compared to the general population.<sup>370,371</sup> Cancer is also a major cause of mortality and morbidity in patients with advanced kidney disease (CKD G4-G5D). Registry and linked data analyses reported at least a 1.5-fold increase in risk of cancer related death in patients on dialysis compared to the age-matched general population.<sup>372</sup> Early detection through screening and eradication of pre-cancerous lesions is one of the few strategies proven to reduce the risk of cancer-related morbidity and mortality in the general population. Trials have reported significant reductions in cancer mortality, of at least 20% for solid organ cancers such as colorectal cancer, in the screened versus unscreened arms.<sup>373</sup>

Despite the increased risk of cancer and cancer-related death in potential transplant candidates, cancer screening uptake in those with ESKD is much lower than those without kidney disease.<sup>374</sup> The rationale behind the reduced screening uptake is unclear, but may reflect patients' preferences for preventive medicine in the context of chronic illness.<sup>375,376</sup>

Also, potential candidates may experience a lower likelihood of benefits from screening even if cancer is diagnosed early because of the reduced life expectancy compared to the general population. Prior modeling analyses reported the projected gains in life years to be gained by applying screening mammography, colorectal and cervical cancer screening of patients on dialysis were at least 50% less than expected in the general population, largely because of the risk of competing events in this high-risk population including risk of death from CVD.<sup>369,377-381</sup> Uncertainties also exist in the test performance characteristics of individual screening tests, patient preferences, and the choice of the screening tool.<sup>382</sup> Currently, there are no quality primary data to inform cancer screening practices specifically in the ESKD population (Summary Table and Evidence Profile: Cancer screening).

As such, it would be appropriate for potential transplant candidates to follow the current cancer screening practices for common cancer types such as colorectal, breast, cervical, lung and prostate cancers as per the general population (Table 13).<sup>380,382</sup> For other common cancer types that are specific to the ESKD populations, such as cancers of the urinary tract system, previous research has indicated some benefits of routine ultrasonographic screening for renal cell cancers and urinary cytology/cystoscopies for bladder cancers among high-risk individuals.<sup>369,383–385</sup> It has been suggested that screening for renal cell carcinoma be performed in those with three or more years of dialysis.<sup>384–387</sup>

### Potential candidates with a prior cancer

Patients with ESKD and a cancer history in need of a transplant typically pose a challenge for transplant health professionals (Summary Table: Cancer recurrence risk; Evidence Profile: Cancer recurrence risk). While the long-term overall risk of cancer recurrence after transplantation may be low (between 5-10%), cancer prognoses after recurrence are poor.<sup>388</sup> A recent systematic review reported an increased risk of cancer-related mortality by at least 3-fold in patients with a pre-transplant cancer history compared to recipients without prior cancers. Recipients with prior cancer also have an increased risk of developing *de novo* malignancy after transplantation.<sup>389</sup>

Although a prior cancer history is not an absolute contraindication for kidney transplantation,<sup>390</sup> waiting time between two and five years for most cancer types has been recommended by clinical practice guidelines.<sup>91</sup> This recommendation arises from several large registry analyses indicating that the risk of cancer recurrence was maximal within the first five years after kidney transplantation. The highest risk of recurrences occurs among symptomatic renal cell carcinomas, sarcomas, melanocytic skin cancers, invasive bladder cancers and multiple myeloma.<sup>391</sup> Consequently, a waiting period of five years or more between cancer remission and kidney transplantation has been recommended for these cancers. Other solid organ tumors such as breast, prostate and colorectal cancers confer a lesser risk, with a recommended minimum waiting period before transplantation of 2 years. More recently, data from Norway found no association between waiting time and all-cause mortality after kidney transplantation for those with prior cancer. However, an increased risk of cancer-related death was observed among recipients with a prior history of kidney, prostate, breast, lung or plasma cell cancers compared to those without a cancer history.<sup>390</sup> Given the findings, the authors recommended a shorter waiting time (one year) to transplantation from disease remission, particularly for those with localized cancer. In a recent case series study, prostate cancer recurrence risks were shown to be related to the stage of disease at initial diagnosis, with the recurrence rates of stage I and II diseases, 14% and 16% respectively, significantly lower than stage III disease at 33%, suggesting a longer waiting time may be necessary for advanced disease.<sup>392</sup> Analyses using the ANZDATA registry found a much lower rate of cancer recurrence compared to the US study. Between the years 1963 and 1999, the overall cancer recurrence rate in 210 kidney transplant recipients with a prior cancer history was only 5%, with a much higher rate of death among those whose prior cancers were diagnosed after commencement

of dialysis compared to those diagnosed before dialysis.<sup>391</sup> Differences between the two registries, probably due to selection bias of recipients, ascertainment bias of cancer diagnoses and unadjusted residual confounders, imply further unbiased analyses are necessary to address these unresolved issues in detail.

Recent analyses from the ANZDATA registry reported the overall survival for recipients who developed cancer after transplantation was generally poor, with less than 50% surviving five years after cancer diagnosis. For those who did not die from cancer, less than 20% survived more than 10 years after cancer diagnosis. Cancer of the digestive, respiratory and urinary tract systems were the three most common causes of cancer death regardless of cancer types (first cancer, recurrence and second primary). However, there were no significant differences in the risk of cancer-specific and all-cause mortality between patients who developed their first cancer after transplantation and those with cancer recurrence and those with second primary cancers.<sup>388</sup>

When considering the prospect of transplantation in potential candidates with a prior cancer, clinicians must balance the risk of death and associated morbidities against the reduced life expectancy and quality of life while waiting on dialysis instead of receiving a kidney transplant. To better define and stratify the risk of disease recurrence in a potential transplant candidate, genomic profiling may represent a novel application that distinguishes between breast cancers that are likely to result in early recurrence versus those that are unlikely to recur. Currently, there are two commercially available assays including the Oncotype DX Breast Recurrence Score (Genomic Health Inc., Redwood City, CA) and MammaPrint (Agendia, Amsterdam, Netherlands). These assays can calculate a Breast Cancer Recurrence Score that correlates with the risk of cancer recurrence 10 years after transplantation, thus representing a potentially effective prognostic tool to guide treatment and future management.<sup>393</sup>

### What prior guidelines recommend

Most guidelines recommend that potential transplant candidates should undergo age- and sex-specific cancer screening consistent with what is recommended for the general population. For potential transplant recipients with a prior history of cancer, clinical guidelines generally recommend a waiting time of between two and five years prior to transplantation, largely due to the fear of recurrent disease.<sup>23,27,28,143</sup>

Instead of imposing a strict waiting time-period, we have provided a suggested list of waiting-time parameters in Table 14. These recommendations are based on previous studies which showed a reduction in cancer recurrence with time.<sup>391</sup> Approximately 50% of cancer recurrences occurred in patients treated for cancer within 2 years of transplantation and only 13% in patients treated more than 5 years prior to transplantation.

Given the rapid advancement in cancer genome sequencing, we also suggest the use of genomic profiling assays, which may help to better assess potential transplant candidate's risks of cancer recurrence and the timing of transplant eligibility. Assays are now commercially available for early stage breast cancer and similar assays are also under

investigation for other cancers such as early colorectal cancer and lung cancer.

## RESEARCH RECOMMENDATIONS

- There is a lack of trial-based evidence of cancer screening in the transplant population; therefore, reliance has been placed on evidence from observational cohort and registry studies and modeling analyses. Given variations in the accuracy of screening tests in kidney transplant recipients and differing prognoses and life expectancies for individual transplant patients, future research that focuses on a personalized approach to shared-decision making for cancer screening, which takes into consideration a patient's individual risks of cancer, the competing risks associated with other comorbidities and the patient's preferences towards cancer screening should be encouraged.
- Emerging evidence has shown that prior cancer site, histology and stage are key factors that determine the risk of post-transplant cancer recurrence for most potential candidates with prior cancers. However, often the risk of death from cardiovascular causes or infection outweighs the projected risk of cancer recurrence. Future work is needed to model the tradeoff for early transplantation versus remaining on dialysis for these patients.

## RELEVANT SUPPLEMENTAL MATERIAL

Summary table: Cancer screening  
 Summary table: Cancer screening (quality assessment)  
 Evidence profile: Cancer screening  
 Summary table: Cancer recurrence risk  
 Summary table: Cancer recurrence risk (quality assessment)  
 Evidence profile: Cancer recurrence risk

## SECTION 12: PULMONARY DISEASE

- 12.1: Assess candidates with lung disease in collaboration with a pulmonary specialist to determine suitability for transplantation (*Not Graded*).
- 12.2: We suggest chest imaging prior to transplantation in all candidates (2C). (Same as Rec 11.1.1.1)
- 12.2.1 We suggest chest CT for current or former heavy tobacco users ( $\geq 30$  pack-years) as per local guidelines, and chest radiograph for other candidates (2C). (Same as Rec 11.1.1.2)
- 12.3: We recommend pulmonary function testing in candidates with impaired functional capacity, respiratory symptoms, or known pulmonary disease (1C).
- 12.4: We recommend counseling all candidates to avoid tobacco products before and indefinitely after transplantation (1B). (Same as Rec 6.2)
- 12.5: We recommend excluding patients with severe irreversible obstructive or restrictive lung disease from kidney transplantation (1C).

## RATIONALE

There are very little data on pre-transplant evaluation of patients with pulmonary disease. As such, the recommendations are based on evidence from the general population

who undergo preoperative pulmonary assessment for non-transplant surgery.<sup>394,395</sup> Post-operative pulmonary complications prolong hospital stay and results in increased morbidity and mortality.<sup>28,396</sup> Preoperative chest radiographs have not been shown to be of benefit in routine non-pulmonary surgery.<sup>394,396</sup> However, in kidney transplant candidates a routine chest x-ray might demonstrate localized fluid collections or volume overload.<sup>397,398</sup> The American Cancer Society recommends that patients who have at least a 30 pack-year smoking history and who currently smoke or have quit within the past 15 years undergo lung cancer screening with a chest CT.<sup>399</sup> It seems reasonable to apply these recommendations to transplant candidates as well.

Pulmonary function tests are not needed in most transplant candidates without significant pulmonary disease or symptoms given the lack of benefit seen with the use of these tests in the preoperative setting in the general population. However, preoperative pulmonary function tests may offer benefit in patients with impaired functional capacity, known pulmonary disease, or unexplained dyspnea.

Cigarette smoking increases the risk of cancer and CVD in the general population. In kidney transplant recipients, a smoking history of more than 25 pack-years was associated with a 30% higher risk of graft failure (RR 1.30, 95% CI: 1.04-1.63;  $P = 0.021$ ), mainly due to an increased risk of death.<sup>400</sup> For patients who quit smoking > 5 years before transplantation, the RR for graft failure was reduced by 34% (RR 0.66, 95% CI: 0.52-0.85;  $P < 0.001$ ). Given the evidence in the general population and transplant recipients, transplant candidates must be advised to stop smoking.<sup>400</sup>

Candidates with underlying pulmonary disease should be assessed and evaluated in collaboration with a pulmonary specialist. The benefit of kidney transplantation in patients with severe pulmonary disease will be offset by poor outcomes related to their lung pathology.<sup>401,402</sup> Given the poor prognosis, patients with the following conditions should not be candidates for kidney transplantation: lung disease requiring home oxygen therapy; uncontrolled asthma; severe cor pulmonale; irreversible moderate to severe pulmonary hypertension; and severe chronic obstructive pulmonary disease, pulmonary fibrosis or restrictive disease.<sup>89</sup> Patients with underlying bronchiectasis and previously treated pulmonary TB may need additional pulmonary assessments for consideration of impact of long-term immunosuppression on these diseases (see Section 10 on pre-transplant infectious disease assessment).

## What prior guidelines recommend

The European Renal Best Practice and the UK Renal Association evaluation guideline recommend tobacco cessation pre-transplant but no other specific statements are made regarding pulmonary evaluation.<sup>23,143</sup> In a review by Bunnapradist and Danovitch, they have recommended evaluation to include assessment for general anesthetic risk and cessation of smoking prior to transplantation.<sup>403</sup> Both the AST and the CST evaluation guidelines make several suggestions regarding pulmonary assessment that are very similar to our recommendations with no notable discrepancies.<sup>28,29</sup> The KHA-CARI guidelines make no specific mention of pulmonary assessment pre-transplantation.<sup>27</sup>

## RESEARCH RECOMMENDATIONS

- Further studies should examine the costs and benefits of screening for lung cancer in kidney transplant candidates.
- Transplant outcome data are limited for patients with functional impairment due to pulmonary disease. However, a subset of these patients may benefit from kidney transplantation. Prospective cohort studies should be done assessing survival and quality of life in patients with pulmonary functional impairment who undergo transplant compared to those remaining on dialysis.

## SECTION 13: CARDIAC DISEASE

13.1: Evaluate all candidates for the presence and severity of cardiac disease with history, physical examination, and electrocardiogram (ECG) (*Not Graded*).

13.2: Patients with signs or symptoms of active cardiac disease (eg, angina, arrhythmia, heart failure, symptomatic valvular heart disease) should undergo assessment by a cardiologist and be managed according to current local cardiac guidelines prior to further consideration for a kidney transplant (*Not Graded*).

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 non-invasive 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*).

13.4: 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 catheterization) 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*).

13.6: Patients with severe valvular heart disease should be evaluated and managed by a cardiologist according to local cardiac guidelines (*Not Graded*).

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*).

13.8: Perform cardiac imaging in patients with systemic amyloidosis. Exclude such patients from kidney transplantation if significant cardiac amyloid is confirmed (*Not Graded*). (see Rec 9.13.3.1)

13.9: We suggest that candidates who have a myocardial infarction be assessed by a cardiologist to determine whether further testing is warranted and when they can safely proceed with kidney transplantation (*2B*).

13.10: We suggest that transplantation be delayed an appropriate amount of time after placement of a coronary stent as recommended by the patient's cardiologist (*2B*).

13.11: We suggest that maintenance aspirin,  $\beta$ -blockers, and statins be continued while on the waiting list and perioperatively, according to local cardiac guidelines (*2A*).

## Definitions

- Coronary angiogram: Imaging modality of coronary arteries by injection of contrast medium usually by selective catheterization of coronary arteries.
- Coronary artery disease (CAD): CAD is a narrowing or blockage of the arteries supplying the heart caused by atherosclerosis.
- Heart failure: The pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate sufficient for the requirements of the body.
- Metabolic equivalents (METs): The ratio of the work metabolic rate to the resting metabolic rate. One MET is defined as 1 kcal/kg/hour and is roughly equivalent to the energy cost of sitting quietly.
- Myocardial infarction (MI): Myocardial necrosis in a clinical setting consistent with acute myocardial ischemia.
- Perioperative: Around the time of surgery
- Pulmonary hypertension: A mean pulmonary arterial pressure  $\geq$  25 mm Hg at rest usually confirmed by right heart catheterization.
- Valvular heart disease: Any *disease* process involving one or more of the four valves of the heart (the aortic and mitral valves on the left and the pulmonary and tricuspid valves on the right)

## BACKGROUND

Cardiac disease is the most common cause of death in dialysis patients and the incidence of cardiac events increases with worsening CKD. Patients with ESKD being assessed for kidney transplantation have an increased risk of CAD, impaired left ventricular function, pulmonary hypertension and valvular heart disease compared to the general population. These risks are further increased in

patients with older age, DM, and previous vascular events. Risks are also elevated in smokers and those with a longer duration of dialysis. Additionally, patients with cardiac disease have a higher risk of death and cardiac events in the peri-transplant and post-transplant periods. Kidney transplantation is generally classified as intermediate risk surgery, however many patients have comorbidities that increase the risk for cardiac events. For these reasons, assessment for cardiac disease is important in the evaluation of candidates.

