THE REPUBLIC OF UGANDA
MINISTRY OF HEALTH

INTEGRATED CHRONIC KIDNEY DISEASE MANAGEMENT GUIDELINES

FOR UGANDA

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UGANDA KIDNEY FOUNDATION
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CONTENTS

Purpose of the integrated CKD management guidelines ix

Foreword vii

Lead team, work group, peer review and support group membership viii

Executive Summary x

Abbreviations and Acronyms xii

CHAPTER 1 - QUICK REFERENCE GUIDE TO THE CKD GUIDELINES 1

1.1 Definition of chronic kidney disease (CKD) 1

1.2 Spectrum of kidney disease 1

1.3 Grading of Kidney disease 2

1.4 Risk factors of CKD 3

1.5 Prevention of CKD 4

1.6 Screening & diagnostic approaches 4

1.7 Principles of management 5

CHAPTER 2 - BURDEN OF KIDNEY DISEASE IN UGANDA 6

2.1 Prevalence of chronic kidney disease (CKD) 6

2.2 Risk Factors for CKD 7

2.3 Mortality and morbidity from CKD 7

2.4 Kidney Replacement Therapies 8

CHAPTER 3 - SCREENING AND DIAGNOSIS OF CKD 10

3.10 Screening of CKD 10

3.11 Objectives of screening 10

3.12 Who should be screened? 10

3.13 Screening tools. 10

3.14 Frequency of screening 11

3.20 Diagnostic evaluation of CKD 12

3.21 Criteria for diagnosis of CKD 12

3.22 Steps in diagnosing CKD 12

Serum creatinine, electrolytes, bicarbonate 23

CHAPTER 4 - MANAGEMENT OF CKD 17

4.1 Principle 1: Stage and risk stratify all CKD patients to determine the aims and level of care. 17

4.2.0 Principle 2: Health educate & promote lifestyle modification 18

4.2.1 Health Educate 18

4.2.2 Promote lifestyle modification 18

4.3.0 Principal 3: Slow progression of CKD 22

4.3.1 Treatment of Proteinuria 22

4.3.2 Identify and manage the underlying cause / risk factors 23

4.3.2.1 Hypertension 23
4.3.2.2 Diabetes Mellitus 25
4.3.2.3 Heart failure 28
4.3.2.4 Lipid metabolism abnormalities in CKD 30
4.3.2.5 Sickle cell disease in CKD 31
4.3.2.6 Infections 32
4.3.2.7 Autoimmune Diseases 35
4.4.0 Principle 4: Screen and manage complications 36
4.4.1 Anemia in CKD 36
4.4.2 Chronic kidney disease and mineral and bone disorder (CKD-MBD) 38
4.4.3 Metabolic acidosis in CKD 38
4.4.4 Hyperkalemia 39
4.4.5 Volume overload 40
4.4.6 Management of Uremic Complications in CKD 41
4.4.6.1 Malnutrition 41
4.4.6.2 Uremic neuroppathy 41
4.4.6.3 Pericarditis 42
4.5.0 Principle 5: Identify and prepare patients for kidney replacement therapy or comprehensive conservative care. 43
4.5.1 When to refer patients to a nephrologist or regional and national referral Hospitals. 43
4.5.2 Preparation for kidney replacement therapy 44
4.5.2 Comprehensive conservative care 45
CHAPTER 5 – MANAGEMENT OF CKD IN WOMEN AND CHILDREN 46
5.1 Special consideration in women 46
5.2.0 Special consideration in children 50
5.2.1 Etiology of CKD in children 50
5.2.2 Diagnosis of CKD in Children 50
5.2.3 Risk stratification of CKD in Children 51
5.2.4 Management of CKD in children 52
5.2.5 Management of complications of CKD in children 54
References 58

LIST OF TABLES

Table 1: Urine dipstick equivalence of UACR[4] 3

Table 2: Prevention of CKD at different levels of care 4

Table 3: Screening tests available at different levels of healthcare in Uganda 11

Table 4: The equivalence of urine albumin-creatinine ratio (UACR) and urinary dipstick protein. 14

Table 5: Test recommended for CKD patients at different levels of care 14

Table 6a: Management of CKD at different level of the health care system 17

Table 6b: Management of CKD at different level of the health care system 18

Table 7: Lifestyle consideration in patients with CKD 19

Table 8: Detailed physical activity recommendations in patients with CKD 21

Table 9: Considerations in the use on antihypertensive agents for BP lowering in CKD 24

Table 10: Choice of antidiabetic agents used in diabetic patients with CKD. 27

Table 11: Consideration of Pharmacotherapy in heart failure patients with CKD 28

Table 12: ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dl) 30

Table 13: Management of dyslipidemia in CKD 30

Table 14: Management of severe hyperkalemia (K> 6.5mmol/l) 40

Table 15: Primary providers of various domains of care in the multidisciplinary team management during comprehensive conservative kidney failure care. 45

Table 16: Fetal Risks of Common Kidney Medications in Pregnancy and Suggested Alternatives 49

Table 17: Common cause of kidney disease in children 50

Table 18: Plasma pediatric creatinine reference intervals (2.5th to 97.5th percentiles) 51

Table 19: Supplementary Table S1. Antiretroviral dose adjustments in chronic kidney disease according to creatinine clearance (CrCl) 61

Table 20: Supplementary Table S2. Antituberculous medication dose adjustments in chronic kidney disease. 63

LIST OF FIGURES

Figure 1: Spectrum of kidney disease:[3] SCr: Serum creatinine; eGFR: estimated glomerular rate 1

Figure 2: Grading of kidney disease: CKD: Chronic Kidney Disease; eGFR: estimated glomerular rate. Adapted from: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. 2

Figure 3: Risk factors in Low- and middle-income countries: 3

Figure 4: Screening tools for CKD in Low- and Middle-Income Countries. 4

Figure 5: Management strategies for CKD at different levels of the healthcare system guided by the stage of CKD. 5

Figure 6: Map of Uganda showing regional prevalence of kidney disease 6

Figure 7: Domains of comprehensive conservative care. CKD- Chronic Kidney Disease 9

Figure 8: Screening tools for CKD in Low- and Middle-Income Countries. 10

Figure 9: Clinical diagnosis of chronic kidney disease 12

Figure 10: Clinical features of chronic kidney disease 13

Figure 11: Recommended screening algorithm for chronic kidney disease (CKD) 15

Figure 12: The foods recommended in patients with CKD. 20

Figure 13: Self-management model. [19] Adapted from Slev, Vina Et al, 21

Figure 14: Suggested algorithm for management of hypertension in CKD 24

Figure 15: Treatment Algorithm for Selecting Antihyperglycemic Drugs for People with Type 2 Diabetes and CKD. 26
Figure 16: Targets for glucose control in CKD patients with diabetes mellitus 27
Figure 17: Algorithm for the management of heart failure in CKD 29
Figure 18: Clinical manifestations and management strategies of sickle cell disease in CKD. 31
Figure 19: Recommendations for kidney disease screening and monitoring in HIV-positive adults. 33
Figure 20: Management of chronic hyperkalemia in CKD. 39
Figure 21: Indications for urgent initiation of Hemodialysis include: 44
Figure 22: Domains of comprehensive conservative care. CKD- Chronic Kidney Disease 45
Figure 23: Fertility-Related Abnormalities in WomenWith CKD 46
Figure 24: Recommended contraception methods in women with CKD 47
Figure 25: Management of pregnant women with Chronic Kidney Disease 48
Figure 26: Multi-disciplinary team required in management of CKD in children 52
Figure 27: Approach to diagnosis and management of anaemia in chidren with CKD 55

Foreword

The Ministry of Health, Uganda and its partners continue to prioritize non-communicable disease (NCD) prevention and management for the Ugandan population. The vision of our health system is "a responsive, resilient and people centered health system that protects and promotes the health and wellbeing of all the people". The purpose for which these integrated chronic kidney disease (ICKD) guidelines have been developed clearly espouses the spirit of our Ministry of Health vision.

These guidelines have been put in place to guide policymakers, health practitioners and providers at different tiers of care on what they need to do to prevent CKD from occurring. They also provide guidance on early detection and management to minimize disease progression and improve the survival rate as well as the quality of life.

It has been clearly documented that in our region many people get exposed to CKD at various stages of life without their knowledge. Even those who eventually get diagnosed with CKD present very late when chances of reversing their condition are limited.

The CKD predisposing and risk factors have not been comprehensively elaborated to the health care providers. There is also no doubt that the health worker's capacity to screen and sensitize for CKD prevention and management has been grossly lacking. The referral system for management of CKD has not been streamlined.

These guideline will be used as a treatment guide and will provide training materials for health workers seeking to integrate kidney prevention, screening, diagnosis, and management in their continuum of care. It will be used by health service managers in identifying diagnostics, supplies, devices, and equipment required for prevention and management of CKD. It is the hope of the Ministry of Health that this guideline will assist health care providers, health service managers, planners, and partners as we seek to improve the quality of CKD prevention and care in Uganda and beyond.

I wish to appreciate the team of experts that drafted this guideline from scratch, the stakeholders and the Ministry of Health technical teams who reviewed and endorsed it for use.

In a special way, I wish to thank Healthy Heart Africa (HHA) for funding this important undertaking and the Uganda Protestant Medical Bureau (UPMB) through which the funding was delivered and coordinated in collaboration with the NCD Department of the Ministry of Health.

I take the honor of inviting you to use it.

Hon Dr. Aceng Jane Ruth Ocero
Minister of Health, Uganda

LEAD TEAM, WORK GROUP, PEER REVIEW AND SUPPORT GROUP MEMBERSHIP

1 Lead Team

Robert Kalyesubula, MD, FISN, FCP (ECSA) PhD, FRCP (London)
Makerere University College of Health Sciences

James Kayima, MBChB, MMED, FRCP(London), FCP(ECSA), PhD
Uganda Heart Institute, Makerere University College of Health Sciences

William Lumu, MBChB, MMED, Msc. Dm, PhD
Mengo Hospital, Uganda Christian University, Uganda Non-Communicable Disease Alliance, Uganda Diabetic Association

2 Working Group

Gerald Mutungi, MBChB, MPH, MHSM
Ministry of Health, Dept. of Non-Communicable Diseases

Frank Mugabe Rwabinumi, MBChB, MSc. HSM, MBA, Dip TB control &management/Epidemiology
Ministry of Health, Dept. of Non-Communicable Diseases

James Ocakacon, MBChB, MPH
Ministry of Health, Dept. of Non-Communicable Diseases

Susan Nakireka Tumwesigye, MBChB, MMED, FCP (ECSA)
Mengo Hospital, Uganda Christian University, Uganda Non-Communicable Disease Alliance, East Africa Non-Communicable Disease Alliance

Evelyn Nabankema, MBChB, DPPM, MIPH, MMED, FCP (ECSA)
St Francis Hospital Nsambya, Mother Kevin Post Graduate School Uganda Martyrs University

Dan Oriba Langoya, MBChB, MMED
St Mary's Hospital Lacor, Gulu University

Rose Muhindo, MBChB, MMED, ISN scholar
Mbarara University of Science & Technology

Asad Muyinda, MBChB, MRCP(UK), FCP (ECSA)
Mbale Regional Referral Hospital

Irene Nakabugo Katumba, MBChB, MMED
St Francis Hospital Nsambya

3 Peer review members

Grace Kansiime, MBChB, MMED
Mbarara University of Science & Technology

Gyagenda Joseph Ogavu, MBChB, MMED, FCP (ECSA), Clinical Nephrology (Fortis India), MBA
St Francis Hospital Nsambya, Mother Kevin Post Graduate School Uganda Martyrs University, Uganda Kidney Foundation

John Wilson Etolu, MBChB, MMED, PgDp.P/Admin.
Soroti University

Daniel Kiggundu, MBChB, MMED, FCP (ECSA), FISN
Kiruddu National Referral Hospital

Anthony Batte, MBChB, MMED, FISN
Makerere University College of Health Sciences

Carolyn Aujo, MBChB, MMED, FISN
Mulago National Referral Hospital

Gyaviira Makanga, MBChB, MMED, Msc Nephrology, Certificate Clinical Nephrology
Makerere University College of Health Sciences, Bank of Uganda medical department

Peace Bagasha, MBChB, MMED
Mulago National Referral Hospital, Uganda Kidney Foundation

4 Coordination Team

James Mwesigwa Lwanga, BSc, MSc. Health Services, MSc quality & patients' safety in health
Uganda Protestant Medical Bureau(UPMB)

David Balikitenda, BSc. Stat, PGD M&E, MSc.Epid.
Uganda Protestant Medical Bureau(UPMB)

Eva Gakumba Kadimba, BA Educ, PGD M&E, BSc. Public Health, MSc. HSM
Uganda Protestant Medical Bureau(UPMB)

Hillary Alima, MBChB, MPH
Uganda Protestant Medical Bureau(UPMB)

Tonny Tumwesigye, MBChB, DPH, MSc. PH
Uganda Protestant Medical Bureau (UPMB)

Purpose of the integrated CKD management guidelines

Chronic kidney disease (CKD) is one of the leading causes of morbidity and mortality worldwide with one in every ten adults living with it. Although often neglected, CKD is one of the key non-communicable diseases. Unfortunately, most of the patients with CKD are not aware of their condition; and screening for it in the general population is not cost effective. Additionally, most healthcare workers in Uganda do not appreciate when to screen for the condition; and their capacity to manage and diagnose chronic kidney disease is limited. Consequently, over 50% of kidney disease patients are diagnosed with advanced disease necessitating urgent and mostly long-term therapies ranging from specialized medicines through to hemodialysis and kidney transplant which are costly and difficult to sustain.

It is therefore imperative that we have a guideline that helps us to screen for kidney disease in those persons at risk, identify those with disease and offer them appropriate management.

The purpose of this guideline is to provide guidance on early screening for CKD among those who are at risk, identifying, staging, and then ultimately providing management to those with the disease.

Throughout the guidelines, emphasis is made on what resources are available at the various levels of care in Uganda and the kind of activities that can be undertaken at each level. They also define the responsibility of practitioners at each level from the lowest to the highest on what to manage and when to refer to higher centers ofcare.

It is our hope that this guideline will help in early identification of CKD and guide the clinicians in providing a comprehensive package to those who are affected by this condition. Ultimately, we hope that they will improve the health outcomes among those who suffer from CKD.

These are neither standards nor policies. They are a tool to help healthcare workers provide patients with CKD early interventions consistent with their individual needs and resources, priorities, and concerns of their families. They do not by any means replace the role of healthcare workers in their own capacity. The healthcare workers are therefore, encouraged to use the latest information available to provide the best care for patients with CKD.

Executive Summary

Chronic kidney disease (CKD) is one of the fastest growing chronic diseases in the world. It is the 10th leading cause of morbidity and mortality globally, with an estimated prevalence of 13.4% in the adult population. By the year 2040, CKD is projected to be the 5th leading cause of years of life lost (YLL).

Chronic kidney disease is an important public health challenge in Sub-Saharan Africa with an estimated prevalence of 13.9%. In Uganda, epidemiological studies have shown a prevalence of 2% to 9% in the community. Additionally, CKD is among the top 10 causes of death in Uganda with a case fatality rate of 21% among admitted patients. While it is much easier to manage CKD in the earlier stages, most people are not aware that they have CKD, and therefore present with advanced disease. With the astronomical cost involved in care of advanced CKD, including expensive medicines, dialysis and transplant services, many countries in Africa including Uganda struggle to provide care to their people.

In Sub-Saharan Africa, the best way to reduce the CKD burden lies in amplifying efforts to identify the unique risk factors associated with kidney disease, avail tools for early diagnosis and treatment and enhance the capacity of health workers in managing CKD at all levels of care. It is also important to provide health workers with guidance that will improve decision making in screening and management of CKD.

Therefore, Uganda Protestant Medical Bureau (UPMB) in partnership with Healthy Heart Africa-Astra Zeneca (HHA) supported by Ministry of Health has developed the first integrated chronic kidney disease (ICKD) guidelines for Uganda. The ICKDs are premised on primary prevention that aims at appropriate prevention and management of CKD risk factors, secondary prevention that embraces early diagnosis, timely referral, and delay of progression; and tertiary prevention aimed at managing complications.

Aims of ICKD guidelines

1 To help healthcare workers to identify, detect, and manage patients with and at risk of chronic kidney disease (CKD) from the community to national referral hospital level, as well as outline criteria for appropriate care.
2 To ensure standardized treatment and strengthen linkage for persons living with CKD and their families.

Target

All health workers in the primary, secondary, and tertiary care facilities in Uganda from the community to the national referral hospitals.

Methodology

This guideline was developed from a review of information from published international guidelines: regional, and local data on the topic of CKD and its comorbidities. A synthesis of this information was done with prioritization for data from low and middle income (LMIC) countries because these are more relevant to the Uganda setting. This guidance was contextualized to the locally available resources and technologies.

Scope

This ICKD guideline covers the burden of CKD in Uganda, screening and diagnosis of CKD, management of CKD, management of CKD in special groups and algorithms on management of some comorbid conditions in CKD.

How to use the ICKD guidelines

While the management of CKD needs a multipronged approach to control comorbidities and prevent the progression of CKD and its associated complications, care should be individualized according to the patients' presentation and available resources and technologies. In this guideline, we provide guidance on what should be done at the different levels of health care. Recommendations in this guideline are based on class evidence from randomised controlled trials (RCTs) while suggestions are based on other evidence other than RCTs.

Recommendation

Inasmuch as the ICKD guidelines provides guidance on screening and management of CKD, they do not by any means replace the discretion of healthcare workers in the care of individual patients.

Abbreviations and Acronyms

ACEi: angiotensin-converting enzyme inhibitor(s)

ACR: albumin-to-creatinine ratio

AKD: Acute kidney disease

AKI: Acute kidney injury

ASCVD: Atherosclerotic cardiovascular disease

ARB: Angiotensin II receptor blocker

CCC: Comprehensive conservative care

Cr: Creatinine

CKD: Chronic kidney disease

CKD-MBD Chronic kidney disease-mineral and bone disorder

CVD Cardiovascular disease

eGFR: Estimated glomerular filtration rate

GLP-1 RA: Glucagon-like peptide receptor agonists

GN: Glomerulonephritis

HIV: Human immunodeficiency virus

HD: Hemodialysis

i.v. Intravenous

KDIGO: Kidney Disease: Improving Global Outcomes

KRT: Kidney replacement therapy

LMIC Low- and-middle-income countries

MI: Myocardial infarction

NSAIDS: Nonsteroidal anti-inflammatory drugs

SCr: Serum creatinine

SLE: Systemic lupus erythematosus

SGLT2i: Sodium-glucose cotransporter-2 inhibitor(s)

T2D: Type 2 diabetes

UAC: Urine albumin concentration

UACR: Urine albumin-to-creatinine ratio

CHAPTER 1 - QUICK REFERENCE GUIDE TO THE CKD GUIDELINES

This chapter presents the summary of the subsequent chapters including definition, spectrum of chronic kidney disease, grading, risk factors, prevention, screening, diagnosis, and principles of management of CKD. It is intended to provide a quick source of information for users of the guideline.

1.1 Definition of chronic kidney disease (CKD)

CKD is defined by the presence of kidney damage or decreased kidney function for three or more months, irrespective of the cause.

- **Decreased kidney function** - estimated glomerular filtration (eGFR) rate of less than 60 mL/min per 1.73 m^2
  AND/OR
- Kidney damage - evidence of structural damage or other markers of functional kidney abnormalities including proteinuria, pathologic abnormalities detected by histology or inferred by imaging and patients with functioning kidney transplants.

1.2 Spectrum of kidney disease

Kidney disease is defined based on functional or structural changes to the kidney. It is comprised of acute kidney injury (AKI), acute kidney disease (AKD) and chronic kidney disease (CKD). Details are shown in figure 1.