## RATIONALE

- There is evidence that patients with ESKD have a higher risk of cardiac disease than the general population.
- There is evidence that abnormal echocardiography findings and positive non-invasive stress testing are predictive significant CAD, cardiac events and death in patients assessed for kidney transplantation. However, evidence that screening for CAD results in improved survival or a reduction in CAD events is lacking.
- There is no evidence that revascularization of coronary artery stenoses exclusively to reduce perioperative events is beneficial.
- There is evidence that the risk of death is highest in the first month after a MI.
- There is evidence that dual antiplatelet therapy should be maintained for at least one month after insertion of a bare metal stent.
- There is evidence that dual antiplatelet therapy should be maintained for at least six months after insertion of a drug eluting stent.
- There is evidence from the general population that patients benefit from continuing cardioprotective medication in the perioperative period.
- There is evidence that echocardiography does not accurately measure right heart pressures in patients with severe pulmonary hypertension.
- There is evidence that patients with an ejection fraction of less than 30% are at increased risk of death after kidney transplantation.

Patients with CKD G5 and those on dialysis (G5D) have a significantly higher incidence of CAD than those of the general population.<sup>404</sup> The diagnosis of CAD is challenging as many patients are asymptomatic with no clinical evidence of cardiac ischemia. There are a number of guidelines and consensus statements in the literature regarding cardiac assessment for patients prior to both general and kidney transplant surgery.<sup>28,89,405–407</sup>

The goal of a perioperative assessment is to establish whether there is active cardiac disease present. Active conditions include unstable coronary syndromes, significant heart failure, arrhythmias and valvular heart disease. Hence, a thorough history and full physical examination should be undertaken in all patients assessed for kidney transplantation. The updated American College of Cardiology/American Heart Association (ACC/AHA) guidelines on perioperative cardiovascular evaluation and care for non-cardiac surgery suggests consideration of a 12-lead electrocardiogram (ECG) in asymptomatic patients without known CAD except for those undergoing low risk surgery.<sup>405</sup> Statements from the AHA/ACC scientific statement on cardiac evaluation for kidney and liver transplantation recommend a 12-lead ECG in potential

kidney transplant candidates with known CAD, peripheral vascular disease, or any cardiovascular symptoms and suggest that a 12-lead ECG is reasonable in candidates without known CVD.<sup>406</sup>

Due to the high risk of CAD in patients with ESKD, non-invasive stress testing of asymptomatic patients has become commonplace in patients assessed for kidney transplantation with the aim of diagnosing occult CAD and thereby reducing peri-transplant cardiac events and mortality. While multiple studies have demonstrated reasonable sensitivity and specificity for the detection of significant CAD with non-invasive stress testing in addition to reasonable positive predictive value for death and major adverse cardiac events, there are no studies demonstrating a survival benefit in patients assessed for kidney transplantation undergoing stress testing for asymptomatic CAD.<sup>408,409</sup> Patients with a positive stress test are however less likely to be listed for kidney transplantation.<sup>410</sup> In the diabetic population, the Detection of Ischemia in Asymptomatic Diabetes (DIAD) trial did not show a benefit in survival or cardiac events in patients randomized to non-invasive screening versus medical management, with 7 nonfatal MIs and 8 cardiac deaths (2.7%) in the screened group and 10 nonfatal MIs and 7 cardiac deaths (3.0%) among the not screened group (hazard ratio [HR] 0.88, 95% CI: 0.44–1.88;  $P = 0.73$ ).<sup>411</sup>

In the general population, patients with excellent functional capacity ( $> 10$  METs) have a low risk of cardiac events and recommendations from the ACC/AHA state that it is reasonable to forgo exercise testing in this population but suggests that cardiac stress testing be considered in patients with poor ( $< 4$  METs; eg, unable to climb one flight of stairs) or unknown functional capacity.<sup>405</sup> Similarly in the European Society of Cardiology (ESC)/European Society of Anaesthesiology guidelines on non-cardiac surgery, cardiovascular management and assessment recommend stress testing in patients who have poor functional capacity ( $< 4$  METs) and greater than 2 risk factors for CAD.<sup>407</sup>

As patients assessed for kidney transplant have at least one clinical risk factor for CAD (kidney failure) and there is a high incidence of additional risk factors in this population, the AHA/ACC scientific statement recommends that non-invasive stress testing be considered for kidney transplant candidates with three or more CAD risk factors regardless of functional status.<sup>406,412</sup> Relevant risk factors include DM, prior CVD, a duration of dialysis of  $> 1$  year, older age, smoking, hypertension and dyslipidemia.

There is little evidence to support periodically screening asymptomatic candidates while on the waiting list although this is common practice. This practice is currently the subject of a RCT (CARSK [Canadian Australasian Randomized Trial of Screening Kidney Transplant Candidates for Coronary Artery Disease]).<sup>413</sup>

Coronary revascularization exclusively to reduce perioperative cardiac events is not recommended in the general population prior to surgery. The Coronary Artery Revascularization Prophylaxis (CARP) trial randomly assigned over 500 patients with stable CAD requiring elective vascular surgery to either medical therapy alone or medical therapy plus revascularization and found no difference in mortality between the two groups.<sup>414</sup> Similar findings were found in the Dutch Echocardiographic Cardiac

Risk Evaluation Applying Stress Echo (DECREASE) V trial where 101 patients with significant stress-induced ischemia on dobutamine stress echocardiography were randomized to medical therapy or revascularization prior to elective vascular surgery.<sup>415</sup> In guidelines for the general population it is not recommended that coronary revascularization be undertaken prior to non-cardiac surgery exclusively to reduce perioperative events in low and intermediate risk surgery.<sup>405,407</sup>

In patients in whom revascularization is recommended according to existing clinical practice guidelines, this should occur prior to transplantation.<sup>406</sup> Risks associated with major cardiac surgery are increased in the people with ESKD; however one large, multicenter, retrospective analysis has documented declining mortality rates over successive eras, reporting a 30-day mortality rate of 7% between 2000 and 2003.<sup>416</sup> Only one RCT has evaluated the outcome of revascularization in patients assessed for kidney transplantation.<sup>417</sup> Twenty-six patients with insulin-dependent DM and clinically significant CAD were randomized to medical therapy or revascularization prior to kidney transplantation. The outcome for those managed medically was markedly inferior to that of those who were revascularized. Only 2 of 13 revascularized patients reached a cardiovascular endpoint in 8.4 months of follow-up compared to 10 of 13 who were managed medically. This trial, however, was limited by the use of short-acting calcium channel blockers in the medically managed group, suboptimal use of aspirin, small sample size, and short follow-up (Summary Table and Evidence Profile: CABG and cardiac revascularization pre-transplantation).

There have been a number of publications including systematic reviews examining the role of perioperative medical therapy. Continuation of  $\beta$ -blockade has been shown to be beneficial in multiple observational studies in the general population<sup>418-420</sup> and continuation has been recommended by the ACC/AHA and ESC.<sup>405-407</sup> Similarly, these guidelines recommend continuation of statins in the perioperative period. The KDIGO guideline for lipid management in CKD recommends statin treatment in kidney transplant recipients to reduce cardiac death and non-fatal MI and therefore maintaining statin use in those about to be transplanted is reasonable.<sup>421</sup> There is an increased risk of rhabdomyolysis with the use of calcineurin inhibitors—in particular cyclosporine—and hence, surveillance for this rare but important side effect is warranted.<sup>422</sup> There are no RCTs evaluating the efficacy of aspirin to prevent CVD in dialysis and CKD patients. However, observational studies suggest that aspirin is associated with a reduction in mortality in patients with a previous MI and hence maintaining aspirin in patients with known vascular disease is reasonable.<sup>423,424</sup> There are similar recommendations from the ACC/AHA regarding angiotensin-converting enzyme inhibitors.<sup>405</sup>

In patients prescribed with anticoagulant therapy, the risk of bleeding needs to be weighed against the risk of thrombosis. Vitamin K antagonists such as warfarin are commonly used in patients with atrial fibrillation or prosthetic heart valves. In patients with atrial fibrillation without mechanical heart valves requiring interruption of anticoagulation for procedures, guidelines from the AHA/ACC state that decisions on bridging therapy

should balance the risks of stroke and bleeding.<sup>425</sup> In patients with prosthetic heart valves, bridging anticoagulation with either intravenous unfractionated heparin or low molecular weight heparin is recommended in the perioperative period in patients with a mechanical aortic valve replacement and any thromboembolic risk factor, older generation mechanical aortic valve replacement or mechanic mitral valve replacement.<sup>426</sup> The use of oral direct thrombin inhibitors or anti-Xa agents in patients with mechanical valves is not recommended, due to the role of kidney function in drug clearance and the difficulties involved in reversing anticoagulation in the case of excess bleeding at the time of transplantation.

There is an increased risk of mortality in patients having surgery after a recent MI. The ACC/AHA task force recommends waiting for 4-6 weeks after a MI prior to undertaking elective surgery.<sup>427</sup> A study using discharge data showed that the post-operative MI rate decreased substantially as the length of time from MI to operation increased from 32.8% at less than 30 days after MI to 5.9% at 90-180 days after MI. Similarly 30-day post-operative mortality was highest in the first month after MI.<sup>427</sup> Both the ESC and AHA/ACC guidelines recommend that in the setting of an acute coronary syndrome, guidelines for treatment for ST-segment elevation MI or non-ST-segment elevation MI should be followed. In those patients with a MI who have been treated with revascularization and dual antiplatelet therapy, guidelines for duration of antiplatelet therapy should be followed.<sup>405,407</sup>

Coronary artery revascularization using percutaneous angioplasty and coronary artery stenting after both MI and in patients with stable CAD generally requires the use of dual antiplatelet therapy. Dual antiplatelet therapy is associated with an increased risk of bleeding which is likely to be increased in the CKD population.<sup>428</sup> Additionally there is an increased risk of cardiac events in the first six months after coronary artery stenting.<sup>429</sup> The ACC/AHA recommends delaying non-cardiac surgery for a duration of at least 14 days after balloon angioplasty and at least 30 days after insertion of a bare metal stent.<sup>405</sup> Similarly they recommend delaying elective surgery for at least a year after insertion of a drug eluting stent although more recent data has suggested that surgery after 6 months may be possible with no increase in risk.<sup>407,430,431</sup> Guidelines have recommended delaying elective non-cardiac surgery until completion of a full course of dual antiplatelet therapy to reduce the risk of perioperative bleeding and requirement for transfusion.<sup>405</sup> In patients who have had coronary artery stenting, both the ESC and ACC/AHA guidelines recommend continuation of aspirin at a dose of 75-100 mg daily.

Valvular heart disease is common in the setting of ESKD with an incidence in dialysis patients that is five times greater than that of the general population.<sup>432</sup> Additionally, survival after valve replacement surgery is significantly lower than that of the general population with a 2-year mortality of 39.5-60% as previously reported.<sup>433</sup> Similarly the incidence of pulmonary hypertension increases with worsening CKD with an incidence of 32.8% reported in patients with CKD G5 in the Chronic Renal Insufficiency Cohort (CRIC) study participants.<sup>434</sup> Pulmonary hypertension as defined by a pulmonary artery systolic pressure (PASP) > 35 mm Hg and or

tricuspid regurgitant velocity > 2.5 m/s had an adjusted 38% increased risk of all-cause mortality and 23% risk for cardiac events with a significantly higher risk in patients with a PASP > 55 mm Hg. In patients assessed for kidney transplantation, pulmonary hypertension has been shown to be associated with an increased risk of cardiac events and death.<sup>435</sup> As volume status may impact on right heart pressure estimates, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) recommends that echocardiograms should be performed once "dry weight" has been achieved.<sup>436</sup> Echocardiographic estimates of PASP may be inaccurate and hence, the 2012 AHA/ACC scientific statement on evaluation of cardiac disease in kidney and liver transplant candidates recommends consideration of right heart catheterization in candidates with PASP  $\geq$  50 mm Hg.<sup>437</sup> Severe pulmonary hypertension is defined as PASP > 60 mm Hg. There are a number of therapeutic and management strategies that may be beneficial in patients with severe pulmonary hypertension although these have not been rigorously tested in the ESKD population. Therefore, patients with moderate (PASP 45 – 59 mm Hg) or severe pulmonary hypertension who are at a satisfactory dry weight should be referred to a cardiologist for assessment and management. Despite the association of pulmonary hypertension with increased mortality and morbidity, there is some evidence that regression of elevated pulmonary pressure may occur after transplantation. Thus, assessment of this risk should be integrated with other known risk factors when deciding if an individual will benefit from kidney transplantation.<sup>437</sup>

In the general population, the European guidelines recommend that patients with established or suspected heart failure scheduled for high or intermediate risk surgery undergo evaluation of left ventricular function with echocardiography while the ACC/AHA guidelines suggest it is reasonable for patients with dyspnea of unknown origin or heart failure to undergo echocardiography.<sup>405,407</sup> The KDOQI guidelines for CVD in dialysis patients recommend a resting echocardiogram in all patients at the initiation of dialysis once the patient has achieved a dry weight.<sup>436</sup> Impaired left ventricular function has been shown to be a strong predictor of mortality in both the general population and kidney transplant candidates (Summary Table and Evidence Profile: Echocardiography).<sup>438,439</sup> In a large series of hemodialysis patients, the risk of cardiovascular death in patients with a left ventricular ejection fraction (LVEF) of < 30% was more than nine times that of those with a LVEF of  $\geq$  60%.<sup>440</sup> Due to the high risk of mortality with severe impairment of left ventricular function, dialysis treatment to improve fluid overload and consideration of carvedilol which has been shown to reduce mortality in the general population and in a small cohort of dialysis patients, may be beneficial.<sup>441</sup> Patients with severe heart failure (New York Heart Association [NYHA] Functional Class III/IV) or with a LVEF persistently < 30% despite adequate fluid removal on dialysis who are otherwise suitable for kidney transplantation should be referred to a heart transplant service for assessment for combined heart-kidney transplantation.

There are a number of cardiology guidelines recommending optimal investigation and treatment of valvular heart disease, and patients with ESKD should be evaluated

according to up-to-date guidelines unless evidence emerges to the contrary.<sup>426,442</sup>

Systemic amyloidosis is a rare multisystem disease that can result in ESKD. Registry data have shown that patients with amyloid have inferior survival both on dialysis and after kidney transplantation. However, in carefully selected cases (i.e., those without significant amyloid heart disease), successful kidney transplantation has been undertaken.<sup>274,443,444</sup> Cardiac involvement is a leading cause of mortality and morbidity and can occur in amyloidosis of all etiologies. In particular cardiac involvement is most common in primary light chain AL amyloid.<sup>445</sup> Cardiac amyloid is a restrictive cardiomyopathy which causes progressive diastolic and later biventricular dysfunction. Additionally, myocardial ischemia can result from amyloid deposits in the microvasculature. There is no consistent ECG finding in cardiac amyloid although low QRS voltages occur in up to 50% of patients with cardiac AL amyloidosis. Recommendations from amyloid centers are that all patients with amyloidosis undergo echocardiography. Findings of advanced disease have prognostic significance and these patients are unlikely to be suitable for kidney transplantation. Assessment and decisions about more advanced imaging should be undertaken by a cardiologist with expertise in amyloidosis.

### What prior guidelines recommend

Our Work Group is in general agreement with multiple guidelines outlining recommendations for assessment and management of cardiac disease in candidates.<sup>23,27–29,143,405,406</sup> Specifically, the Work Group agrees with guidelines which recommend that candidates be assessed for cardiac disease and that patients with significant risk of CAD be assessed with non-invasive testing prior to acceptance for transplantation. The Work Group also agrees with guidelines suggesting that non-invasive testing is not necessary in asymptomatic patients at low risk of CAD. Due to the lack of evidence, we differ from previous guidelines<sup>27,29</sup> which recommend periodic non-invasive screening for occult CAD after admission to a waitlist. There is no evidence that angiography is required in asymptomatic patients who have a negative non-invasive stress test. We are also in general concordance with most guidelines that recommend assessing transplant candidates for left ventricular dysfunction, valvular heart disease and pulmonary hypertension, initially by echocardiography.<sup>27,29,405,406</sup>

The Work Group agrees with most guidelines that recommend continuing maintenance cardioprotective medications while waiting for kidney transplantation. In terms of revascularization, the Work Group agrees with the AHA/ACC Scientific Statement on cardiac disease evaluation and management among kidney and liver candidates,<sup>406</sup> that routine prophylactic coronary revascularization is not recommended in patients with stable CAD who have no symptoms and have no survival indication for revascularization.

Our recommendations on timing of transplantation after MI and coronary artery stenting differ slightly from other guidelines<sup>29,406</sup> but overall the Work Group is in general agreement with guidance provided by the recent ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery.<sup>405</sup>

## RESEARCH RECOMMENDATIONS

- RCTs should be conducted to examine the costs and benefits of non-invasive cardiac testing for CAD in patients being assessed for kidney transplantation, and similarly for periodic screening of patients already listed for transplantation. The results of the CARSK study are awaited.<sup>413</sup>
- RCTs should be conducted to compare revascularization versus optimal medical management prior to kidney transplantation in patients with severe but asymptomatic CAD. The results of the randomized controlled trial ISCHEMIA-CKD are awaited.<sup>446</sup>
- Further research on the development of valid prediction scores for survival after kidney transplantation for cardiac disease, including combinations of cardiac comorbidities, should be encouraged.
- Studies should examine the efficacy of treatment options for pulmonary hypertension in patients with ESKD.

## RELEVANT SUPPLEMENTAL MATERIAL

Summary table: CABG

Summary table: CABG (quality assessment)

Evidence profile: Cardiac revascularization pre-transplantation

Summary table: Echocardiography

Summary table: Echocardiography (quality assessment)

Evidence profile: Echocardiography pre-transplantation

## SECTION 14: PERIPHERAL ARTERIAL DISEASE (PAD)

- 14.1: Evaluate all candidates for presence and severity of peripheral arterial disease (PAD) with history and physical examination (*Not Graded*).
- 14.2: We suggest that candidates without clinically apparent PAD, but who are at high risk for PAD, undergo non-invasive vascular testing (*2D*).
- 14.3: Candidates with clinically apparent PAD should undergo imaging and management of their PAD in consultation with a vascular surgeon prior to transplantation (*Not Graded*).
- 14.4: We suggest that candidates with clinically apparent PAD, abnormal non-invasive testing, or prior vascular procedures, undergo non-contrast CT imaging of the abdomen/pelvis to evaluate arterial calcification and improve operative planning (*2D*).
- 14.5: Exclude candidates with non-healing extremity wounds with active infection from transplantation until the infection is resolved (*Not Graded*).
- 14.6: We suggest not excluding patients with prior aortoiliac procedures including iliac artery stent placement from kidney transplantation if there is sufficient native artery available for vascular anastomosis (*2D*).
- 14.7: We suggest not excluding patients with severe aorto-iliac disease or distal vascular disease from kidney transplantation; however, the risk of progression after transplantation should be a key consideration and the patient should have an estimated survival which is acceptable according to national standards (*2D*).

## RATIONALE

### Prevalence of PAD in transplant candidates

Peripheral arterial disease (PAD) is highly prevalent in the ESKD population due to high rates of hypertension,

DM, tobacco abuse, and altered calcium and phosphorus balance. Population-based estimates of dialysis-dependent patients demonstrate that 24% of patients with CKD have evidence of PAD using non-invasive studies.<sup>447</sup> Among dialysis patients, 24% have clinical evidence of PAD (eg, claudication, rest pain, or tissue loss), 35% have evidence of an abnormal ankle-brachial index, and nearly 46% have health care claims related to peripheral vascular disease. Overall survival among ESKD patients who develop critical limb ischemia is less than 23% at five years.

The incidence of PAD among transplant candidates is lower as patients with advanced disease are excluded. While reporting of PAD to registries may be incomplete, one registry analysis reported that only 7% of kidney transplant candidates in UNOS (listed 1994-2008) were listed as having PAD. PAD was a risk factor for waitlist mortality (HR 1.47;  $P < 0.001$ ) and subsequent allograft loss (HR 2.01;  $P < 0.001$ ).<sup>448</sup> Furthermore, the degree of iliac artery calcification increases with length of dialysis prior to evaluation and listing.<sup>449</sup> However, when compared to remaining on dialysis, kidney transplant in patients with PAD was associated with 50% reduction in mortality at five years (68.1% vs. 34.5%,  $P < 0.0001$ ). For this reason, the Work Group believes that PAD is not an absolute contraindication to transplantation. Candidates with evidence PAD should be counseled regarding the cessation of tobacco as this is a major risk factor for progression of disease.

### Evaluation of PAD

Previous KDIGO guidelines have emphasized the need for appropriate assessment of PAD among patients with CKD.<sup>3</sup> Characterization of PAD in transplant candidates relies on history, physical examination and imaging studies. The Work Group believes that all patients with risk factors for PAD (eg, DM, tobacco use, history of CAD and long-term dialysis dependence) or clinical evidence of limb ischemia (eg, claudication, rest pain, or prior amputations) should be screened for PAD. In addition, a complete history of all prior open and endovascular interventions should be obtained prior to the determination of candidacy.

Assessment of the severity of PAD can be accomplished through lower extremity segmental flow and pressure studies and non-invasive duplex evaluation.<sup>450</sup> These tests have been demonstrated to be reliable and correlate with post-transplant outcomes.<sup>451</sup> In patients with established PAD, arteriography (with CO<sub>2</sub> or iodinated contrast dye) or CT scan without contrast can provide important information on the degree of proximal iliac artery and aortic calcification which assists with preoperative planning.<sup>449</sup> Andres *et al.*, in a prospective evaluation of 114 helical CT scans of pre-transplant candidates with risk factors for iliac stenosis, reported a 29% rate of iliac artery calcification sufficient to preclude transplantation.<sup>452</sup> Infrainguinal arterial disease is best assessed using angiography.

### Severe aortoiliac disease is a relative contraindication to kidney transplant

Advanced aortoiliac disease is a relative contraindication to kidney transplantation.<sup>453</sup> High-grade, calcific stenosis precludes kidney transplant in the ipsilateral iliac fossa, if there is an insufficient length of soft artery to allow safe clamp placement and anastomosis. Selected patients can

be considered for placement of an interposition graft with donor iliac artery (when available) or prosthetic with immediate or staged transplantation.<sup>454-456</sup> Small clinical series report successful outcomes from both approaches with a low rate of vascular graft infection or allograft loss. Patients with common iliac artery disease or aortic/iliac aneurysms can be considered for pre-transplant endovascular repair provided the external iliac arteries are not overly diseased and there is room for a vascular clamp below the level of the stent.

### Infringuinal vascular disease in transplant candidates

PAD below the inguinal ligament is common in patients with advanced CKD and ESKD who are candidates for kidney transplant.<sup>457</sup> The manifestations of distal PAD include claudication, rest pain, tissue loss, infection, and amputation. Successful transplant has the potential to stabilize distal disease and reduce arterial stiffness.<sup>458</sup> There is no evidence that kidney transplant to the ipsilateral iliac artery worsens steal syndrome or increases the risk of tissue loss.<sup>459</sup> However, pre-transplant correction of PAD should be considered to reduce potential post-transplant exposure to iodinated contrast dye and other complications.

### Aortic aneurysmal disease

Patients being evaluated for kidney transplant should be evaluated for abdominal aortic aneurysm if they have established risk factors (eg, males, advanced age, tobacco abuse, chronic obstructive pulmonary disease, PAD, prior MI, prior transient ischemic attack [TIA]). Endovascular repair of abdominal aortic aneurysm does not preclude transplant provided the iliac limbs are not extended into the external iliac arteries bilaterally.

### What prior guidelines recommend

Prior guidelines point to peripheral vascular disease as a marker for general cardiovascular morbidity as well as a risk factor for technical complications. The AST guidelines<sup>28</sup> suggest that peripheral vascular occlusive disease alone is not a contraindication, though patients should be carefully screened for associated CVD and cerebrovascular disease. No specific imaging modality was recommended, though routine angiography was unlikely to be beneficial. The presence of large unrepaired aortic aneurysms, advanced aortoiliac disease, active atheroembolic disease, or gangrene should be considered as absolute contraindications until treated and resolved. Patients with advanced aortoiliac occlusive disease should not be considered for transplant as the risk of graft loss is excessive in patients with inadequate arterial inflow. The CST<sup>29</sup> similarly classified peripheral vascular occlusive disease as a risk factor for poor outcomes though not as an absolute contraindication unless symptomatic. Patients with symptomatic, recurrent peripheral vascular occlusive disease experienced markedly lower post-transplant survival (5-year survival 81% vs. 10-year survival 26%) and may not benefit from transplantation.<sup>460</sup> The use of arterial grafts for arterial inflow should be seen as a last resort as higher complication rates have been reported. The ERA-EDTA guidelines<sup>88</sup> state only the patient should be screened for peripheral vascular occlusive disease and symptomatic or clinical significant disease should be treated as soon as possible and preferably prior to transplantation as these conditions are associated with poor long-term patient survival.

## RESEARCH RECOMMENDATIONS

- RCTs should be conducted to examine the costs and benefits of different non-invasive testing (eg, Doppler ultrasound, non-contrast CT scan) for PAD in patients being assessed for kidney transplantation.
- Similar studies could be conducted on patients already listed for transplantation to determine the utility and frequency of periodic screening for PAD.

## SECTION 15: NEUROLOGIC DISEASE

- 15.1: We suggest waiting at least 6 months after a stroke or 3 months after a transient ischemic attack (TIA) before kidney transplantation (2D).
- 15.2: We recommend not screening asymptomatic candidates for carotid artery disease (1D).
- 15.3: We suggest screening candidates with autosomal dominant polycystic kidney (ADPKD) disease for intracranial aneurysms only if they are at high risk due to prior history of or a family history of subarachnoid hemorrhage (2D).
- 15.4: Patients with progressive central neurodegenerative disease should not undergo kidney transplantation if survival and quality of life are not expected to be substantially improved by transplantation (Not Graded).
- 15.5: Assess mental status in candidates with known or suspected cognitive impairment (Not Graded).
- 15.5.1: We recommend not excluding candidates from kidney transplantation because of non-progressive intellectual, developmental, or cognitive disability (1D).
- 15.6: Patients with symptomatic peripheral neuropathy should be assessed by a neurologist (Not Graded).
- 15.6.1: We suggest people with progressive peripheral neuropathy attributed to uremia be considered for urgent kidney transplantation, if available (2D).
- 15.6.2: We recommend not excluding candidates from kidney transplantation because of peripheral neuropathy (1D).

### Definitions

- Transient ischemic attack (TIA): Episode of temporary and focal cerebral dysfunction of vascular origin, rapid in onset which commonly last 2-15 minutes but occasionally up to 24 hours with no permanent neurologic deficit.<sup>461</sup>
- Carotid artery disease: Stenosis of carotid arteries, generally caused by atherosclerosis and only rarely caused by radiation therapy, vasculitis, dissection, or fibromuscular dysplasia.
- Central neurodegenerative disease: Neurologic diseases that cause diminished quality of life and survival despite treatment (eg, Alzheimer's disease and other progressive dementias, Parkinson's disease, Huntington's disease, and motor neuron diseases).

## RATIONALE

### Waiting period

There are no data to guide decisions on when it is safe for CKD patients who have had a stroke or TIA to undergo transplantation. Observational data from the general population indicate that the risk of poorer outcomes

after elective non-cardiac surgery is increased if surgery is performed within 12 months of a stroke or TIA.<sup>462,463</sup> However, since the risk of death is substantially higher on dialysis compared to transplant, waiting too long may increase the patients overall risk of death. The Work Group agreed that waiting for at least 6 months after a stroke or 3 months after a TIA seemed reasonable, based on expert opinion. This suggestion assumes there is not a quality-of-life-limiting neurologic deficit from the stroke, such as vascular dementia, dense hemiplegia, etc.

### Screening in patients with a history of stroke or TIA

It is good medical practice to screen for treatable causes of stroke or TIA when they occur. This includes echocardiography to determine if there is valvular heart disease that might be the source of emboli; ECG to rule out atrial fibrillation; and carotid artery imaging to rule out a treatable cause of stroke or TIA. Therefore, the Work Group concluded that these tests should be done at some time before transplantation based on expert opinion.

### Screening for carotid stenosis

A systematic review of evidence from the general population found no trials comparing screening versus no screening, or carotid stenting versus medical therapy.<sup>464</sup> The specificity of ultrasonography for detecting carotid artery stenosis was found to be low, so that many false positives could be expected. A study of patients undergoing kidney transplantation found no association between pre-transplant carotid stenosis found on duplex ultrasonography and post-transplantation risk of stroke or TIA (Summary Table and Evidence Profile: Carotid screening).<sup>465</sup> For carotid endarterectomy versus medical management, the absolute reduction of non-perioperative strokes was 5.5% (95% CI: 3.9-7.0%) in 3 trials with 5223 participants with approximately 5 years of follow-up. However, the 30-day rates of stroke or death after carotid endarterectomy in trials and cohort studies were 2.4% (95% CI: 1.7-3.1%) in 6 trials with 3435 participants, and 3.3% (95% CI: 2.7-3.9%) in 7 studies with 17,474 participants. Other harms of interventions included MI, nerve injury, and hematoma. The authors of the systematic review concluded that the evidence did not indicate an overall benefit of carotid endarterectomy, stenting, or intensification of medical therapy.<sup>464</sup> Based on this evidence, the US Preventative Services Task Force recommended against screening for asymptomatic carotid stenosis.<sup>466</sup>

There have been no trials investigating the potential benefits and harms of screening and intervention for asymptomatic extracranial disease in CKD. Similarly, there have been no trials comparing intervention with no intervention or medical management for carotid artery stenosis in patients with CKD. However, there is no reason to believe that screening in CKD would be more specific than screening in the general population, or that the prevalence of carotid stenosis would be greater in advanced CKD than in the general population. In a recent series of 882 transplant candidates, only 1.5% had evidence of significant stenosis on screening carotid ultrasound.<sup>467</sup> Therefore, given these factors, it is unlikely that the benefits would outweigh the harms of screening for asymptomatic carotid artery stenosis in transplant candidates.