Acute kidney injury (AKI) occurs when there is an abrupt loss of kidney function and is defined based on an increase in serum creatinine or reduction in urine output usually occurring within 7 days of an insult. AKI can further be subdivided into transient AKI which is the rapid reversal of AKI within 48 hours and persistent AKI which is the reversal of AKI within 2–7 days.

Acute kidney disease (AKD) follows AKI and can occur either in the context of subclinical AKI where there is gradual worsening in kidney function over time or following AKI when there is incomplete recovery of kidney function. AKD occurs after a week up to 3 months.

Chronic kidney disease (CKD) occurs when there is loss of kidney function or structural damage that persists for more than 3 months.

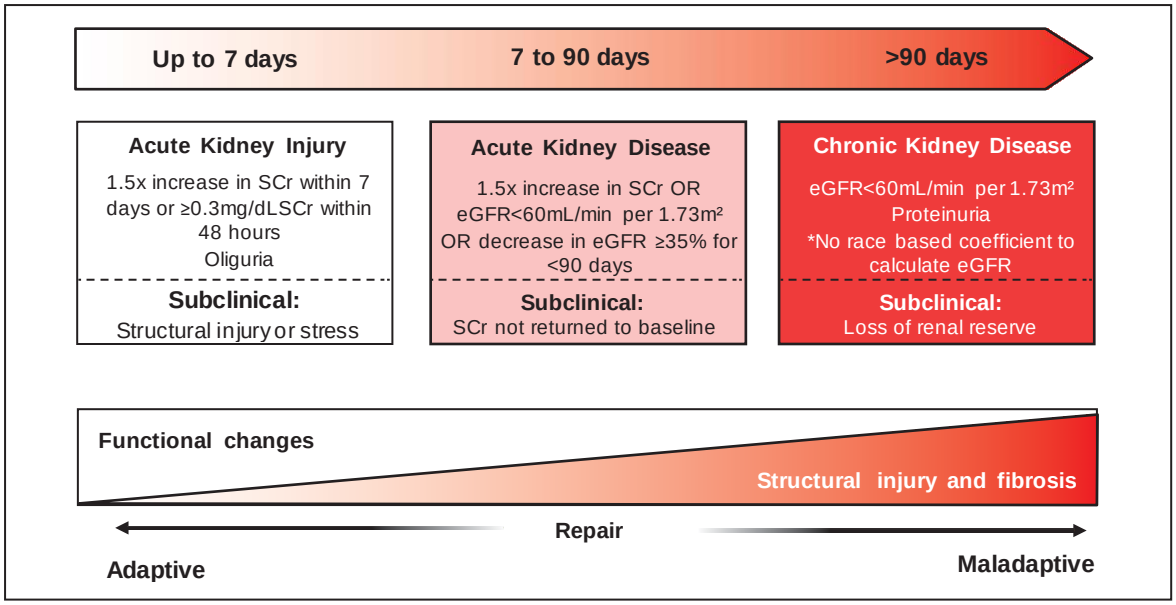


Figure 1. Spectrum of kidney disease:[3] SCr: Serum creatinine; eGFR: estimated glomerular rate
Adapted from: Batte A, Conroy LA, Langoya DO, Kalyesubuula R et al.
Accessed at https://africa-health.com/wp-content/uploads/2023/05/10-Kidney-Disease-in-Africa.pdf

1.3 Grading of Kidney disease

Grading of chronic kidney disease requires an estimation of the glomerular filtration rate (derived from serum creatinine or cystatin C) and the measurement of albuminuria. According to Kidney Disease: Improving Global Outcomes (KIDGO) CKD work group, kidney disease is graded according to eGFR (G1 to G5) and severity of albuminuria (A1, A2, A3) as shown in figure 2.

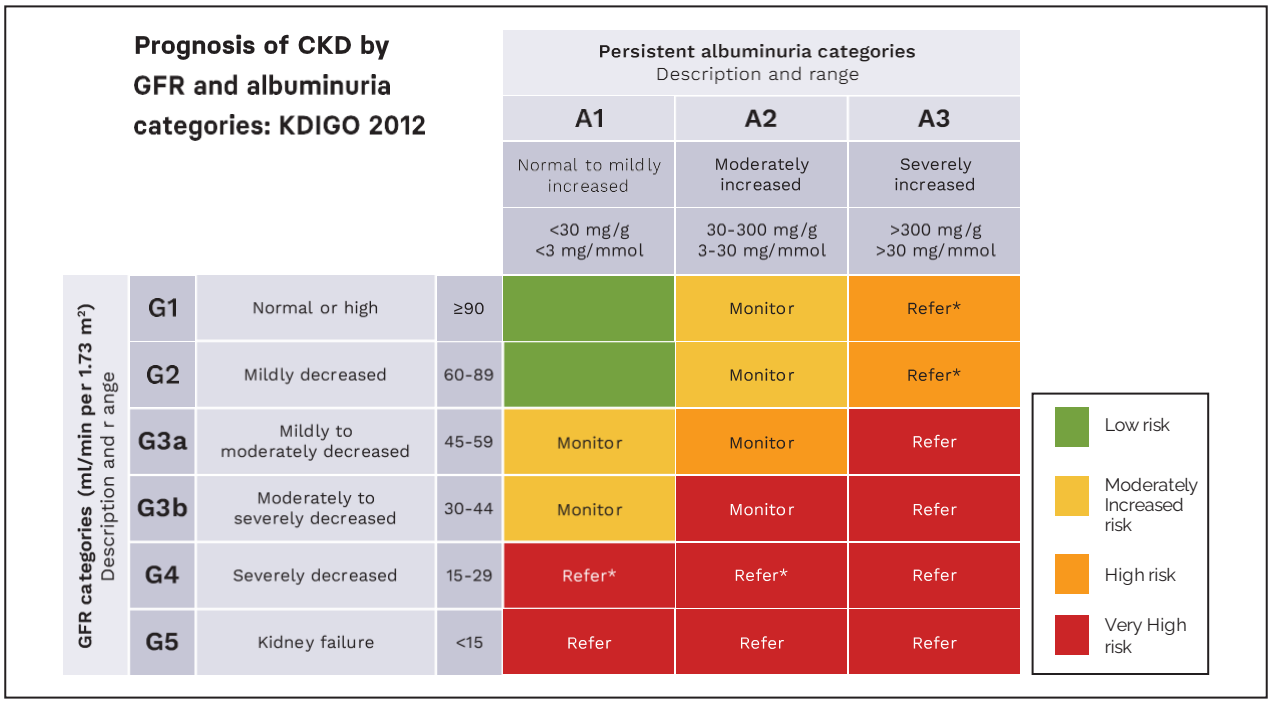


Figure 2: Grading of kidney disease: CKD: Chronic Kidney Disease; eGFR: estimated glomerular rate. *Adapted from: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease.*

CKD is graded as low risk, moderately increased risk, high risk and very high risk (Figure 2) according to the level of albuminuria and estimated GFR. It is very important to grade all patients diagnosed with CKD because these grades have management and prognostic implications.

- Low risk – eGFR of >60 with normal to mildly increased albuminuria (UACR- <30mg/g OR <3mg/mmol)
- Moderate risk – eGFR of 45- 59 with normal to mild albuminuria (UACR – <30 mg/g) OR eGFR of >60 ml/min/ 1.73m^2 with moderately increased albuminuria (UACR – 30-300mg/g)
- High risk – eGFR of 30-44 ml/min/ 1.73m^2 with mild albuminuria OR eGFR of 45 – 59 ml/min/ 1.73m^2 with moderate albuminuria OR eGFR of >90 ml/min/ 1.73m^2 with severely increased albuminuria.
- Very high risk – eGFR of <30 ml/min/ 1.73m^2 with normal to mild albuminuria OR eGFR of 30 ml/min/ 1.73m^2 to 44 ml/min/ 1.73m^2 with moderate albuminuria OR eGFR of 45- <60 with severe albuminuria.

NB: For purposes of this guideline, proteinuria measured by urine dipstick can be used in cases where the capacity to determine albuminuria is not available[4].

Table 1: Urine dipstick equivalence of UACR[4]

Category	UACR (mg/ g)	Urine dip stick protein	Terms
A1	<30	1+	Normal to mildly increased
A2	30 -300	2+	Moderate increased
A3	>300	3+	Severely increased

1.4 Risk factors of CKD

Recognizing the risk factors of CKD is key to the strategy of screening at-risk populations (described in section 1.5). It also allows early detection and treatment of modifiable risk factors for end-stage kidney disease (ESKD), along with appropriate treatment for CKD.

- Comorbidities: diabetes mellitus, hypertension and other cardiovascular disease
- Genetics: apolipoprotein-1 (APOL-1), sickle cell disease, adult polycystic kidney disease (APKD), family history of kidney disease
- Infections: HIV, Hepatitis B & C, tuberculosis, severe complicated malaria, UTIs, etc.
- Use of Nephrotoxic drugs like NSAIDs, herbal medicine and illicit drug use.
- History of kidney disease in childhood or acute kidney injury
- Pregnancy-related complications (hypertensive diseases, hyperglycemia, eclampsia and preeclampsia AKI- inducing complications)
- Intra-uterine and early childhood conditions (Low birth weight, intrauterine growth restriction, malnutrition, any condition leading to severe neonatal sepsis)
- Congenital anomalies of the kidneys and urinary tract (CAKUT)
- Glomerular diseases including IgA nephropathy and other forms of glomerulonephropathy
- Autoimmune diseases e.g., Rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis
- Presence of cancer.
- Age above 60 years regardless of the absence of the above risk factors
- Obesity
- Kidney stones

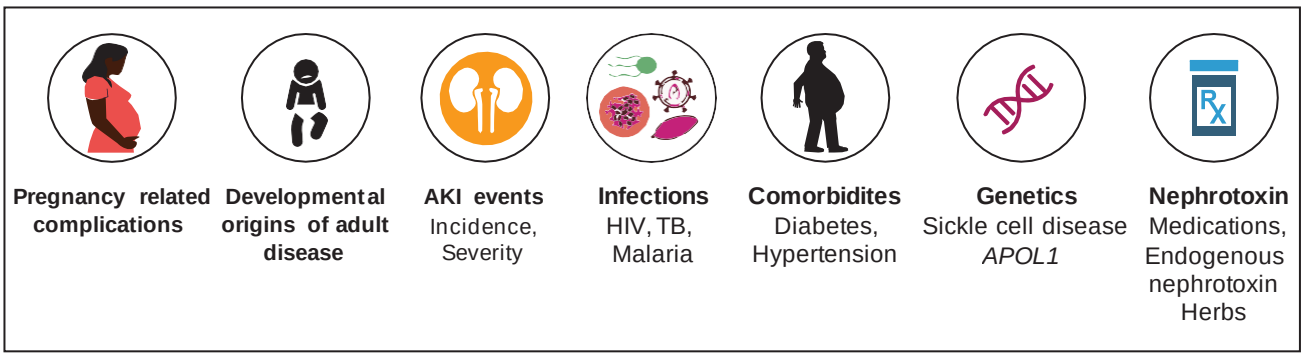


Figure 3: Risk factors in Low- and middle-income countries:[5] APOL1: Apolipoprotein 1

Adapted from Kalyesubula R, Conroy AL, Calice-Silva V, Kumar V, Onu U, Batte A, Kaze FF, Fabian J, Ulasi I. Screening for Kidney Disease in Low- and Middle-Income Countries. Semin Nephrol. 2022 Sep;42(5):151315. doi: 10.1016/j. semnephrol.2023.151315. Epub 2023 Mar 29. PMID: 37001337

1.5 Prevention of CKD

Prevention of CKD is done at primary, secondary and tertiary levels of care with different aims as stipulated in table 2.

Table 2: Prevention of CKD at different levels of care

Primary prevention	Secondary prevention	Tertiary prevention
AIM: Prevent and minimize risk of occurrence of CKD **Strategies** • Health educates about CKD and its risk factors • Promote healthy lifestyle such as increased physical activity, cessation of smoking, reduction of alcohol intake and dietary salt restriction • Screen and manage risk factors for CKD like DM/ HTN, SCD, infections • Restrict use of nephrotoxic medicines such as NSAIDs, aminoglycosides like gentamycin and herbal medicines • Encourage mothers to adequately attend antenatal care to prevent low birth weight, prematurity, neonatal infections, childhood malnutrition	**AIM:** Detect early & treat CKD **Strategies:** • Screen those at risk of CKD • Offer appropriate treatment for CKD • Screen and treat for risk factors for CKD	**AIM:** Prevent progression of & treat complications of CKD **Strategies:** • Treat and control hypertension and proteinuria using appropriate medication • Screen and treat complications

1.6 Screening & diagnostic approaches

All asymptomatic patients at risk of CKD and those that present with clinical features of kidney disease should be screened. The following tests are used in screening and diagnosis of CKD

- Urine dipstick to detect proteinuria
- Urine albumin creatinine ratio (UACR) to detect structural abnormalities
- Creatinine or Cystatin C to calculate eGFR
- Kidney ureters and bladder (KUB)ultrasound to detect structural abnormalities in the urinary system

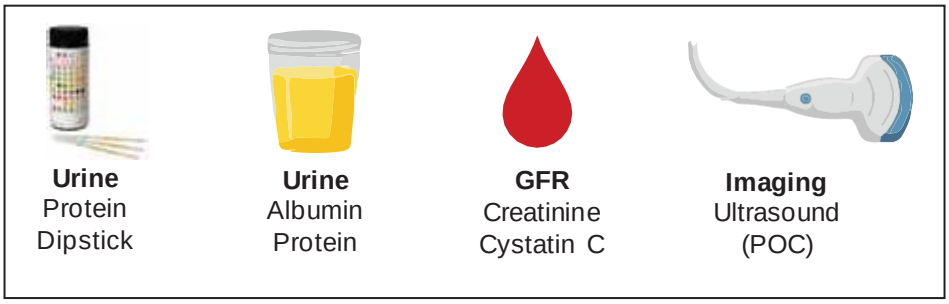


Fig 4: Screening tools for CKD in Low- and Middle-Income Countries.

Adapted from Kalyesubula R, Conroy AL, Calice-Silva V, Kumar V, Onu U, Batte A, Kaze FF, Fabian J, Ulasi I. Screening for Kidney Disease in Low- and Middle-Income Countries. Semin Nephrol. 2022 Sep;42(5):151315. doi: 10.1016/j. semnephrol.2023.151315. Epub 2023 Mar 29. PMID: 37001337.

1.7 Principles of management

The management of CKD aims at slowing or halting the progression of disease by identifying and treating the cause where possible; and recognizing, and treating the pathologic manifestations and complications of both entities. It also allows timely planning for long-term kidney replacement therapy or comprehensive conservative care (CCC). Figure 5 below shows what can be done at the different stages of CKD progression, and at the different levels of the healthcare system in Uganda. In terms of renal replacement therapies, while hemodialysis and kidney transplant may only be offered at higher levels of care (RRH or NRH), CCC, once initiated at the higher level of care, can be maintained and monitored at lower level health centers.

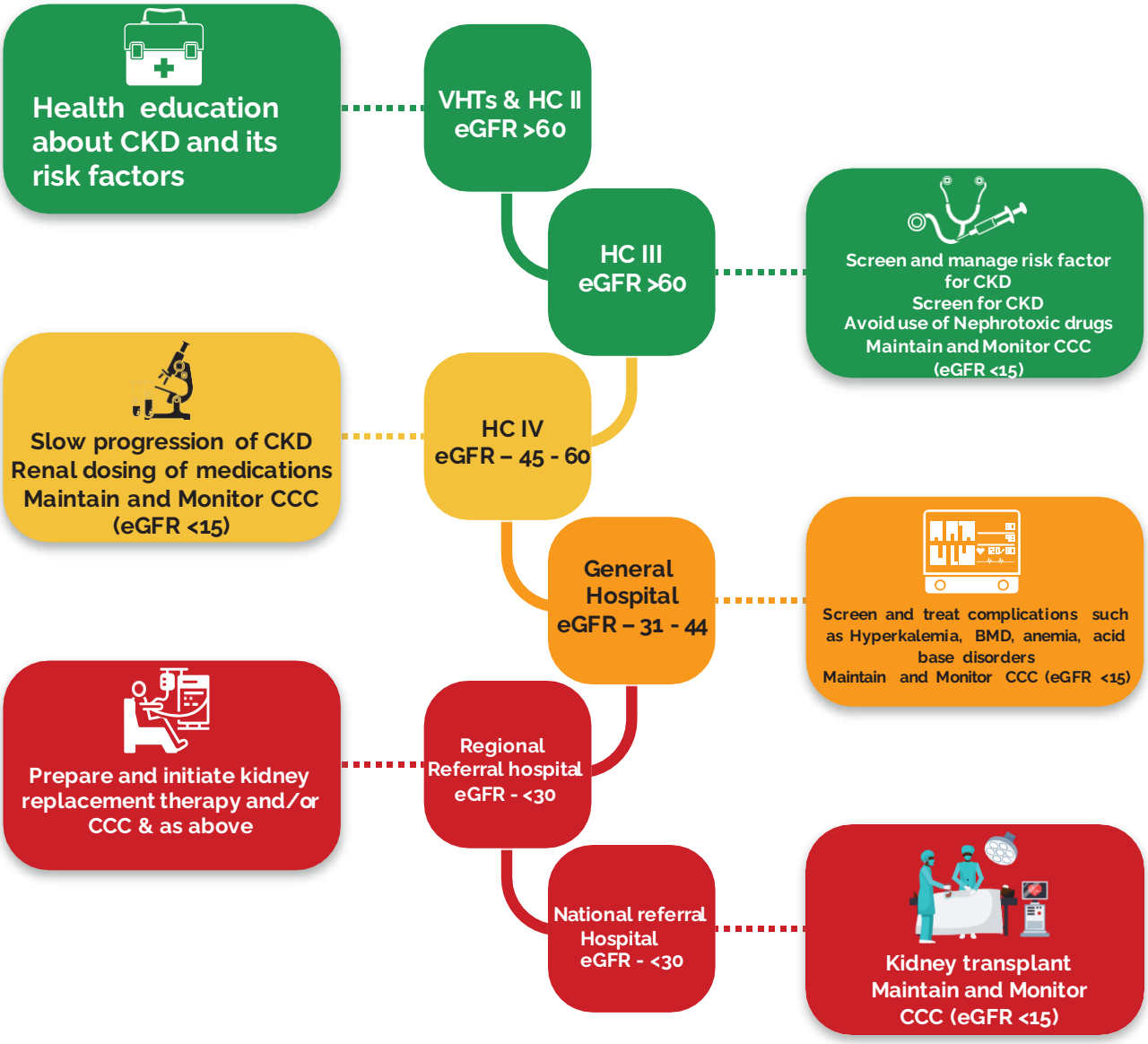


Figure 5. Management strategies for CKD at different levels of the healthcare system guided by the stage of CKD. CCC- Comprehensive Conservative Care, CKD- Chronic Kidney Disease eGFR- estimated Glomerular Filtration Rate, HC- Health Center

CHAPTER 2 - BURDEN OF KIDNEY DISEASE IN UGANDA

Kidney disease is defined as the presence of an abnormality in kidney function or structure. Each person usually has two kidneys which are very important in ensuring the normal body function. The kidneys are crucial in water balancing and ensuring that the by-products of metabolism are excreted. The kidneys also support the production of red blood cells and control of blood pressure. Kidneys can sense changes in the chemical composition of the body and bring it back to normal though different mechanisms. Kidneys are important in ensuring acid base balance as well as the proper regulation of calcium and phosphorous levels in the body.

Once the kidney function gets impaired, the kidneys fail to carry out the functions outlined above, and the individual affected begins to develop kidney disease which could be either acute or chronic depending on the duration of illness.