### Screening for intracranial aneurysms in ADPKD

Intracranial aneurysms (ICAs) occur in 9-12% of patients with ADPKD<sup>468,469</sup> compared with 2-3% in the general population.<sup>470</sup> From studies in the general population, ICAs less than 7mm in diameter are more often identified with screening but are lower risk for rupture compared to larger ICAs. Patients with ADPKD and a family history of ICA rupture may be at higher risk of rupture. However, surgical repair of asymptomatic ICA is associated with a high incidence of morbidity and mortality.<sup>471</sup>

A 2014 KDIGO Controversies Conference did not recommend routine screening for ICA.<sup>472</sup> However, screening could be considered in patients with a family history of ICAs or subarachnoid hemorrhage, previous ICA rupture, high-risk professions (eg, airline pilots), and increased patient anxiety<sup>473</sup> (Summary Table and Evidence Profile: ADPKD-related cerebral aneurysm). The Conference participants concluded that time-of-flight magnetic resonance imaging without gadolinium enhancement is the method of choice if screening is undertaken. Individuals with ICAs should be reevaluated every 6-24 months.<sup>468,474,475</sup> Patients with a family history of ICA but no ICA on screening should be rescreened at 5 to 10-year intervals.<sup>474</sup>

Peripheral neuropathy is common among people with ESKD, particularly when ESKD has been caused by a multisystem condition known to impact nerves and kidney, such as diabetes, vasculitis or amyloidosis. The etiology of neuropathy may be clinically evident in some cases, but not so in others. In rare instances of painful, progressive sensory-motor peripheral neuropathy, uremia itself may be the cause. To better define the cause, type, extent and prognosis of peripheral neuropathy, consultation by a neurologist is recommended. Although the diagnosis of peripheral neuropathy is unlikely to limit suitability for kidney transplantation, information on cause, prognosis, symptom management and suggestions for perioperative management may be of use to the patient and transplant team. For cases attributed to uremia, which progress despite aggressive dialysis, successful kidney transplantation may halt progression and reverse both symptoms and nerve conduction defects in some cases.<sup>476</sup> We recommend considering priority access to transplantation for such cases, if available.

### What prior guidelines recommend

The US Preventative Services Task Force and several other guideline organizations recommend against screening for asymptomatic carotid artery stenosis in the general population.<sup>466</sup> These guidelines are consistent with our recommendation against screening in asymptomatic transplant candidates. KHA-CARI ADPKD guidelines are consistent with our recommendation of screening for ICA only in transplant candidates at increased risk.<sup>473</sup> The CST transplant eligibility guidelines make no distinction between stroke and TIA; a delay of at least 6 months is suggested for each condition.<sup>29</sup>

### RESEARCH RECOMMENDATIONS

- Further studies should examine the outcomes of patients transplanted with known cerebrovascular disease.
- RCTs should be conducted to examine the utility of different cognitive screening tests (eg, Mini-Mental

State Examination, Montreal Cognitive Assessment) in patients being evaluated for transplantation.

## RELEVANT SUPPLEMENTAL MATERIAL

Summary table: Carotid screening

Summary table: Carotid screening (quality assessment)

Evidence profile: Carotid artery testing

Summary table: ADPKD-related cerebral aneurysm

Summary table: ADPKD-related cerebral aneurysm (quality assessment)

Evidence profile: Intracranial imaging in patients with ADPKD

## SECTION 16: GASTROINTESTINAL AND LIVER DISEASE

16.1: Evaluate all candidates for the presence of gastrointestinal disease, including liver disease, with a targeted history and physical examination (*Not Graded*).

### 16.2 Peptic ulcer disease

16.2.1: We recommend that candidates with symptoms suggestive of active peptic ulcer disease undergo esophagogastroscope and *H. pylori* testing prior to kidney transplantation (*1C*).

16.2.2: Delay kidney transplantation in candidates with endoscopically-proven peptic ulcer disease until symptoms have resolved (*Not Graded*).

16.2.3: We recommend not screening candidates with a history of peptic ulcer disease with esophagogastroscope (*1C*).

16.2.4: We recommend not excluding candidates with a history of peptic ulcer disease from kidney transplantation (*1D*).

### 16.3 Diverticulitis

16.3.1: Delay kidney transplantation in candidates with active diverticulitis until symptoms have resolved (*Not Graded*).

16.3.2: We recommend not screening asymptomatic candidates for diverticulosis (*1C*).

16.3.3: We recommend not performing prophylactic colectomy in patients with a history of diverticulitis or asymptomatic diverticulosis (*1C*).

16.3.4: We recommend not excluding candidates with a history of diverticulitis from kidney transplantation (*1C*).

### 16.4 Pancreatitis

16.4.1: Delay kidney transplantation in candidates with acute pancreatitis a minimum of three months after symptoms have resolved (*Not Graded*).

16.4.2: We suggest not excluding candidates with a history of acute or chronic pancreatitis from kidney transplantation (*2C*).

### 16.5 Cholelithiasis

16.5.1: Delay kidney transplantation in candidates with symptomatic gallstone or gallbladder disease until symptoms have resolved (*Not Graded*).

16.5.2: We recommend that candidates with a history of cholecystitis undergo cholecystectomy before kidney transplantation (*1C*).

16.5.3: We recommend not screening asymptomatic candidates for cholelithiasis (*1C*).

16.5.4: We recommend not performing prophylactic cholecystectomy in candidates with asymptomatic cholelithiasis (*1C*).

16.5.5: We recommend not excluding candidates with asymptomatic cholelithiasis from kidney transplantation (*1A*).

### 16.6 Inflammatory bowel disease

16.6.1: Delay kidney transplantation in candidates with active symptomatic inflammatory bowel disease (*Not Graded*).

16.6.1.1: Determine timing of transplantation for such patients in consultation with a gastroenterologist (*Not Graded*).

16.6.2: We recommend screening for bowel cancer in candidates with inflammatory bowel disease as per local guidelines (*1C*). (Same as Rec 11.1.5)

16.6.3: We recommend not excluding candidates with a history of inflammatory bowel disease from kidney transplantation (*1D*).

### 16.7 Liver disease

16.7.1: Screen kidney transplant candidates for liver disease with a total bilirubin, alanine aminotransferase, international normalized ratio, and albumin (*Not Graded*).

16.7.2: Delay kidney transplantation until acute hepatitis, of any cause, has resolved and a long-term strategy for managing liver disease has been implemented (*Not Graded*).

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*).

For liver disease associated with HBV or HCV infection, see Sections 10.5.2 and 10.5.3

16.7.4: We recommend screening for hepatocellular carcinoma in candidates with cirrhosis prior to transplantation using techniques (eg, ultrasound, alpha-fetoprotein) and frequency as per local guidelines (*1C*). (Same as Rec 11.1.4)

## RATIONALE

### Purpose of the evaluation

- To provide an accurate assessment of the risk factors for perioperative morbidity and post-transplant complications related to gastrointestinal organs
- To determine the severity of the comorbid gastrointestinal conditions as a contraindication to transplantation

Peptic ulcer disease is the most common post-transplant gastrointestinal complication.<sup>477,478</sup> One study conducted in the 1990s reported a 3.7% incidence of post-transplant peptic ulcer disease, including 1.3% with serious

complications (1.0% bleeding and 0.3% perforation).<sup>477</sup> Peptic ulcer disease was present in 16.9% of patients in a post-transplant esophagogastroduodenoscopy (EGD) study, which was 1.7-fold higher than that of the general gastroenterology patients.<sup>477,478</sup> Although the incidence and severity of peptic ulcer disease after kidney transplantation has been reduced,<sup>479,480</sup> treatment of active peptic ulcer disease and eradication of *H. pylori* infection prior to transplantation is recommended. These recommendations are based on the relatively higher incidence of early post-transplant peptic ulcer disease, which is often serious and requiring surgical treatment.<sup>28,89,481</sup>

There is little evidence to support pre-transplant *H. pylori* screening for all transplant candidates. Observational studies have reported a 20% to 60% prevalence of *H. pylori* in kidney transplant candidates, which is similar to rates found in the general population.<sup>478</sup> Eradication of *H. pylori* has been shown to significantly reduce the incidence of post-transplant peptic ulcer disease and mucosa-associated lymphoid tissue (MALT) lymphoma.<sup>481,482</sup> However, the association of pre-transplant *H. pylori* with the occurrence of peptic ulcer disease within the first year post-transplant has not been proven.<sup>478,483</sup>

Post-transplant immunosuppression leads to an increased risk of colonic perforation and may mask typical signs and symptoms of diverticulitis.<sup>484</sup> As such, evaluation for diverticulosis and consideration of pre-transplant partial colectomy have been previously recommended.<sup>89</sup> However, a recent systematic review found that the incidence of post-transplant diverticulitis (0.8%) and complicated diverticulitis (1%) were both relatively low.<sup>485</sup> These incidence rates do not support routine screening for diverticulosis and pre-transplant colectomy in kidney transplant candidates. Moreover, there is a lack of evidence for prophylactic colectomy and elective resection is not totally benign with a reported mortality rate of 1.9% and a major complication rate of 25%.<sup>486</sup>

Post-transplant acute pancreatitis is relatively uncommon (1 to 2%) but is associated with an increased risk for both local complications and death.<sup>487</sup> There is no evidence to support the routine pre-transplant evaluation of the pancreas in asymptomatic patients. However, patients with a history of pancreatitis should be evaluated for traditional risk factors (eg, gallstones, hyperlipidemia) and, if present, manage these prior to transplantation. There are limited data on when to proceed with transplantation after an episode of acute pancreatitis but 3 months seems reasonable to prevent an early recurrence. In the case of chronic pancreatitis, patients should be stable and exocrine insufficiency symptoms should be managed with pancreatic enzyme replacement therapy.

Cholecystectomy for transplant candidates with asymptomatic cholelithiasis is a controversial issue. The incidence of post-transplant emergency cholecystectomy (1%) and mortality (1%) are low. Observational studies have not definitively shown benefit of elective, pre-transplant cholecystectomy on post-transplant morbidity or mortality.<sup>488-491</sup> Prophylactic cholecystectomy for selective high-risk patients (eg, older, obese, previous gallstone pancreatitis) could be considered, although supportive data are lacking.<sup>492,493</sup>

Approximately 30% of patients with inflammatory bowel disease will develop an acute exacerbation following

transplantation.<sup>494</sup> In a liver transplant study, active inflammatory bowel disease at the time of transplant was a risk factor for a post-transplant flare of disease activity.<sup>495</sup> The use of tacrolimus might be a risk factor for inflammatory bowel disease relapse, although the causal relationship is unclear.<sup>496-498</sup> Anti-tumor necrosis factor therapy is now an option for transplant patients with inflammatory bowel disease who previously were treated with escalating doses of steroid.<sup>499</sup> Inflammatory bowel disease is a major risk factor for the development of colorectal cancer.<sup>500</sup> As such, virtually all major societies and guidelines recommend screening for bowel cancer in patients with inflammatory bowel disease.<sup>501-503</sup> Given the added risk of cancer with immunosuppression, it seems appropriate to also screen kidney transplant candidates with inflammatory bowel disease for colorectal malignancies.

The decision to proceed with isolated kidney transplantation or combined liver-kidney transplantation in the setting of liver disease and CKD is complex and practice is highly variable worldwide. Discussion of the merits of combined organ transplantation is beyond the scope of the guideline. We have, however, recommended the involvement of specialists with expertise in combined liver-kidney transplantation for evaluation of patients with known or suspected cirrhosis. This recommendation follows standard clinical practice in most regions of the world. Although there are exceptions, most transplant candidates without decompensated cirrhosis or severe portal hypertension can safely and successfully undergo isolated kidney transplantation.<sup>504</sup>

### What prior guidelines recommend

Both the AST and the CST evaluation guidelines suggest that patients with a prior history of peptic ulcer disease be considered for screening with EGD.<sup>28,29</sup> We have recommended against this practice as there is no evidence to support EGD in the absence of symptoms.

The AST evaluation guidelines suggest that diabetic patients be screened for cholelithiasis and offered a pre-transplant cholecystectomy if gallstones are found.<sup>28</sup> We have recommended against routine screening and prophylactic cholecystectomy for all patients except those with a history of cholecystitis. This recommendation is based on the relatively low incidence of post-transplant acute cholecystitis and the lack of measurable impact of prophylactic cholecystectomy on clinical outcomes.

The CST guidelines suggest that patients with a history of diverticulitis be evaluated and considered for partial colectomy before transplant.<sup>29</sup> We have advised against this practice. Similar to cholecystectomy, there is little supporting evidence that prophylactic colectomy alters the post-transplant course in patients with diverticulitis or diverticulosis.

The CST guidelines recommend a 6-month remission period following acute pancreatitis and a 12-month remission for those with chronic pancreatitis before proceeding with transplantation.<sup>29</sup> These recommendations were based on expert opinion at the time of publication in 2005. Given improvements in overall medical care for pancreatitis and the known benefits of kidney transplantation, we have suggested only a 3-month wait following acute pancreatitis. Similar to the CST guideline, this recommendation is based on expert opinion with little supporting evidence.

Similar to our recommendations, the UK Renal Association guideline<sup>23</sup> suggests that there is no evidence to support routine screening for diverticular disease, peptic ulceration or gallbladder stones in asymptomatic transplant candidates but makes no mention of liver disease. The KHA-CARI evaluation guideline and the ERA-EDTA evaluation guideline do not specifically address issues related to the gastrointestinal system or liver disease with the exception of viral hepatitis.<sup>27,77</sup>

## RESEARCH RECOMMENDATION

- Future studies should determine the incidence of post-transplant diverticulitis among those with at least one episode of diverticulitis prior to transplantation.