2.1 Prevalence of chronic kidney disease (CKD)

Kidney disease is common affecting one in ten adults worldwide and over 850 million people are living with kidney disease[6] Up to 70% of patients with kidney disease live in low- and middle-income countries. However, 90% of people with kidney disease do not know that they have it. This figure is higher in low-income countries like Uganda that do not routinely screen for kidney disease. In Sub-Saharan Africa, an estimated 13% of adults have some form of kidney disease (Stanifer, 2014).

In Uganda, the prevalence of chronic kidney disease (CKD) in the community ranges from 2% to 7%,[7] and up to 15% among patients with HIV or hypertension (Kalima N, Gabriel B; 2015). The prevalence of kidney disease varies across the country with 12.5% of adults living with CKD in Eastern Uganda, 3.9% in Southwestern Uganda; 6.7% in Wakiso and 2.4% in Kyamulibwa. In Gulu, the prevalence of kidney disease was noted in 14.4% among those with HIV while in Mbarara 15.3% of patients admitted on Mbarara Hospital general ward had CKD.[8] Whereas the key risk factors for CKD have been identified as hypertension, diabetes mellitus and related cardiovascular disease, most CKD patients in East Africa do not have these traditional risk factors. In a study among 3686 individuals from 22 communities in Uganda and Kenya, 66% of patients with CKD based on eGFR of less than 60mls/min/1.73m2 and a proteinuria of 1+ did not have hypertension, diabetes mellitus or HIV-infection.[9]

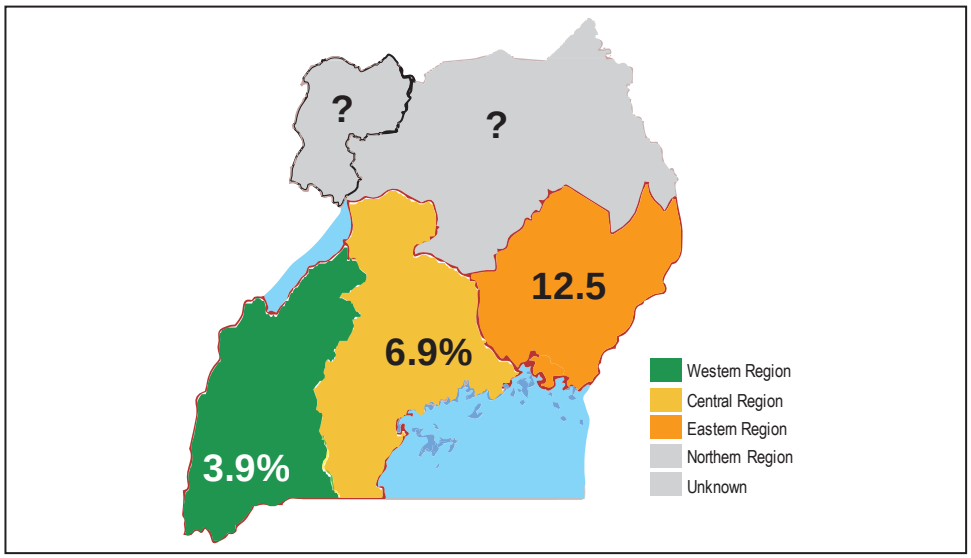


Figure 6: Map of Uganda showing regional prevalence of kidney disease

2.2 Risk Factors for CKD

Globally, the key risk factors for CKD have been identified as diabetes mellitus, hypertension, and related cardiovascular complications; and race or ethnicity with individuals of African ancestry being at a much higher risk.[6] Chronic kidney disease increases with age and after thirty years, an estimated loss of about 1ml/min/1.73m^2 occurs every year.[10] Female sex may be at increased risk of kidney disease because of exposure to pregnancy-related complication and other biological factors.[11]

The most common causes of CKD/ESKD in our population are not yet well established. Large population-based studies have found that close to two thirds of those with CKD do not have the traditional risk factors of diabetes mellitus, hypertension, or HIV infection.[7] However, 16% of patients admitted with CKD in Mulago National Referral Hospital had diabetes mellitus, 15% had HIV infection, whereas 90% had hypertension. [12] This suggests that hypertension is a common complication but may not be the main cause of CKD.

Population-based studies in Uganda have found that close to two thirds of those with CKD do not have traditional risk factors of diabetes mellitus, hypertension, or HIV infection.

Other risk factors include genetic abnormalities as sickle cell disease, autosomal dominant polycystic kidney disease (APKD) as well as APOL-1 genetic abnormalities. The APOL-1 genetic abnormalities mainly have been identified in people living with HIV and CKD. [13]

Pregnant women are at an increased risk of kidney disease if they have hypertension or other chronic diseases. Once women are undernourished during pregnancy this predisposes them to having children with low kidney mass which further predisposes these children to kidney disease once they grow up. This risk is further aggravated if the children do not have adequate nutrition or get recurrent infections during early childhood. In children, the leading cause of kidney disease is infections, such as malaria, and hematological conditions such as sickle cell disease which lead to acute kidney injury (AKI) and CKD. [14]

Other risk factors that need to be noted in our settings include chronic or recurrent infections like tuberculosis, HIV, hepatitis B and C and schistosomiasis. [15]

2.3. Mortality and morbidity from CKD

Chronic kidney disease in Uganda is increasing and is among the leading causes of death among admitted patients. A study conducted from 2011 to 2014 among 50,624 individuals admitted to the medical wards of Mulago National Referral Hospital showed that kidney disease like other non-communicable diseases was on the rise and was among the top 10 causes of death with a case fatality rate of 21% among patients admitted with CKD. [16] Another study conducted in the renal outpatient clinic of Mulago National Referral Hospital involving 217 adults with an average age of 47 years showed that up to 51% of the patients who presented to the clinic for the first time had ESKD which would require kidney replacement therapy (KRT). [12]

Once kidney failure or stage five of kidney disease are established, they may need KRT such as dialysis or kidney transplantation. The procedures are very expensive and are not readily affordable or available within the country.

The care and management of kidney disease in Uganda is expensive and unaffordable to most Ugandans.
Our best choice is early identification and prevention of kidney disease.

2.4. Kidney Replacement Therapies

Kidney replacement therapies may be grouped into three, namely: - i) dialysis which included hemodialysis and peritoneal dialysis, ii) kidney transplant and iii) comprehensive conservative care which focuses on quality of life rather than survival . Dialysis and kidney transplant are not easily accessible and are costly in Uganda.[17] There is inadequate infrastructure, such as dialysis units and limited human resources. The country has only 14 formally trained nephrologists (11 adult and three pediatric) for a population of 48 million people. Additionally, there is no access to peritoneal dialysis in the country and efforts to start this procedure have been sporadic.

Kidney transplant provides the best quality of life and survival odds amongst all three options in the management of kidney failure. Until recently this option was not available to Ugandans who had to travel elsewhere to access this lifesaving procedure. Uganda performed it's first kidney transplant in December 2023, and this was a great milestone. However, the infrastructure to sustain kidney transplant procedures is still limited and the cost will be out of reach for most patients in the foreseeable future. In 2024, the total cost of kidney transplant varied from 90 to 130 million Uganda shillings.

Comprehensive Conservative Care is a domain of kidney supportive care as highlighted in Figure 7. It is an approach to care that focusses on improving the quality of life of not just the patient, but their family as well, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of symptoms in a holistic manner. This includes exploration of physical, psychological, social and spiritual contributions to the presenting symptoms. It involves input from a multi-disciplinary team of providers but once care has been initiated patients may than be referred back to their homes to continue care. Although this option does not improve patient survival, it is the cheapest option of renal replacement therapy and therefore the most frequently utilized in Uganda.

For the benefit of improving patient survival, it is crucial that every clinician, at every level of care, has a high index of suspicion for kidney disease particularly among those individuals who have been identified in our communities to be at a high risk. This can help to prevent CKD before it is established and to identify kidney disease early and offer appropriate care which could potentially reverse or delay progression of kidney disease from advancing into kidney failure or even death.

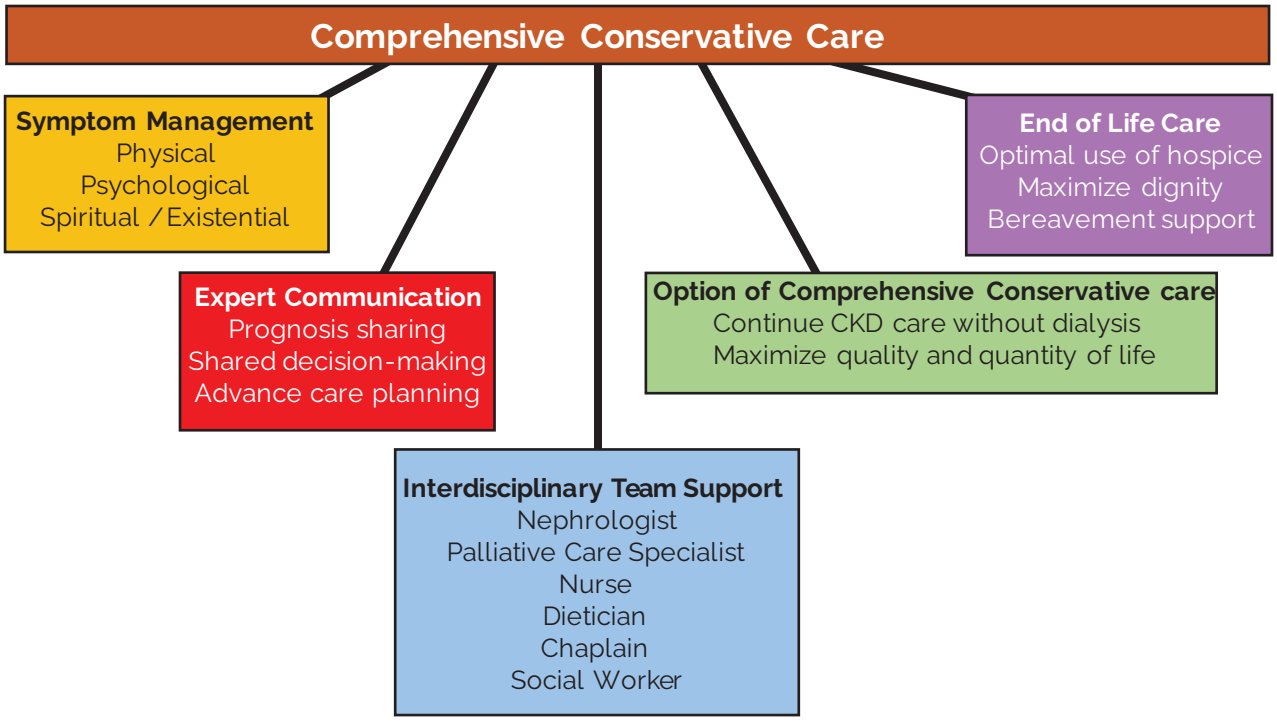


Figure 7: Domains of comprehensive conservative care. CKD- Chronic Kidney Disease
Adapted from, Gelfand, S.L., Scherer, J.S. and Koncicki, H.M., 2020. Kidney supportive care: core curriculum 2020. American Journal of Kidney Diseases, 75(5), pp.793-806.