## SECTION 17: HEMATOLOGIC DISORDERS

- 17.1: We recommend not routinely screening for thrombophilia in candidates (1C).
- 17.1.1: We suggest screening for thrombophilia only in candidates who have experienced a venous thromboembolic event, recurrent arteriovenous access thromboses, non-atherosclerotic arterial thrombosis, or family history of venous thromboembolism to identify candidates at higher risk of graft thrombosis (2C).
- 17.2: We suggest testing for antiphospholipid antibodies (APLAs) in patients with systemic lupus erythematosus or features of antiphospholipid syndrome (APS) (2C).
- 17.3: Candidates should not be excluded from consideration for kidney transplantation because of their need for anticoagulation, antiplatelet therapy or a history of HIT (Not Graded). [same as Rec 7.4]
- 17.3.1: Single antiplatelet agents (eg, aspirin, clopidogrel, ticagrelor) can be continued while waiting for deceased donor transplant (Not Graded). [same as Rec 7.4.1]
- 17.3.2: Delay transplantation for the mandated period of treatment with dual antiplatelet therapy (eg, aspirin plus clopidogrel) when the risk of stopping medication (eg, stent thrombosis) or operating while on treatment (eg, surgical bleeding) exceeds the anticipated benefit of transplantation (Not Graded). [same as Rec 7.4.2]
- 17.3.2.1: Antiplatelet agents (except aspirin) should be stopped 5 days prior to living donor transplantation (unless cessation is contraindicated) and during the perioperative period for deceased donor transplantation (Not Graded). [same as Rec. 7.4.2.1]
- 17.3.3: Do not transplant patients on direct-acting oral anticoagulants (DOACs; eg, apixaban, rivaroxaban) except when there is specific expertise using DOACs perioperatively and access to DOAC reversal agents (Not Graded). [same as Rec 7.4.3]
- 17.3.3.1: Switch to an alternative anticoagulant (eg, warfarin) prior to waitlisting or living donor

transplantation if recommended by a thrombosis expert/hematologist or if there is no expertise using DOACs perioperatively or access to DOAC reversal agents (Not Graded). [same as Rec. 7.4.3.1]

- 17.3.4: Use non-heparin based agents for perioperative anticoagulation in candidates with a history of HIT (Not Graded). [same as Rec. 7.4.4]
- 17.4: Evaluate transplant suitability of patients with significant cytopenias based on cause and severity (Not Graded).
- 17.5: We recommend that candidates with sickle cell disease or thalassemia not be excluded from kidney transplantation [see sections on recurrent disease: Section 9.19: sickle cell disease] (1C).
- 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).
- 17.7 Acute leukemia and high-grade lymphoma, including post-transplant lymphoproliferative disease (Same as Section 11.3.1)
- 17.7.1: Avoid transplanting patients with leukemia or lymphoma until they have received curative therapy, achieved remission and remained cancer free for a period to be determined in consultation with the patient, a hematologist/oncologist and the transplant program (Not Graded).
- 17.8 Myelodysplasias, chronic leukemia and chronic/low-grade lymphoma (Same as Section 13.3.2)
- 17.8.1: Decisions about kidney transplantation in patients with myelodysplasia should be made in collaboration with a hematologist (Not Graded).
- 17.8.2: Advise consultation with a hematologist with transplant experience in determining transplant candidacy since many lesions may be deemed to be at high risk of accelerated progression or transformation post-transplant (Not Graded).
- 17.9: Decisions about kidney transplantation in patients with a prior history of hematological malignancy who are now in remission should be made in collaboration with a hematologist (Not Graded). (Same as Rec 11.3.3)

## RATIONALE

Arterial or venous thrombosis represents an important cause of early graft loss, leading to loss of approximately

2% of grafts.<sup>505</sup> There are inherited and acquired risk factors that predispose to thrombosis. Inherited factors include Factor V Leiden (FVL), prothrombin variants and deficiencies in antithrombin III and Protein C or S with acquired defects including APS and hyperhomocysteinemia. FVL is most common and can be found in 5-8% of European populations, 20% of patients who have a thrombotic episode and up to 50% of patients with recurrent thromboses, and FVL is associated with a 4-fold increased risk of graft vein thrombosis.<sup>506,507</sup> Although other inherited deficiencies are reported to increase thrombotic risk, data definitively linking them to graft thrombosis is lacking.

Low-titer APLAs are found commonly in healthy populations and more commonly in ESKD populations. They are found in 10-26% of patients with a clinical thrombosis and in up to 50% of patients with systemic lupus erythematosus. The outcome of transplantation in patients with APS (as opposed to APLAs without clinical manifestations) is poor with 100% graft loss reported in one study without anticoagulation.<sup>508</sup> However, in patients without clinical manifestations, APLAs did not predict graft thrombosis. Other acquired risk factors for thrombosis are common in the ESKD population, for example hyperhomocysteinemia, acquired protein C and S deficiency, but their impact on graft thrombosis is unknown.

Screening all candidates for thrombophilia is likely to have a high false-positive rate and may lead to unnecessary use of perioperative anticoagulation and higher risk of bleeding. There is insufficient evidence for untargeted screening and it is therefore not recommended (Summary Table and Evidence Profile: Thrombophilia testing). Screening patients with a history of venous, arterial or dialysis access thrombosis, particularly if recurrent, features of APS or a family history of recurrent thrombosis is more likely to identify clinically significant thrombophilia and is the approach suggested. Screening should include coagulation tests (activated partial thromboplastin time and prothrombin time), FVL, prothrombin variants, Protein C and S, antithrombin III and APLAs/anticardiolipin. This will allow use of anticoagulation in candidates most at risk of graft thrombosis. This strategy is anecdotal however, with current evidence being sparse and inconsistent.<sup>509-511</sup>

CAD is common in kidney transplant candidates and may have been treated with drug-eluting stents. Dual antiplatelet therapy is frequently used in this situation, combining aspirin with a P2Y<sub>12</sub> inhibitor such as clopidogrel, ticagrelor and prasugrel.<sup>512</sup> There is a risk of in-stent thrombosis if antiplatelet therapy is discontinued before full stent endothelialization. Continuing dual therapy will increase the risk of perioperative bleeding. There are different considerations for a living donor, when the date of transplant is known, and a deceased donor transplant, which would require the candidate to be off dual antiplatelet therapy for longer periods. Newer P2Y<sub>12</sub> inhibitors with shorter duration of action may provide greater flexibility. The complex balance of risk and benefit to the transplant candidate requires careful consideration by a multidisciplinary team involving transplant surgeons, hematologists and cardiologists.<sup>405</sup>

The ESC recommends avoiding elective surgery in patients on dual antiplatelet therapy for the mandated period of treatment, usually 6 months for stable CAD or 12 months

for acute coronary syndrome.<sup>513</sup> When surgery is being considered in transplant candidates on aspirin and clopidogrel, standard advice is to withdraw clopidogrel more than 5 days prior to surgery. Testing platelet function may allow a shorter period of withdrawal.<sup>513</sup> Withdrawal of ticagrelor for 5 days and prasugrel for 7 days is recommended.<sup>513</sup> Aspirin should be continued through the procedure.

Oral anticoagulation with the vitamin K antagonist warfarin is not a contraindication to transplantation as the effect can be reversed. Direct thrombin inhibitors are difficult to reverse, not licensed for use in CKD G4 or G5 in many jurisdictions and we suggest they should generally be avoided in candidates awaiting transplantation.

Significant cytopenias require investigation and the impact on kidney transplantation depends on the cause and severity. Myelodysplastic syndromes have the potential to progress to hematological malignancy. The risk of this transformation should be considered prior to kidney transplantation in consultation with a hematologist. Specific considerations are required when transplanting patients with sickle cell disease.<sup>294</sup> Patients with forms of thalassemia who develop ESKD can be considered for transplantation.

MGUS is a pre-cancerous state preceding multiple myeloma. The prevalence in kidney transplant candidates varies between 1-5%. It is characterized by the presence of < 3 g/dl monoclonal protein in the serum and bone marrow involvement by less than 10% of plasma cells.<sup>514</sup> Systemic involvement such as lytic bone lesions, anemia, hypercalcemia and kidney dysfunction is not present in MGUS.<sup>514</sup> The risk of disease progression to multiple myeloma has been reported to be approximately 1-1.5% annually. The main risk factors for progression to multiple myeloma include a non-IgG isotype, an M protein concentration of more than 15 g/l and an abnormal serum free-light-chain ratio.

Smouldering multiple myeloma (also termed smouldering myeloma) follows the next stage of MGUS in the spectrum of plasma cell dyscrasias. While it is considered a pre-malignant condition, the risk of progressing to multiple myeloma is higher than candidates with MGUS, and ranges between 8-10% within the first 5 years of diagnosis, but tapers to approximately 3% annually thereafter. The standard care for patients with smouldering multiple myeloma is regular monitoring without treatment, until progression to multiple myeloma. However, the management for candidates with smouldering multiple myeloma and renal lesions is less well-defined. Guidelines from the International Myeloma Working Group suggest candidates with smouldering multiple myeloma and renal lesions should not be regarded as having myeloma defining events and do not warrant immediate myeloma treatment.<sup>515</sup> Currently, there is no consensus regarding the definitive treatment strategies for these patients. However, it would not be unreasonable to adopt similar treatment strategies as for candidates with monoclonal gammopathy of renal significance prior to kidney transplantation to prevent disease recurrence in the allograft and malignant transformation into multiple myeloma.<sup>516</sup>

The risk of transformation from these pre-malignant conditions into multiple myeloma after kidney transplantation is uncertain. The current evidence is limited to observational data, with short follow-up time, small events

rates, and single center studies of retrospective designs. There is no conclusive evidence to suggest an increased risk of disease progression to multiple myeloma compared to those without MGUS.<sup>517</sup> However, some have suggested an increased risk of monoclonal B cell lymphocytosis and post-transplant lymphoproliferative disease among those who have MGUS prior to transplantation.<sup>518</sup> Observational data also suggested no differences in the overall risk of graft and patient survival and other complications such as infection between potential candidates with and without MGUS, but the certainty of the evidence of low<sup>518</sup> (Summary Tables: MGUS; Study Limitations).

It is in the Work Group's opinion that patients with acute leukemia and high-grade lymphomas should avoid transplantation until the potential candidate has received potentially curative therapy, achieved remission, and remained cancer free for a period to be determined in consultation with the patient, treating hematologist/oncologist and the transplant program. For patients with myelodysplasias, chronic leukemia and chronic/low-grade lymphomas, the Work Group advises consultation with a hematologist with transplant experience in determining transplant candidacy since many lesions may be deemed to be at high risk for accelerated progression or transformation post-transplant.

### What prior guidelines recommend

The CST guideline also considers thrombophilia and recommends that this is not a contraindication to transplantation.<sup>29</sup> There is also agreement that routine screening for thrombophilia, in the absence of a history of thrombotic events, is not required. Previously published guidelines have not considered patients on either dual antiplatelet or direct acting oral anticoagulant therapy, reflecting the more recent introduction of some of these agents. Similar to the CST guideline, we recommend evaluation of patients for the cause of cytopenia. We are in agreement with the AST guideline<sup>28</sup> with regards to sickle cell disease and with KHA-CARI<sup>27</sup> with regard to MGUS. Thalassemia is not considered in the other guidelines.

For patients with high grade lymphoma, leukemia and post-transplant lymphoproliferative disease, the KDIGO guideline states that transplantation be avoided until the patient has been cancer free for a period of determined duration following discussion with the patient and the hematology/oncology team. In contrast, other guidelines have suggested a definitive period (2 years for CST,<sup>29</sup> KHA-CARI<sup>27</sup> and AST guidelines<sup>28</sup> and 1-3 years for European Renal Best Practice<sup>143</sup>). The difference in guidance reflects the changes in treatment and prognosis in this patient group and emphasizes the need for a multidisciplinary approach. Most of other chronic hematologic disorders are not generally considered in other published guidelines.

### RESEARCH RECOMMENDATIONS

- Future research should identify the best strategy for anticoagulation in the peri-operative period to minimize bleeding or thrombotic events in patients who are identified at an increased risk of graft thrombosis.
- The increasing use of DOACs in patients with advanced kidney disease has significant implications for

transplantation. Future research should address whether the use of DOAC reversal, when available, prior to transplantation is a safe strategy to permit DOAC use in ESKD patients on the transplant waiting list.

- The length of time required after the successful treatment of a hematological malignancy and kidney transplantation is not known for many cancer types. More research is required to understand how newer cancer treatment strategies will affect the time a patient should wait, balancing risk of earlier transplantation with the increased morbidity and mortality associated with dialysis treatment.

### RELEVANT SUPPLEMENTAL MATERIAL

Summary table: Thrombophilia

Summary table: Thrombophilia (quality assessment)

Evidence profile: Thrombophilia testing

Summary table: MGUS

Summary table: Study Limitations (MGUS and non-MGUS)

### SECTION 18: BONE AND MINERAL METABOLISM

18.1: Measure serum parathyroid hormone (PTH) at the time of transplant evaluation (*Not Graded*).

18.2: We suggest not transplanting patients with severe hyperparathyroidism until they are adequately treated (medically or surgically) as per KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) guideline (2D).

18.3: Bone mineral density (BMD) should not be measured as part of the transplant evaluation (*Not Graded*).

### BACKGROUND

Most patients with advanced CKD have disorders of bone and mineral metabolism to some extent. Studies showed that up to 30% of bone mineral density (BMD) is lost within the first six months after kidney transplantation.<sup>519,520</sup> Recent studies have shown that despite this persistent decrease in BMD, trabecular microarchitecture remains normal in long-term transplant recipients suggesting that there is bone recovery occurring late post-transplantation.<sup>521</sup>

No intervention has been proven to prevent fractures after transplantation. Thus, prevention of bone loss is of key importance in this population. The overriding risk for fractures can be appreciated from large registry data. Recent data from Canada suggest that kidney transplant recipients have a 10-year cumulative incidence of hip fracture of approximately 2%, which is lower than previously reported.<sup>522</sup> The same group, however, previously reported in a systematic review that the 5-year cumulative incidence for fracture varied from 0.9% to 27%.<sup>523</sup> American registry data showed that the median 5-year fracture rate was 23%.<sup>524</sup> The variability in reported fracture rate suggests that individual parameters such as age, gender, dialysis vintage and immunosuppressive regimen, have a substantial impact on fracture occurrence. Preventive measures of bone disease and fractures after kidney transplantation include interventions such as vitamin D, bisphosphonates, denosumab and calcitonin. However, the preferred intervention and timing of intervention have yet to be determined.<sup>525</sup>

## RATIONALE

- Kidney transplantation causes considerable bone loss within the first months after transplantation.
- Most patients evaluated for transplantation already have a reduced BMD.
- Risk factors for bone loss and fracture included age, sex, frailty, previous fractures, hyperparathyroidism and cumulative steroid exposure.
- Post-transplant interventions for prevention of bone loss/fracture include vitamin D, bisphosphonates, denosumab and calcitonin which should be used according to individual risk.
- Pre-transplant measurement of BMD does not help in decision-making regarding the use of post-transplant preventative therapies.
- Severe hyperparathyroidism needs to be treated before transplantation.

## Access to transplantation

All patients with progressive CKD suffer from some degree of mineral and bone disorder (CKD-MBD). Treatment of the original kidney disease with steroids, dialysis vintage as well as previous transplants are key risk factors for CKD-MBD. After transplantation, the complexity of bone disease increases further due to immunosuppression.<sup>526</sup> Bone disorders in transplant candidates are complex and span the whole spectrum from high-turnover to adynamic bone disease.