CHAPTER 3 – SCREENING AND DIAGNOSIS OF CKD

3.10 Screening of CKD

The aim of screening for CKD is to detect individuals at risk of developing CKD and to identify its early stages. Initiation of interventions in the early stages of the disease delays progression to ESKD and reduces the need for kidney replacement therapy.

Screening of individuals at risk is more efficient in identifying individuals who may benefit from interventions and reduces risk of harm from false positive results arising out of population-based screening. [18]

3.11 Objectives of screening

1. Early detection to allow institution of therapeutic interventions
2. Allow more intense risk factor modification
3. Slow progression to ESKD
4. Reduce morbidity and mortality from CKD

3.12 Who should be screened?

1. We recommend screening of all patients with signs and symptoms of kidney disease (Figure 7)
2. We recommend screening of all individuals at increased risk of kidney disease

Individuals with the following risk factors should be screened:

- Diabetes mellitus, hypertension including other cardiovascular diseases
- Sickle cell disease
- Recurrent kidney stones
- History of low birth weight/preterm births
- Chronic infections like HIV, Hepatitis B & C,
- Cancer
- Use of nephrotoxic drugs like NSAIDs, herbs for more than two weeks
- History of kidney disease in childhood.
- People born with low birth weight or preterm
- Family history of kidney disease
- Recurrent infections like severe complicated malaria, UTIs, Tuberculosis etc.
- Adults above the age of 60years
- Autoimmune diseases

3.13. Screening tools.

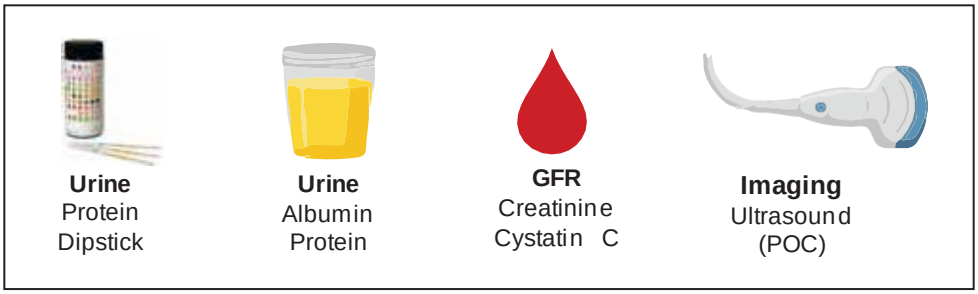


Fig 8: Screening tools for CKD in Low- and Middle-Income Countries.

Adapted from Kalyesubula R, Conroy AL, Calice-Silva V, Kumar V, Onu U, Batte A, Kaze FF, Fabian J, Ulasi I. Screening for Kidney Disease in Low- and Middle-Income Countries. Semin Nephrol. 2022 Sep;42(5):151315. doi: 10.1016/j. semnephrol.2023.151315. Epub 2023 Mar 29. PMID: 37001337.

The following tests are recommended for screening:

- **Urine protein dipstick:** This test measures the presence of all proteins, including albumin, in a urine sample. It is graded as negative, trace, or positive. While it is common, cheap, and accessible, it is inferior to urine albumin o creatine ratio (UACR) **It is best used for screening and not diagnosis.**
- **Urine albumin to creatinine ratio:** This is the preferred test for detection of elevated urine protein. A spot urine test is used to measure albumin and creatinine; and the ratio is calculated.
- **Serum Creatinine OR Cystatin C:** These tests are used to estimate glomerular filtration rate. We recommend using the CKD-EPI 2021 equation which is race-neutral and has been found to have modest accuracy in sub-Saharan Africa (Fabian J, Kalyesubula R, et al, 2021). Cystatin C-based equations are more accurate in SSA but because of cost, it should only be used to confirm CKD diagnosis where accessible or in evaluation of kidney donors.

The following online calculator can be used:
https://www.mdcalc.com/calc/3939/ckd-epi-equations-glomerular-filtration-rate-gfr

- **Ultrasound scan of kidney, ureters, and bladder (KUB):** This imaging test is recommended to evaluate disorders of the kidneys, ureters, or the urinary bladder.

Table 3. Screening tests available at different levels of healthcare in Uganda

Health facility	Screening Tests done	Action taken
VHT & Health Centre II	Identify risk	Refer them for CKD screening
Health Centre III	Urine dipstick	Proteinuria of 1+, repeat within 3 months Proteinuria >1+ refer to higher of care for diagnostic tests
Health Centre IV	Above tests plus • urea & creatinine, • urine albumin creatinine ratio (UACR)	Confirm (from eGFR and UACR) and treat CKD
General Hospital	Above tests plus • KUB ultrasound scan • Screen for causes and complications • HepBSAg, Anti-HCV, HIV screen, TPHA	Confirm CKD, determine the cause and treat (comprehensive conservative care)
Regional Referral Hospital	Above tests plus cystatin C (if available) More extensive individualised investigations Renal biopsy	Confirm CKD, determine the cause and treat (CCC and dialysis)
National Referral Hospital	Above tests	Confirm & Treat CKD Prepare for Kidney replacement therapy (dialysis & transplant) Offer CCC

CCC: Comprehensive conservative care CKD: Chronic Kidney Disease; eGFR:Estimated glomerular filtration rate; KUB: Kidney, ureter and bladder; UACR: Urine albumin creatinine ratio; VHT: Village Health Teams;

3.14 Frequency of screening

Screening of patients at risk of CKD should be done every year.
If the level of decline of eGFR is greater than 5ml/min/1.73m2 per year, assess for a secondary cause of CKD or screen more frequently.

3.20 Diagnostic evaluation of CKD

The aim of evaluation of a patient with CKD is to confirm the diagnosis, to establish the cause of the disease, to assess for any conditions that may drive progression of kidney disease and to uncover complications of CKD that may require management.

3.21 Criteria for diagnosis of CKD

CKD is diagnosed when there is presence of **decreased kidney function or kidney damage for three or more months,** irrespective of the cause (KDIGO-Kidney Disease Improving Global Outcomes).

- **Decreased kidney function** defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1.73 m2
  AND/ OR

- **Kidney damage** defined as evidence of structural damage or other markers of functional kidney abnormalities including proteinuria, pathologic abnormalities detected by histology or inferred by imaging and patients with functioning kidney transplants.

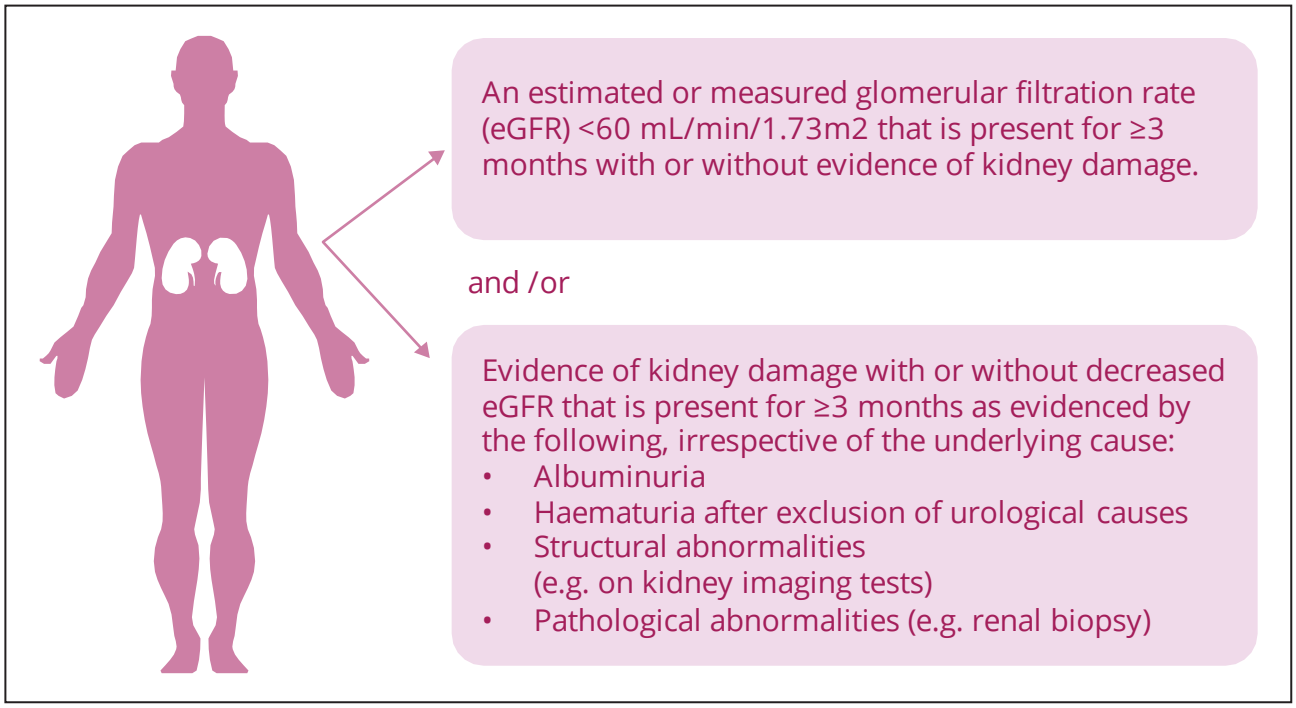


Figure 9. Clinical diagnosis of chronic kidney disease

3.22. Steps in diagnosing CKD

a) Screening all asymptomatic patients with risk factors
All patients with a high risk of CKD should be screened as in section 3.13 above.

b) Assessment of clinical features
Patients with CKD are usually asymptomatic. However, in advanced cases, CKD may present with nonspecific symptoms and signs as shown in figure 7 below.
The healthcare worker should look for these signs and symptoms.