In general, serum biomarkers of bone turnover in patients with advanced CKD or on dialysis have low diagnostic accuracy when compared to the gold standard of bone histology on biopsy.<sup>527</sup> Nevertheless, intact parathyroid hormone (PTH) is determined at routine intervals in most CKD patients because values in the extremes, when used in combination with alkaline phosphatase, potentially help to guide treatment decisions before transplantation. As per recent KDIGO CKD-MBD update,<sup>528</sup> patients requiring PTH-lowering therapy should first receive medical therapy in the form of calcimimetics, calcitriol, or vitamin D analogs. Patients who fail to respond to medical therapy should undergo parathyroidectomy before transplantation. Several reports have shown worsening kidney function if parathyroidectomy is performed after transplantation,<sup>529,530</sup> however, this finding has not been universal.<sup>531</sup> Patients with adynamic bone disease represent an even more challenging population because no intervention has been shown to be effective. Small studies on the use of recombinant PTH for this indication, either on dialysis or after transplantation, were inconclusive.<sup>532,533</sup>

## What prior guidelines recommend

Prior 2013 guidelines from KHA-CARI do not specifically address the topic of bone and mineral metabolism as a part of recipient assessment prior to transplantation.<sup>27</sup>

The AST evaluation guideline suggests measuring serum calcium, phosphorus, and PTH as part of the pre-transplant evaluation. They also recommend pretransplant parathyroidectomy for patients with symptomatic secondary hyperparathyroidism.<sup>28</sup> The 2009 KDIGO guideline on the management of the kidney transplant recipient does not make any recommendations regarding bone and mineral metabolism in the transplant candidate.<sup>30</sup> Similarly, the recent 2017 KDIGO Clinical Practice Guideline update for the diagnosis, evaluation, prevention, and treatment of

CKD-MBD do not have a specific bone disease recommendations for transplant candidates.<sup>528</sup>

The 2005 CST consensus guideline on eligibility for kidney transplantation suggests that calcium, phosphorus and PTH levels should be measured as part of the pre-transplant evaluation (Grade A) and that parathyroidectomy should be considered for those who have failed medical management or have severe, persistent complications of hyperparathyroidism (Grade B).<sup>29</sup> The ERA-EDTA recommended in 2013 that a deceased donor allograft should not be refused only because of uncontrolled hyperparathyroidism in the recipient (Level 1D).<sup>77</sup> The UK Renal Association and the British Transplant Society have no specific directions on bone and mineral disease in their 2011 guidelines about the assessment of the potential kidney transplant recipient.<sup>23</sup>

## RESEARCH RECOMMENDATIONS

- An adequately powered RCT should be conducted to examine the effect of teriparatide (recombinant PTH) on BMD and fracture risk in transplant candidates with adynamic bone disease.
- A large, multicenter cohort study should be conducted to examine the association between pre-transplant PTH level and clinically important post-transplant outcomes.

## SECTION 19: 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*).

## BACKGROUND

Sensitizing events including pregnancy, blood transfusion and prior transplant can lead to the formation of

HLA antibodies in transplant candidates. These antibodies, depending on donor HLA typing and donor potential, may significantly limit a candidate's access to donors. The goal of HLA testing during candidate evaluation and while waitlisted is to estimate the risk of reduced access to potential donors based upon HLA antibodies/HLA typing. In addition, up-to-date testing will ensure the ready availability of the necessary recipient information required to facilitate allocation, perform transplant decision making and donor-recipient immunologic risk assessment at the time of transplant. This section contains clinical recommendations for histocompatibility testing, basic technical interpretation and actions as they relate to immunologic risk assessment of the potential transplant recipient during workup and while waitlisted. The spectrum of potential use of the testing results in allocation and transplant decision making, as well as HLA testing for potential kidney donors, are beyond the scope of this guideline. HLA testing of living and deceased donors, testing to guide allocation or the interpretation of the testing for specific donor-recipient transplant decision making or risk assessment are outside of the scope of this guideline.

### Definitions

- HLA antibody: Any antibody to any HLA antigen or allelic variant of an antigen
- PRA: Panel reactive antibody, the presence of any detectable HLA antibody
- cPRA: Calculated PRA, an estimate of the percentage of donors in a population to whom a transplant candidate has at least one HLA antibody specificity directed

### RATIONALE

Sensitizing events (blood product transfusions including platelets, pregnancy/miscarriage, and prior transplant) as well as clinical events that can impact PRA (including vaccination, significant infection, withdrawal of immunosuppression/non adherence and nephrectomy) should be communicated to the HLA laboratory in a timely fashion.<sup>534-543</sup> A sensitization history is essential for HLA laboratory staff to interpret testing results where antibody levels can be dynamic over time and not always captured with PRA testing while on the waitlist. Documenting and reporting a reliable clinical history is an ungraded recommendation as there are no specific studies addressing the impact of this practice; however it is low cost, of high benefit, and universally accepted as necessary for good clinical practice. Equally importantly, patients with a history of a sensitizing event, even without circulating HLA antibodies detected, should be considered as having potential for memory responses after transplant.<sup>544-546</sup> As such, the immunologic history is also critical for perioperative management of patients.

A precise recommendation for the optimal frequency of HLA antibody testing cannot be made. Laboratories often use their own data to determine the stability of patient results over time to then inform the recommended testing frequency in their unique populations and best identify humoral alloreactivity and potential for memory responses. Protocols widely in use vary in testing frequency from 4 to 24 weeks to have greater reassurance that test

results used in allocation (eg, virtual crossmatching, donor-specific antibody [DSA] assessment) are representative of the patient's immunologic state at the time of transplant. The Work Group acknowledges that both fiscal and clinical considerations (eg, history reliably negative for sensitizing events, whether HLA antibody specificity is used to guide allocation) may reduce the frequency of testing without clinical impact in certain settings. This recommendation for testing frequency is made with the intent that the clinical team liaise with their respective laboratories about the testing frequency that can be supported at their site, which would provide adequate immunologic risk assessment for a given patient. Indeed, testing frequency may also vary between patients at a given center depending on the relevant clinical circumstances. Additional testing after interval sensitizing events is recommended in all patients to accurately document *de novo* as well as memory responses which may in some cases be transient and not readily detectable at the time of the next routinely schedule clinical test. *De novo* HLA IgG antibodies may take up to 6 weeks to form, whereas memory responses can occur within 7-14 days. The timing of testing after a sensitizing event may be sooner than six weeks depending on clinical need. Where financial considerations may prevent regular testing, we encourage a baseline test and repeat testing 2 to 6 weeks after sensitizing events. Where live donors and recipients are reliably shown to be HLA identical at all loci, testing may also be reduced without impacting clinical risk assessment.

There are two basic assays for detecting HLA antibodies: cytotoxic and solid phase. In the former, serum from the recipient is mixed with a panel of cells derived from a population that is immunogenetically comparable to the donor population of interest. The proportion of different cells lysed in the presence of complement estimates the percentage of donors in the population to whom the recipient would be expected to have cytotoxic DSA. These assays are both insensitive<sup>547-549</sup> (i.e., can miss clinically relevant low level antibody including antibodies to HLA-C<sup>550</sup> and DP<sup>551-554</sup> antigens) and non-specific, with frequent false positive results due to irrelevant IgM or non-HLA antibodies.<sup>555,556</sup> Conversely, solid phase assays are engineered to specifically detect HLA antibodies and are significantly more sensitive ensuring lower level and other clinically relevant antibodies are not missed.<sup>547-554,556-562</sup> Although far more specific than cytotoxic assays, recent data suggest that some non-specificity may occur with solid phase assays as well.<sup>563,564</sup> Furthermore, where resources permit the use of single antigen bead assays, full delineation of antibody specificities should be performed. This will permit the calculation of a cPRA and a list of antibody specificities can be compiled for comparison to all future potential donors.<sup>565,566</sup>

Notwithstanding regulatory requirements of any particular jurisdiction, complete HLA typing by molecular methods is optimal for interpreting HLA antibody results and describing donor-recipient mismatch with chronic rejection, *de novo* DSA and graft loss. At a minimum, typing should be completed at loci required to interpret any detectable HLA antibodies (i.e., corresponding to the loci of the detected antibody). Optimally, HLA typing should be completed at all loci (HLA-A, B, C; DRB1, 3, 4, 5; DQA1, DQB1; DPA1, DPB1).

Serologic (cell-based complement dependent) methods of HLA typing do not provide sufficient resolution to adjudicate allele-specific HLA antibodies as DSA, nor to reliably and routinely identify antigens from HLA-C, DQA, DPA1 and DPB1. There are increasing data that antibodies to these loci may also be deleterious after transplant, requiring that they be fully characterized in recipients; this will provide a robust antibody analysis as well as quantify mismatches with future donors.<sup>550-554,567,568</sup> Although no direct comparisons have been made with serologic testing, studies using molecular methods for HLA typing have identified more meaningful metrics associated with transplant outcomes of interest including the ability to more specifically identify donor and recipient differences with the greatest immunologic relevance.<sup>569-575</sup>

Histocompatibility-based quantification of access to transplant lies at the complex intersection of breadth of sensitization (cPRA or PRA) to the local donor pool;<sup>576</sup> the absolute (not relative) number of ABO compatible deceased donors available; the allocation prioritization given to sensitized candidates; the HLA phenotypes and frequencies in the accessible donor population; the potential for living donors; and the access to specialty programs (eg, acceptable mismatch programs,<sup>577,578</sup> prioritization for highly sensitized patients, kidney paired donation, desensitization). It is imperative to utilize a region's own data to determine what level of cPRA (or equivalent) antibody metric is associated with reduced HLA-based access to transplantation.<sup>565,579,580</sup> No specific PRA, cPRA or other equivalent local metric (such as calculated reaction frequency utilized in the UK) threshold should be defined as "highly sensitized" across different populations. HLA-based access to transplant is indeed a continuum of risk and the cPRA level above which access is considered reduced must be considered not only in the context of the metric, but also wait times and waitlist mortality for a given degree of sensitization in the local region.<sup>581</sup> We specifically note that cPRA (or equivalent) itself is not a measure of rejection risk. In regions where a DSA positive donor may be allocated, the cPRA is representative of an increased risk of having DSA whereas it is the presence of DSA that confers the immunologic risk.<sup>578,582,583</sup> We also note the importance of race in HLA phenotype determination and allele frequency,<sup>584-587</sup> and the resultant importance of cPRA (or equivalent metric) being determined in a population with comparable racial/HLA distribution to the recipient's local donor population. Finally, we acknowledge the importance of the loci included in the cPRA calculator in determining the calculated value. It is imperative to include all loci where DSA at those loci would influence transplant decision-making as this will provide the best estimate of transplant access.<sup>566</sup>

Despite associations reported between non-HLA antibodies (eg, anti-angiotensin II type 1 receptor antibody,<sup>588-590</sup> major histocompatibility complex class I chain-related gene A (MICA) antibody,<sup>590-593</sup> anti-endothelial antibodies<sup>594-596</sup> and others), with rejection and or graft loss, the role of these antibodies independent of HLA antibodies in identifying humoral risk pre-transplant remains controversial. We note that these antibodies may augment the effect of HLA DSA in some,<sup>589,597</sup> but not all, patients. In patients where history or clinical status indicates that these antibodies may have clinical relevance, testing should

be performed on a case-by-case basis. However, routine pre-transplant measurement of non-HLA antibodies cannot be recommended.

Complement binding single antigen bead assays test for the presence of high titer anti-HLA IgG1 and IgG3 antibodies capable of binding C1q or C3 *in vitro*, and are not a unique property of the antibody itself.<sup>598-600</sup> Complement-based assays do not accurately quantify antibody titer. Serum dilution can abrogate a positive assay and serum concentration can change a previously negative assay to positive.<sup>598</sup> Additionally, the assay cannot account for variation in target antigen expression on endothelium which may also impact complement activation *in vivo*. For all antibodies of unique specificity detected in a serum, the occurrence of isolated weak/non-complement-binding HLA DSA is rare, estimated to be in the range of 1-5%.<sup>601-604</sup> Readily available single antigen bead metrics (eg, mean fluorescent intensity after serum dilution) may also estimate complement binding capacity in many cases. Conflicting data exist as to the relationship between complement binding assay results and transplant outcomes.<sup>605-607</sup> In the largest study to date<sup>608</sup> pre-transplant DSA conferred higher odds of graft loss compared to pre-transplant C1q assay positivity.<sup>598-609</sup> For the reasons noted above, routine testing in all patients for complement binding HLA antibodies cannot be recommended with the current level of data, but may have a role in specific patient testing algorithms.

For transplant candidates in whom histocompatibility testing indicates a general reduction in transplant access (high cPRA or equivalent) or a specific barrier to a living donor (known DSA), offering increased access to a larger donor pool (eg, national or regional deceased donor sharing or living kidney paired donation) is recommended to increase the chance of finding a DSA-negative donor. Indeed, such HLA antibody avoidance is associated with improved graft survival (comparable to unsensitized recipients) in comparison to transplantation with DSA present.<sup>610-622</sup> However, in those with very high cPRA or fewer absolute donors available in their jurisdiction, desensitization should be explored as an option to achieve transplantation.<sup>623-629</sup> Compared to remaining on dialysis, desensitization has been associated with improved patient survival in the US but not in studies from the UK; the role of desensitization must be considered in any region in the context of the competing risks of additional time on dialysis to wait for a DSA-negative organ.<sup>622,630</sup> No specific desensitization protocol can be recommended based upon the available data; factors in success, regardless of protocol, are the ability of the patient to tolerate immunosuppression, antibody titer, and center experience. Desensitization with anti-B cell agents (eg, rituximab), proteasome inhibitors (eg, bortezomib), alone or in combination with other protocols, may increase transplant opportunities in the short term but, depending on antibody strength, can be associated with shortened long-term survival.<sup>612,623,628,631,632</sup> Therefore, antibody avoidance is still the preferred strategy where patient characteristics and available resources permit.

The KDIGO recommendations presented here are not intended to supplant or replace any local accreditation standards. The American Society for Histocompatibility and Immunogenetics (ASHI) Accreditation Standards should be consulted for those labs under its jurisdiction

([http://www.ashi-hla.org/resource/resmgr/docs/Standards/152017\\_CMS\\_Approved\\_2016\\_ASH.pdf](http://www.ashi-hla.org/resource/resmgr/docs/Standards/152017_CMS_Approved_2016_ASH.pdf)).

The corresponding standards from European Federation of Immunogenetics may be found at:

[https://efi-web.org/fileadmin/user\\_upload/Standardv6.3.pdf](https://efi-web.org/fileadmin/user_upload/Standardv6.3.pdf)

For additional technical recommendations not included in this document, the reader is referred to the relevant sections of ASHI-AST STAR Guideline and The Transplantation Society 2013 Consensus Guideline for antibody testing and clinical management.<sup>633,634</sup>

### What prior guidelines recommend

The most recent comparable guideline for HLA antibody testing are Consensus Guidelines on the Testing and Clinical Management Issues Associated with HLA and Non-HLA Antibodies in Transplantation.<sup>634</sup> In comparison, the current guidance provides specific recommendations as to the nature, frequency and implementation of testing specifically during workup and on the waitlist, and gives updated context for complement binding assay application. The former guidance recommended best practices, with the current guideline providing alternatives to best practices in certain circumstances, while being mindful of international differences in patient populations and resources.