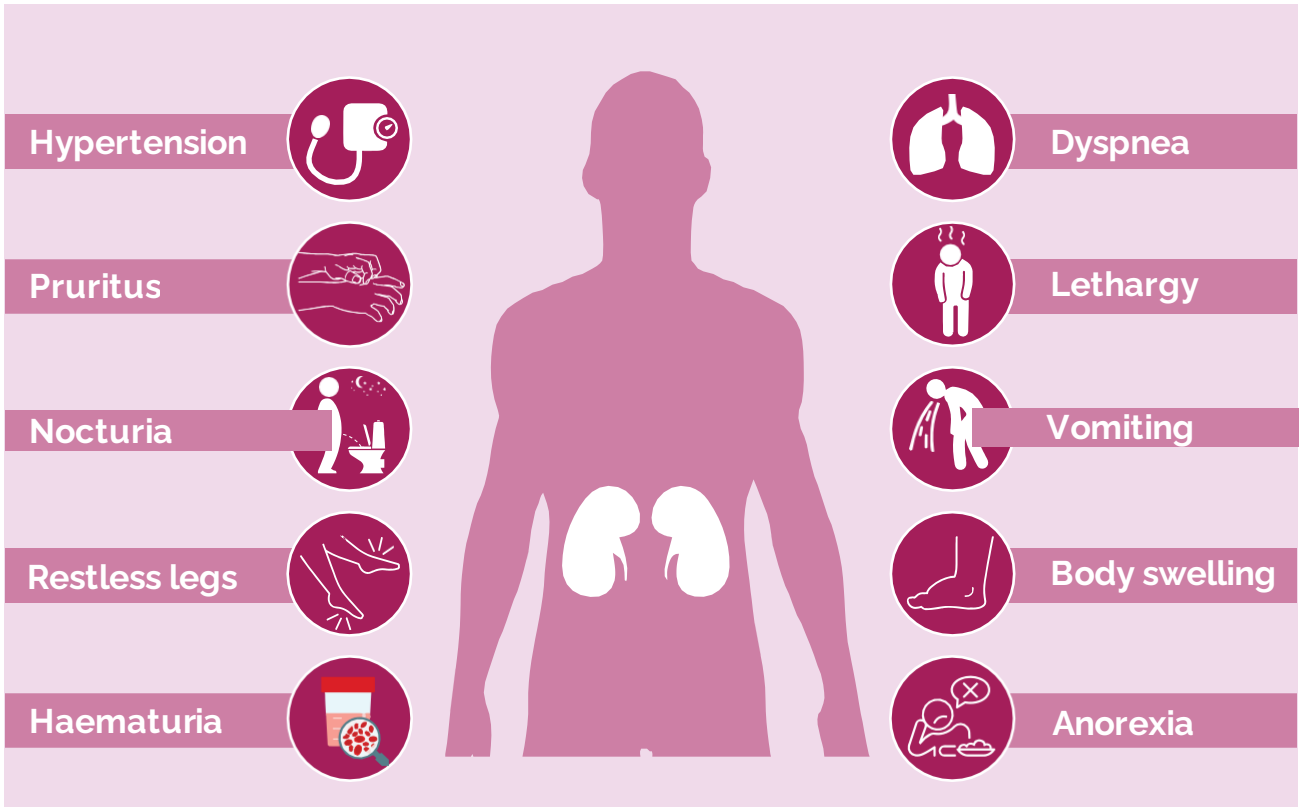


Figure 10. Clinical features of chronic kidney disease

c) Diagnostic tests to confirm CKD

The following diagnostic test are used to confirm the diagnosis of CKD

- **Creatinine OR Cystatin C:**
  Creatinine or cystatin are used to estimate the GFR. The GFR can be estimated using CKD- EPI 2021 equation (for adults) which has accuracy and precision compared to other equations. The eGFR calculator is available https://www.kidney.org/professionals/kdoqi/gfr_calculator
- **Urine albumin to creatinine ratio (UACR).**
  The urine albumin to creatinine ratio (UACR) test to determine presence of albuminuria. Albuminuria can be graded as indicated in table 1.

The UACR is preferred for assessing albuminuria. However, urine dipstick protein can be used in settings where UACR is unavailable.[4]

Table 4 The equivalence of urine albumin-creatinine ratio (UACR) and urinary dipstick protein.

Category	UACR* (mg/g)	Urine dip stick protein	Terms
A1	<30	1+	Normal to mildly increased
A2	30 -300	2+	Moderately increased
A3**	>300	3+	Severely increased

*Relative to young adult level
**Including nephrotic syndrome (albumin excretion >220mg/g)

- **Kidney Ureter Bladder (KUB) Ultrasound scan:**
  An ultrasound should be done to assess of the structure of kidney, ureters, and bladder in patients with suspected CKD.

d) Assessing for possible causes and complications of CKD

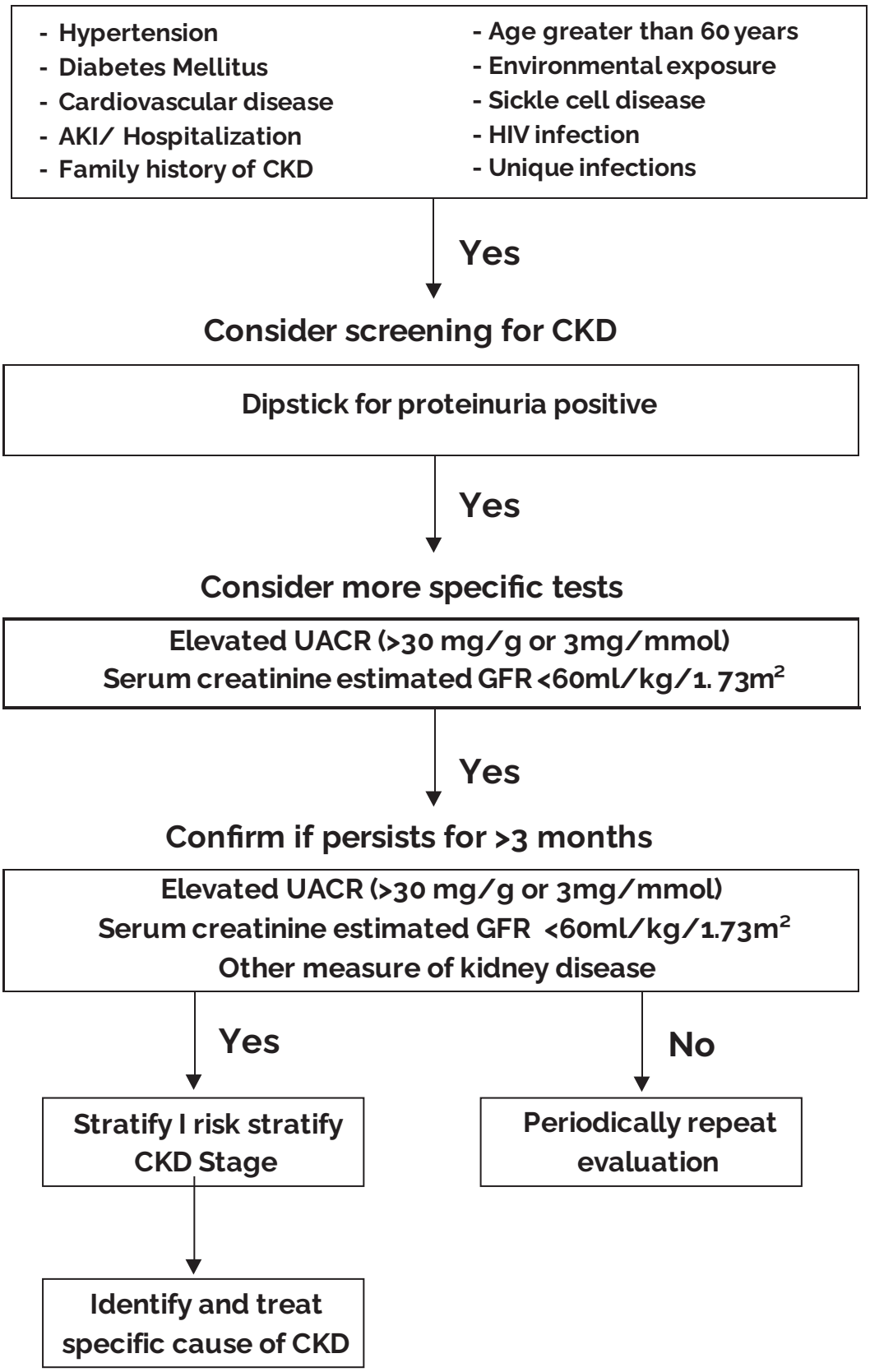
CKD is not a primary diagnosis. Attempts should be made to identify the underlying cause of CKD (KDIGO, 2012). The following tests should be done at the different levels of care to establish the cause of CKD.