## RESEARCH RECOMMENDATIONS

- Future research should determine the optimal frequency of testing on the waitlist in patients with different risks of sensitization.
- Future research should determine at what resolution of typing is optimal in solid organ transplantation to best quantify donor and recipient mismatch and associated outcomes.
- Future research should determine in which groups of waitlisted patients are non-HLA antibody tests of the greatest incremental benefit in predicting transplant outcomes.

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Steven J. Chadban, BMed (hons), PhD, FAAHMS, FRACP  
 Gregory A. Knoll, MD, MSc, FRCPC  
 Work Group Co-Chairs

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## Appendix: Biographic and Disclosure Information

### WORK GROUP



**Steven J. Chadban, BMed (hons), PhD, FAAHMS, FRACP (Work Group Co-Chair)**, received the University Medal for Medicine at the University of Newcastle and completed physician training in Newcastle, Nephrology training and his PhD at Monash, Victoria, Australia. Following his PhD, Dr. Chadban took a postdoctoral position studying immunology at the

University of Cambridge, UK. He later returned to Monash University to run the Transplantation Program from 1999–2002 before moving to the Royal Prince Alfred Hospital, Sydney, Australia, where he is currently area director of renal medicine, senior staff nephrologist, professor of medicine (nephrology) and leader of the Kidney Node, Charles Perkins Centre at the University of Sydney.

Professor Chadban is past-president of the Transplantation Society of Australia and New Zealand and councilor of The Transplantation Society (Oceania Rep), executive member of ANZDATA and a lead investigator in the CARSK and AusDiab (Australian Diabetes, Obesity and Lifestyle Study) Kidney Studies. Chadban's lab has been continuously supported by grant income from National Health and Medical Research Council since 2004 and he also advises the government as Chair of the Transplant Liason Reference Group (Organ and Tissue Authority) and National Vascular Diseases Advisory Group/CKD (Australian Institute of Health and Welfare). Dr. Chadban is associate editor for *Transplantation* and has authored over 250 publications including in journals such as the *New England Journal of Medicine*, *Journal of the American Medical Association*, *Lancet* and the *Journal of Clinical Investigation*. He has lectured at numerous national and international meetings and his works have been cited 14,197 times with an H-index of 59. His research interests include CKD and ESKD epidemiology; the molecular mechanisms of transplant rejection and CKD, with a focus on innate immunity; and improving outcomes for kidney transplant recipients through clinical trials. Dr. Chadban reported no relevant financial relationships.



**Gregroy A. Knoll, MD, MSc, FRCPC (Work Group Co-Chair)**, is head of the Division of Nephrology at the Ottawa Hospital and full professor of medicine at the University of Ottawa, Canada. He currently holds the University of Ottawa Chair in Clinical Transplantation Research and is a senior scientist with the Clinical Epidemiology Program of the Ottawa Hospital Research Institute. Dr. Knoll

completed his nephrology fellowship at the University of Ottawa followed by a kidney transplant fellowship at the University of Alabama at Birmingham. Following this training he took further graduate work and received a master's degree in Epidemiology. For over 15 years he was the medical director of kidney transplantation at the Ottawa Hospital and he assumed his current position as Nephrology Division head in 2016. Dr. Knoll is a past-president of the Canadian Society of Transplantation. His present research interests involve ongoing studies related to cardiac screening in kidney transplant

candidates, systematic reviews on immunosuppressive strategies, and measuring quality in transplantation. He was the lead author on the Canadian Society of Transplantation consensus guidelines on eligibility for kidney transplantation and he is currently serving as a Work Group member on the KDIGO Clinical Practice Guideline Update on Blood Pressure. Grant/Research Support: Canadian Institutes of Health Research\*. \*monies paid to institution



**Curie Ahn, MD, PhD**, is a nephrologist from Seoul, Korea with a special interest in transplantation. After graduating from the College of Medicine of Seoul National University Hospital (SNUH), she was clinically trained there as an internist and a nephrology specialist. From 1986 to 1988, Dr. Ahn worked as a nephrology fellow at the University of Cincinnati Medical Center. Immediately after until 1992, she studied immunology at The Scripps Research Institute in

La Jolla, California as a research fellow.

After returning to Korea, Dr. Ahn began working at her alma mater, the College of Medicine of SNUH, as a professor of nephrology. Concurrently, she also served as the director of the Division of Nephrology, director of the Transplantation Center, and director of the Transplantation Research Institute of SNUH. Currently, she is the director of the Department of Graduate School of Translational Medicine, and director of the Designed Animal and Transplantation Research Institute in Seoul National University.

Dr. Ahn was the chair of the Korean Society for Transplantation and has actively promoted deceased organ transplantation in Korea. As a leading core member of the Society, she was instrumental in revising the Organ Transplantation Law as well as participating in important organizations that promote deceased organ donation. As the Chief Executive Officer of the Korean Transplantation Registry (KOTRY), she leads the major transplantation cohort project in Korea. Internationally, Dr. Ahn is an executive council member of Women in Transplantation (WIT) and the Declaration of Istanbul Custodian Group (DICG) of the Transplantation Society.

Currently, she is the president of the Korean Xenotransplantation Association (KXA) and a member in the International Xenotransplantation Association (IXA). For the past 10 years, she has also been actively working in Mongolia and Myanmar to advance clinical capacity building in nephrology and transplantation. Dr. Ahn reported no relevant financial relationships.



**David A. Axelrod, MD, MBA, FACS**, has two decades of experience in transplant clinical leadership, business development, health services research and economic assessment. He currently serves as professor of surgery and surgical director of Kidney, Pancreas, and Living Donor Surgery at the University of Iowa. In addition, he is the chairman of the Standards Committee for American Society of Transplant Surgeons (ASTS), past chairman of the Business Practice

Committee and creator of the ASTS Leadership Development Program. He has also served as the Pancreas Committee chairman and counselor for Region 1 for the United Network for Organ Sharing. Dr. Axelrod is a nationally recognized leader in transplant economics and management. Consultant: CareDx. Speaker: CareDx. Stock/Stock Options: CareDx. Other: Spouse is employed by CareDx.



**Bethany J. Foster, MD, MSCE**, is the director of the Division of Pediatric Nephrology at the Montreal Children's Hospital of the McGill University Health Centre and a professor of pediatrics at McGill University, Canada. She is also a clinical epidemiologist and an associate member of the Department of Epidemiology, Biostatistics and Occupational Health at McGill University. Her primary research

interest is in the long-term outcomes of children and young adults with kidney transplants. Dr. Foster has been funded by Canadian Institutes of Health Research and US National Institutes of Health to study immunosuppressive medication adherence and graft outcomes in adolescent and young adult kidney transplant recipients. Her work has been instrumental in determining the association between age and graft failure risk among kidney, liver, and heart transplant recipients. She showed that across all three organ groups, late adolescents and young adults have the highest risk for graft loss of all ages. Dr. Foster also led the successful TAKE-IT study, a multi-center, randomized trial of an intervention to improve immunosuppressive medication adherence in adolescents and young adults.

Dr. Foster is a member of the Board of Directors of the Canadian Society of Transplantation, and a member of the Canadian Donation and Transplantation Research Program. Dr. Foster reported no relevant financial relationships.



**Bertram L. Kasiske, MD, FACP**, obtained his undergraduate training at Michigan State University, East Lansing, MI, USA. He received his medical degree from the University of Iowa, Iowa City, IA, USA and completed an internal medicine residency and fellowship training in nephrology at Hennepin County Medical Center, an affiliate hospital of the University of Minnesota in Minneapolis, USA. Dr. Kasiske is former deputy director of the United States (US) Renal Data System, former Editor-in-Chief of the *American Journal of Kidney Diseases*, and former Co-Chair of Kidney Disease: Improving Global Outcomes (KDIGO). Dr. Kasiske recently stepped down from being director of nephrology at Hennepin County Medical Center for 23 years. He was also the director of the Scientific Registry of Transplant Recipients (SRTR) for 9 years, and still serves as a senior staff member of the SRTR, which is a federal registry of solid organ transplants in the US. His research interests currently focus on living donors, and he has conducted a long term, prospective, controlled study of living kidney donors sponsored by the US National Institutes of Health. He is also currently conducting a pilot study to establish a registry of living kidney and living liver donors in the US. Grant/Research Support: Health Resources and Services Administration, Hennepin Healthcare Research Institute.



**Vijay Kher, MD, DM, FAMS, FRCPE, FIMAS**, is chairman, Division of Nephrology & Renal Transplant Medicine, Medanta – The Medicity, Gurgaon, India and was President of the Indian Society of Nephrology (2016-2017). Prof. Kher has established academic and clinical departments of Nephrology at Shere-Kashmir, Institute of Medical Sciences in Srinagar; Sanjay Gandhi Post Graduate Institute, Lucknow; Apollo Hospitals, New Delhi; Fortis Group of Hospitals NCR, Delhi; and Medanta – the Medicity Gurgaon, during the past 30 years.

His research interests include kidney transplantation (clinical immunosuppression, ABO incompatible transplantation, paired exchange donation, and cost containment), progression of kidney disease, acute kidney injury and glomerulonephritis. An astute clinician, a teacher par excellence and a keen researcher, Prof. Kher combines these assets with a friendly and inclusive demeanor to inspire the nephrology fraternity in India and abroad by his professional dedication, academic excellence and social responsibility.

Dr. Kher has been awarded fellowships by the National Academy of Medical Sciences, India; Royal College of Physicians, Edinburg; Indian Society of Nephrology and received numerous orations from various scientific societies. He has published more than 200 papers in peer reviewed journals, authored 43 book chapters and edited 12 books. Consultant: Biocon Pharmaceuticals, India; Intas Pharmaceuticals, India; Novartis, India; Panacea Pharma, India; Roche, India; Sanofi Aventis, India; Torrent Pharmaceuticals, India. Grant/Research Support: Astellas, India\*; Novartis, India\*; Sanofi Aventis, India\*. Expert Testimony/Scientific Adviser: Biocon Pharmaceuticals, India; Medtronic, India; Novartis, India; Dr. Reddy's Laboratories, India; Roche, India; Sanofi Aventis, India; Torrent Pharmaceuticals, India; Wockhardt, India. Speaker: Biocon Pharmaceuticals, India; Intas Pharmaceuticals, India; JB Chemicals & Pharmaceuticals, India; Johnson and Johnson, India; Novartis, India; Panacea Pharma, India; Pfizer, India; Roche, India; Sanofi Aventis, India. \*monies paid to institution



**Deepali Kumar, MD, MSc, FRCPC, FAST**, is professor of medicine at the University of Toronto, Canada. She is attending physician in the Multi-Organ Transplant Program, Transplant Infectious Diseases service at the University Health Network. Dr. Kumar obtained her medical degree from the University of Ottawa and completed infectious disease training at the University of California-San Diego, USA and McMaster University, Canada. She further acquired a Masters degree with a focus in transplantation at the University of Toronto.

Dr. Kumar's research focuses on immunologic responses to viral infections and vaccines in transplant recipients. She has supervised numerous graduate students and medical residents/fellows. She has authored over 175 manuscripts, editorials, and book chapters in the field of transplantation. For her research she was the recipient of the American Society of Transplantation Clinical Investigator Award (2018) and the Royal College Gold Medal in Medicine (2010). Dr. Kumar is presently the Editor-in-Chief of The American

Society of Transplantation (AST) Handbook of Transplant Infections and associate editor of the 4<sup>th</sup> AST Transplant ID Guidelines. She also serves as associate editor for the journals *Transplantation* and *Clinical Transplantation*. Consultant: Atara Biotherapeutics, Avir Pharma, GlaxoSmithKline, Sanofi, Vitaeris. Grant/Research Support: Atara Biotherapeutics, GlaxoSmithKline, Oxford Immunotec, Qiagen, Roche. Speaker: AbbVie, Merck, Shire.



**Rainer Oberbauer, MD, PhD**, received his MD from the University of Vienna, Austria in 1990 and completed his fellowship in nephrology at Stanford University, USA. He also obtained his MSc in Epidemiology from the Harvard School of Public Health, USA in 2005 and PhD from Semmelweis University, Budapest, Hungary in 2017. Since 2014 he is the director of the Department of Nephrology and Dialysis, Medical University of Vienna.

Dr. Oberbauer has a longstanding clinical and scientific interest in kidney transplantation and he has published numerous experimental as well as clinical papers in this field. He is a member of many international transplant societies, past chair of European Kidney Transplant Association (EKITA), Editor-in-Chief of *Transplant International* and serves on the editorial board of several other major international transplant journals. He has also received several academic awards for his scientific papers, which mainly focus on genetic and clinical epidemiology, and new immunosuppressive strategies following kidney transplantation. Consultant: Astellas, Neovii, Vifor. Grants/Research Support: Amgen\*, Astellas\*, Chiesi\*, Fresenius Medical Care\*. Speaker: Astellas, Chiesi, Neovii, Novartis. \*monies paid to institution

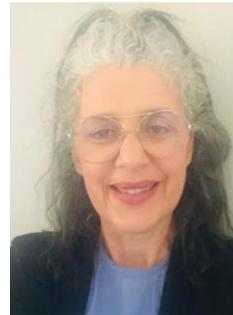


**Julio Pascual, MD, PhD**, is Chief, Nephrology Department and Kidney Transplantation at the Hospital del Mar, Barcelona, Spain, and Professor at Universidad Autónoma, Barcelona. He is also the chief of the Kidney Diseases Research Group at the Biomedical Research Park in Barcelona.

He undertook his residency at the Department of Nephrology, Ramón y Cajal Hospital, Madrid, Spain, before becoming a staff member in 1991. Since 1995, he managed the hospitalization unit within the Kidney Transplantation Program at Ramón y Cajal Hospital, and has had a very active role in the development of new immunosuppressive strategies. Dr Pascual later completed a fellowship in Research and Transplantation at the University of Wisconsin, USA, in 2006-2007.

Dr. Pascual is author/co-author of more than 1000 congress communications and peer-reviewed journal articles, covering all areas of nephrology (cited > 10,000 times, H-index, 48), and has presented at 250 conferences and invited lectures worldwide. Presently he belongs to the Spanish Kidney Research Network (RedinRen), which along with his research group, actively engages in collaborative efforts in nephrology and kidney transplant research. His current main research interests focus on clinical immunosuppression and kidney transplantation in the elderly and frail patient.

Dr. Pascual had been a council-member of the Spanish Society of Nephrology (2008-2014) and the Spanish Society of Transplantation (2011-2014). He was also a board member of the Descartes Group (Developing Education Science and Care for Renal Transplantation in European States), the transplantation group within the ERA-EDTA (2012-2017). Dr Pascual is also a member of the European Best Renal Practices Group and KDIGO work group panel developing guidelines in the area of kidney transplantation; a member of major nephrology and transplantation societies; and is on the editorial boards of several scientific journals. Dr Pascual is currently Editor-in-Chief of the journal *Transplantation Reviews*. Grants/Research Support: Chiesi, Novartis\*. Speaker: Chiesi, Novartis\*. \*monies paid to institution



**Helen L. Pilmore, MD, FRACP**, is an associate professor and a transplant nephrologist from Auckland, New Zealand. She undertook post-graduate training in nephrology in Dunedin, New Zealand and Sydney, Australia, and has been at her current position at Auckland City Hospital since 1999. Since 2008 she has led undergraduate teaching in nephrology at Auckland University Medical School.

Her research interests include the development of chronic allograft dysfunction and in particular, the development and prevention of cardiovascular disease in patients after transplantation. Dr. Pilmore is active in clinical trials in both CKD and kidney transplantation. She is currently the president elect of the Transplant Society of Australia and New Zealand and a previous treasurer of the Australian and New Zealand Society of Nephrology (ANZSN), and chair of the Dialysis, Nephrology and Transplantation sub-committee of the ANZSN. She has also been a panel member to several Caring for Australasians with Renal Impairment (CARI) guidelines with a particular focus on kidney transplantation. Grants/Research Support: New Zealand Heart Foundation Grant - CARSK trial\*. \*monies paid to institution



**James R. Rodrigue, PhD, FAST**, After completing his PhD in Clinical Psychology at the University of Memphis, USA in 1989, Dr. Rodrigue joined the University of Florida faculty and served as director of Transplant Behavioral Health Services until his 2005 recruitment to Beth Israel Deaconess Medical Center in Boston (BIDMC). Currently, he is vice chair for Clinical Research in the Department of Surgery at BIDMC, Director of the Department of Surgery's FIRST Program ([www.bidmcFIRST.com](http://www.bidmcFIRST.com)), and director of the Clinical Scholarship Program for surgical residents. Dr. Rodrigue is professor of surgery and psychiatry at the Harvard Medical School.

Clinically, he is a leader in developing robust behavioral health services to improve the lives of transplant patients and living donors. In 2017, he received the AST's Clinician of Distinction Award in recognition of his outstanding contributions to clinical transplantation.

Currently, Dr. Rodrigue is principal investigator on five federally funded clinical research grants in transplantation. He has been primary investigator or co-investigator on over

30 research grants from the US National Institutes of Health, Health Resources and Services Administration, Patient-Centered Outcomes Research Institute, private research foundations, state agencies, and industry. He has published over 200 peer-review articles, 4 books, and numerous book chapters on organ transplantation and donation, and he has lectured nationally and internationally on the behavioral health aspects of transplantation, living donation, and disparities in transplantation and donation. Dr. Rodrigue has served on the editorial board of *Transplantation*, *Progress in Transplantation*, and *Clinical Transplantation*, and on the NIH Behavioral Medicine study section.

Dr. Rodrigue is actively involved in transplant professional organizations, including the AST, ASTS, The Transplantation Society, and the European Society of Transplantation. He was inducted as an AST Fellow in 2016. His AST service includes serving on the board of directors (2019-present), the inaugural executive committees of three Communities of Practice: Allied Health (2010-2012), Live Donor (2012-2015), and Psychosocial (2013-2016); AST representative on the Joint Steering Committee Workgroup for Live Liver Donation (2012-2013); and co-chair of the Consensus Conference on Best Practices in Live Kidney Donation (2013-2015). He also served on the United Network for Organ Sharing Ethics Committee (2004-2007), Vascularized Composite Allograft (VCA) Committee (2015-2017), and Living Donor Committee (2016-2018), as well as the ASTS Ethics Committee (2009-2012) and Living Donor Committee (2017-2020). Dr. Rodrigue has participated in numerous national and international consensus conferences focused on kidney exchange, transplant program quality and surveillance, non-traditional living donor, living donor follow-up, transplant evaluation criteria, and pediatric deceased donation.

He is an avid Boston sports fan, loves to golf, and enjoys traveling. Speaker: Sanofi.



**Dorry L. Segev, MD, PhD**, is the Marjory K. and Thomas Pozefsky Professor of Surgery and Epidemiology and associate vice chair of Surgery at Johns Hopkins University, USA. He is the founder and director of the Epidemiology Research Group in Organ Transplantation (ERGOT), the largest and most prolific transplant research group in the world. Dr. Segev was the first to demonstrate the survival

benefit of incompatible kidney transplantation across the US, and is responsible for the first HIV-to-HIV transplants in the United States. He studied computer science and electrical engineering at Rice University before attending medical school, and with a graduate degree in biostatistics, Dr. Segev focuses on novel statistical and mathematical methods for simulation of medical data, analysis of large healthcare datasets, and outcomes research.

Dr. Segev has published almost 500 peer-reviewed research articles in top medical and scientific journals. Reflecting his contributions to the field, he was awarded the AST's Clinical Science Investigator Award. Reflecting the creativity and broad reach of his contributions, he recently received the prestigious Global Thinker Award from Foreign Policy Magazine. His work has directly influenced policy, including two Congressional bills (the Norwood Act for kidney exchange and the HOPE Act for HIV-to-HIV transplants), and is

regularly featured in widely read media including *TIME* magazine, *Wall Street Journal*, and the *New York Times*. Dr. Segev reported no relevant financial relationships.



**Neil S. Sheerin, BSc, PhD, FRCP**, is the professor of nephrology at Newcastle University, UK, a consultant nephrologist at the Freeman Hospital, Newcastle upon Tyne and co-director of the National atypical HUS service. He moved to Newcastle in 2007 from Guy's Hospital, London, UK where he was a senior lecturer in Renal Medicine and before that a Wellcome Trust Fellow. His laboratory research is focused on immune mediated renal injury, with a specific

interest the role of the complement system in native and transplant kidney disease, and mechanisms of tissue fibrosis. His clinical interests include kidney transplantation, complement-mediated kidney diseases and the management of patients with progressive CKD. Consultant: Alexion Pharmaceuticals\*. Grants/Research Support: GlaxoSmithKline\*. Speaker: Alexion Pharmaceuticals\*. \*monies paid to institution



**Kathryn J. Tinckam, MD, MMSc, FRCPC, FAST**, is the medical director of the University Health Network (UHN) Regional Histocompatibility Laboratory, the director of Quality Improvement and Innovation for the UHN Transplant Program, and a transplant nephrologist at the UHN. Dr. Tinckam is an associate professor of Medicine and Laboratory Medicine at the University of Toronto, Canada, and currently the vice president of the

Canadian Society of Transplantation. Recently, she was also the medical advisor for Transplantation Canadian Blood Services, supporting interprovincial listing and allocation, and the Canadian Transplant Registry clinical programs. Dr. Tinckam is now the chair of the National Kidney Transplant Advisory Committee supporting Kidney Paired Donation Program and the National Highly Sensitized Patient Registry. She received her undergraduate medical education and Internal Medicine training at the University of Manitoba, Canada; her nephrology and transplant training at University of British Columbia, and completed a fellowship in Histocompatibility and Immunogenetics at Harvard University. Her clinical and research interests encompass the standardization of HLA laboratory testing, clinical programs to increase transplant in highly sensitized patients, innovation in allocation to improve long-term graft outcomes, and the contribution of HLA antibodies to antibody mediated rejection pathways and outcomes. Dr. Tinckam reported no relevant financial relationships.



**Germaine Wong, MD, PhD**, is a transplant nephrologist and director of the Western Renal Service at Westmead Hospital, Sydney, Australia with special interests in transplantation and clinical epidemiology. Dr. Wong is also National Health and Medical Research Council (NHMRC) Career Development Research Fellow and principal research fellow at the School of Public Health, University of Sydney. Her main area of research interests

include transplant epidemiology, cancer and CKD, life-course epidemiology, social ethics in organ donation and allocation, decision analytical modelling, health economics, population health research, and quality of life studies in kidney transplant patients. Grant/Research Support: National Health and Medical Research Council (NHMRC), NHMRC Career Development Fellowship, NHMRC Medical Research Future Fund.

## KDIGO CHAIRS



**Michel Jadoul, MD (Work Group Co-Chair)**, received his MD degree in 1983 at the Université Catholique de Louvain (UCL), Brussels, Belgium. Dr. Jadoul trained in internal medicine and nephrology under the mentorship of Professor Charles van Ypersele de Strihou. He has served as chair at the Department of Nephrology of the Cliniques Universitaires Saint-Luc since 2003 and is currently full clinical professor at UCL. Dr. Jadoul's clinical activities focus on the follow-up of hemodialysis and CKD patients, and his main research interests include  $\beta$ 2-microglobulin amyloidosis, hepatitis C, and other complications (eg, falls, bone fractures, sudden death) in hemodialysis patients, as well as cardiovascular complications after kidney transplantation and various causes of kidney disease (eg, drug-induced).

Dr. Jadoul has co-authored over 230 scientific papers, most of them published in major nephrology journals. He is currently serving as a theme editor of *Nephrology Dialysis Transplantation*, and he is also a country co-investigator for the Dialysis Outcomes and Practice Patterns Study (DOPPS) (2001–present). In 2008, he received the international distinguished medal from the US National Kidney Foundation. He was previously a member of the KDIGO Executive Committee (2010–2015) and the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Council (2013–2016). Presently, Dr. Jadoul is a KDIGO Co-Chair. Consultant: Astellas\*, AstraZeneca\*, GlaxoSmithKline\*, MSD\*, Vifor Fresenius Medical Care Renal Pharma\*. Grant/Research Support: Alexion\*, Amgen\*, Janssen-Cilag\*, Otsuka\*, Roche\*. Speaker: Abbvie\*, Amgen\*, Vifor Fresenius Medical Care Renal Pharma\*, Menarini\*, MSD\*. Travel: Amgen\*. \*monies paid to institution

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**Wolfgang C. Winkelmayer, MD, MPH, ScD**, is the Gordon A. Cain Chair of Nephrology and professor of medicine at Baylor College of Medicine in Houston, USA. Dr. Winkelmayer received his medical degree (1990) from the University of Vienna, Austria, and later earned a Master of Public Health in health care management (1999) and a Doctor of Science in health policy (2001) from Harvard University. He then spent 8 years on the faculty of Brigham and Women's Hospital

and Harvard Medical School, where he established himself as a prolific investigator and leader in the discipline of

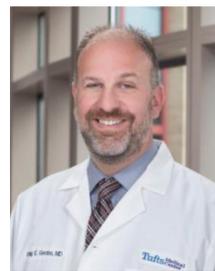
comparative-effectiveness research as it pertains to patients with kidney disease. From 2009 to 2014, he was the director of clinical research in the Division of Nephrology at Stanford University School of Medicine, Palo Alto, USA. He assumed his current position as chief of nephrology at Baylor College of Medicine in September 2014. His main areas of research interest include comparative effectiveness and safety research of treatment strategies for anemia, as well as of various interventions for cardiovascular disease in patients with kidney disease. Dr. Winkelmayer is a member of the American Society of Clinical Investigation. His clinical passion lies in providing quality kidney care to the predominantly disadvantaged and un(der)insured population in the public safety net health system of Harris County, Texas. Dr. Winkelmayer has authored over 300 peer-reviewed publications, and he has a particular interest in medical publishing. He currently serves as an associate editor for the *Journal of the American Medical Association*, was a co-editor of the *American Journal of Kidney Disease* from 2007 to 2016, and has been appointed to several other editorial boards of leading nephrology and epidemiology journals. He also volunteers his time toward important initiatives of the American Society of Nephrology (eg, Public Policy Board) and he joined KDIGO volunteer leadership as an executive committee member in 2015 and has served as its Co-Chair since 2016. Consultant: Akebia, Amgen, AstraZeneca, Bayer, Daichii-Sankyo, Relypsa, Vifor Fresenius Medical Care Renal Pharma.

## EVIDENCE REVIEW TEAM



**Ethan M. Balk, MD, MPH**, is associate director of the Center for Evidence Synthesis in Health and Associate Professor of Health Services, Policy and Practice (Research) at Brown University School of Public Health in Providence, USA. He has been project director of the ERT and has collaborated on numerous KDIGO guidelines, and prior to that on KDOQI guidelines since 2000. As

project director for this guideline, he played a pivotal role in providing methodological expertise in the guideline development process and assisted in the collection, evaluation, grading, and synthesis of evidence and the revisions of the final evidence report. Dr. Balk also provided methodological guidance and training of Work Group members regarding topic refinement, key question formulation, data extraction, study assessment, evidence grading, and recommendation formulation. His primary research interests are evidence-based medicine, systematic review, clinical practice guideline development, and critical literature appraisal. Dr. Balk reported no relevant financial relationships.



**Craig E. Gordon, MD, MS**, is associate professor of medicine at Tufts University School of Medicine and is a member of the division of nephrology at Tufts Medical Center, USA. Dr. Gordon graduated from New York University School of Medicine and received his master's degree from the Tufts University Sackler School of Graduate Biomedical Sciences in

Clinical Care Research. Dr. Gordon previously served as the assistant project director of the ERT for the 2008 KDIGO clinical practice guideline on Hepatitis C in CKD. He served

as the associate director of the evidence review team and assistant project director for the 2018 Hepatitis C guideline update and the 2020 KDIGO Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation. Dr. Gordon provided methodologic expertise to the Work Group during the guideline development process and assisted in the collection, evaluation, grading, and synthesis of evidence for the guideline, as well providing guidance to Work Group members in the areas of topic refinement, key question formulation, data extraction, study assessment, evidence grading, and recommendation formulation. His primary research interests are in the management of hepatitis C in patients with CKD, thrombotic microangiopathy, polycystic kidney disease, as well as evidence-based medicine and systematic review related to other areas of nephrology. Advisory Board: Abbvie. Consultant: Alexion Pharmaceuticals.

**Amy Earley, BS**, was a research associate with the ERT from the Center for Evidence Synthesis in Health at Brown University in Providence, RI, USA. She was key in conducting the evidence review, which included running searches, screening, data extraction, drafting of tables and methods sections, proofing of guideline drafts, and critical literature appraisals. She also held an important role in coordinating the guideline development activities within the ERT, especially in the development of the evidence reports for all guidelines. In addition

to her role with the ERT during the time of this guideline, Ms. Earley worked as a Senior Research Associate at Evidera, where she was a leading researcher and principal investigator on qualitative and quantitative meta-research projects (meta-analyses and indirect treatment comparisons). As of January 2019, she is the Guideline Development Director for KDIGO. Ms. Earley reported no relevant financial relationships.



**Valerie Rofeberg, ScM**, is a biostatistician in the Department of Cardiology at Boston Children's Hospital. Her research focuses on the links between congenital heart disease and neurodevelopment in young children and adolescents. Previously, Mrs. Rofeberg worked as a biostatistician and senior research associate in the Center for Evidence Synthesis in Health at Brown University. There, she assisted in conducting systematic reviews and meta-analyses, as well as the development and delivery of training materials in systematic review methodology. On this guideline, Valerie was a member of the ERT, and as such played a role in the collection, evaluation, grading, and synthesis of the evidence. Mrs. Rofeberg reported no relevant financial relationships.