Table 5: Test recommended for CKD patients at different levels of care

Level of care	Test
H/C I & II	HIV test, Blood pressure and blood sugar monitoring
H/C III	FBG, HIV, Urine dipstick
HC IV & General Hospital	LFTs, uric acid, CBC, urine sedimentation, lipid profile, HBA1C, serum electrolytes, creatinine, abdominal ultrasound scan (BPH, Adult Polycystic kidney disease),
Regional & National Referral Hospitals	ESR, ANA, anti-double stranded DNA antibodies, Cystatin C, serum calcium, phosphorous, albumin, Vitamin D, parathyroid hormone, Iron studies Kidney biopsy, CT scan (be conscious about the nephrotoxic effects of contrast)ECG, cardiac ECHO, Urine electrolytes (sodium, chloride, potassium), Arterial blood gas analysis (PH, PCO2, HCO-3, Renal artery Duplex scan, MR-angiogram, Nuclear medicine tests- DMSA

ANA: Anti-nuclear antibody; BPH: Benign Prostatic Hypertrophy; CBC: Cell blood count; ESR: Erythrocyte Sedimentation Rate; FBG: Fasting blood glucose; HBAIC ; Haemoglobin A1C

Figure 11. Recommended screening algorithm for chronic kidney disease (CKD)



AKI, acute kidney injury; GFR, glomerular filtration rate; HIV: human immunodeficiency virus; UACR, urine albumin-to-creatinine ratio.

(Adapted from Kalyesubula R, Conroy AL, Calice-Silva V, Kumar V, Onu U, Batte A, Kaze FF, Fabian J, Ulasi I. Screening for Kidney Disease in Low- and Middle-Income Countries. Semin Nephrol. 2022 Sep;42(5):151315. doi: 10.1016/j.semnephrol.2023.151315. Epub 2023 Mar 29. PMID: 37001337.

INITIAL ASSESSMENT FOR CKD

- Confirmation of CKD diagnosis (repeat tests after 3 months)
- Staging and progression rate
- Establishing cause of kidney disease
- Identify and treat reversible factors (hypertension, volume loss, obstruction, infection)
- Look for complications (anemia, MBD, electrolyte abnormalities, CVD)

EVALUATION OF NEWLY DIAGNOSED PATIENT WITH CKD

- Serum creatinine, electrolytes, bicarbonate
- Estimate glomerular filtration rate using CKD-EPI equation
- Urinalysis (examine sediment, proteinuria quantitation)
- Ultrasound of kidneys and urinary tract
- Calcium, phosphate, alkaline phosphatase, albumin
- CBC including peripheral blood film
- Iron profile - serum iron, TIBC, TSAT
- HBsAg, anti-HCV

Anti-Hepatitis C virus; CBC: Cell blood count; CKD: Chronic kidney disease; CKD-EPI: Chronic kidney disease epidemiology consortium; CVD: Cardiovascular disease; HBsAg: Hepatitis B surface antigen; MBD: Mineral bone disease; TIBC: Total iron binding capacity; Transferrin saturation

CHAPTER 4 - MANAGEMENT OF CKD

The goals of management of patients with CKD are to:

1) Identify and treat reversible causes of CKD and kidney failure.
2) Prevent or slow the progression of disease.
3) Treat the complications of kidney failure.
4) Identify and prepare patients for kidney replacement therapy or comprehensive conservative care.

The following management principles below should be followed:

1) Stage and risk stratify all CKD patients to determine the aims and level of care.
2) Health educate & promote of lifestyle modification
3) Slow progression of CKD
4) Screen and manage complications
5) Identify and prepare patients for kidney replacement therapy and/ or comprehensive conservative care.
6) Restrict nephrotoxic drugs
7) Medication review and dose appropriate for eGFR

4.1 Principle 1: Stage and risk stratify all CKD patients to determine the aims and level of care.

Upon diagnosis, all CKD patients should be risk stratified according to the KDIGO CKD grading. We recommend management of patients at the appropriate health facility level as summarized in the action plan shown in Tables 4a and 4b.

Table 6a: Management of CKD at different level of the health care system

LOW RISK PATIENTS	MODERATE RISK PATIENTS
eGFR of >60ml/min/1.73m² with normal to mildly increased albuminuria (UACR - <30mg/g OR <3mg/mmol) **MANAGE AT HEALTH CENTER III AND ABOVE** **Aims of care:** ❖ Health educates about CKD and its risk factors ❖ Promote healthy lifestyle such as increased physical activity, stop smoking, reduce alcohol intake and restrict dietary salt ❖ Screen and manage risk factors for CKD like DM/HTN, SCD, infections, ❖ Restrict use of nephrotoxic medicines ❖ Review Creatinine & albuminuria every 12 months	**eGFR of 45 – 59 ml/min/1.73m² with normal to mild albuminuria (UACR – <30 mg/g) OR eGFR of >60 ml/min/1.73m² with moderately increased albuminuria (UACR – 30 -300mg/g)** **MANAGE AT HEALTH CENTER IV & ABOVE** **Aims of care:** ❖ Investigate to determine underlying cause ❖ Reduce progression of kidney disease (manage albuminuria) ❖ Restrict use of nephrotoxic drugs ❖ Health educates and promotion of health lifestyle ❖ Screen and Manage risk factors for CKD like DM/HTN, SCD, infections (immunization) ❖ Screen and treat complications particularly anemia. ❖ Review Creatinine & Albuminuria 6 – 12 months

Table 6b: Management of CKD at different level of the health care system

HIGH RISK PATIENTS	VERY HIGH-RISK PATIENTS
eGFR of 30 -44 ml/min/1.73m² with mild albuminuria OR eGFR of 45 – 59 ml/min/1.73m² with moderate albuminuria OR eGFR of >90 with severely increased albuminuria. **MANAGE AT GENERAL HOSPITAL AND ABOVE** **Goals of care** ❖ Medication review / renal dose appropriate for eGFR ❖ Health educate & promotion of healthy lifestyle ❖ Screen and Manage risk factors for CKD ❖ Screen and treat complications such as Hyperkalemia, BMD, anemia, ❖ Restrict use of nephrotoxic drugs ❖ Appropriate referral to a nephrologist when indicated ❖ Review creatinine & albuminuria every 1- 3 months	**eGFR of <30 ml/min/1.73m² with normal to mild albuminuria OR eGFR of 30 to 44 ml/min/1.73m² with moderate albuminuria OR eGFR of 45 - <60 ml/min/1.73m² with severe albuminuria.** **MANAGE AT REGIONAL REFERRAL HOSPITAL & ABOVE** **Goals of care** ❖ Review medication / renal dose appropriately for eGFR ❖ Health educate about CKD and its risk factors and progression ❖ Promote healthy lifestyle ❖ Manage risk factors/ causes for CKD ❖ Screen and treat complications ❖ Restrict use of nephrotoxic drugs ❖ Prepare and initiate kidney replacement therapy. ❖ If comprehensive conservative care has been instituted patients may than be referred back to lower level HC centers ❖ Review creatinine & albuminuria every 1 month

4.2.0 Principle 2: Health educate & promote lifestyle modification

4.2.1 Health Educate

All patients and their caretakers at all levels of care should be empowered with information concerning the CKD including causes, risk factors, symptoms, treatment and possible complications and prognosis.

The ministry of health recommends linkage of patients to CKD support care networks and provision of information about kidney disease using available media platforms.

The healthcare worker should effectively communicate to patients and their care givers about health improvement goals, diet, and exercise to slow the progression of CKD. The ministry of health recommends linkage of patients to CKD support care networks and provision of information about kidney disease using available media platforms.

4.2.2 Promote lifestyle modification

Lifestyle modification is the first line modality in management of all people diagnosed with CKD. Health care should emphasize lifestyle changes among patients with CKD to delay the progression of the disease.

These lifestyle changes include stopping tobacco use, ensuring proper nutrition, limiting alcohol use, and increasing physical activity. Table 5 shows the lifestyle considerations in patients with CKD.

Table 7: Lifestyle consideration in patients with CKD

Lifestyle parameter	Target
Nutrition & diet	Diets for patients with CKD should be individualized and changed from time to time according to the level of kidney function. The following foods and fruits are largely safe for patients with kidney disease. • Skinless chicken or turkey, fish or seafood, Lean beef like sirloin or tenderloin, eggs, beans, like kidney beans or lentils. Note that these are higher in potassium and phosphorus, so you may need to limit the portion size. • Pomegranates: eating pomegranates may have many health benefits since they are high in fiber, folate, vitamin K, vitamin E, vitamin B6, and potassium. • Other fruits low in potassium are apples, watermelon, grapes and pineapples. • Milk alternatives like schemed yoghurt, healthy oils and fats, strawberries, root vegetables like onions along with other vegetables like cabbage, broccoli, nuts and seeds, wholegrains, squash - In advanced kidney disease it is best to moderate or limit foods with high potassium (eg bananas and green leafy vegetables) or high phosphorous such as dairy products, processed meats, bread, beer, colas, packed drinks, avocado and chocolates. - People who have advanced kidney disease and are not on dialysis should eat less proteins particularly red meat and organ meat (eg liver, kidney, heart, pancreas etc.) - Whenever possible consult a dietary/nutrition expert
Smoking	**Smoking cessation should be advised using counselling if affordable nicotine replacement therapy or other medication.**
Alcohol	Limit alcohol intake to ≤2 standard drinks per day in men and < 1 standard drink per day.
Physical activity	**Be active on most days of the week** Recommend 150 minutes a week i.e. at least 30minutes of mild to moderate exercise per day for 5 days per week
Obesity	In advanced disease, moderate or limit foods with high potassium (eg bananas and green leafy vegetables) or high phosphorous such as dairy products, processed meats, bread, beer, colas, packed drinks, avocado and chocolates. - In advanced kidney disease but not on dialysis, patients should eat less proteins particularly red meat and organ meat (eg liver, kidney, heart, pancreas etc.) - Whenever possible consult a dietary/nutrition expert **Misplaced intervention is shown**
	• Lifestyle modifications like increased physical activity, dietary changes with the aid of a dietitian and consideration the underlying CKD cause. • Anti-obesity drugs like GLP-1 agonists, orlistat (monitor for risk of AKI) and others • Metabolic surgery

Dietary recommendations:

The purpose of diet therapy in CKD is two-fold: to delay progression and to prevent and treat complications, including malnutrition. The first steps in diet therapy are to:

The dietary recommendations in patients with chronic kidney disease depend on the presence of comorbidities such as hypertension, diabetes, cardiovascular disease, and the severity of CKD.

Patients with CKD should receive expert dietary advice and information tailored to severity of CKD and the need to intervene on salt, phosphate, potassium, and protein intake. The foods recommended in patients with CKD are shown in figure 10.

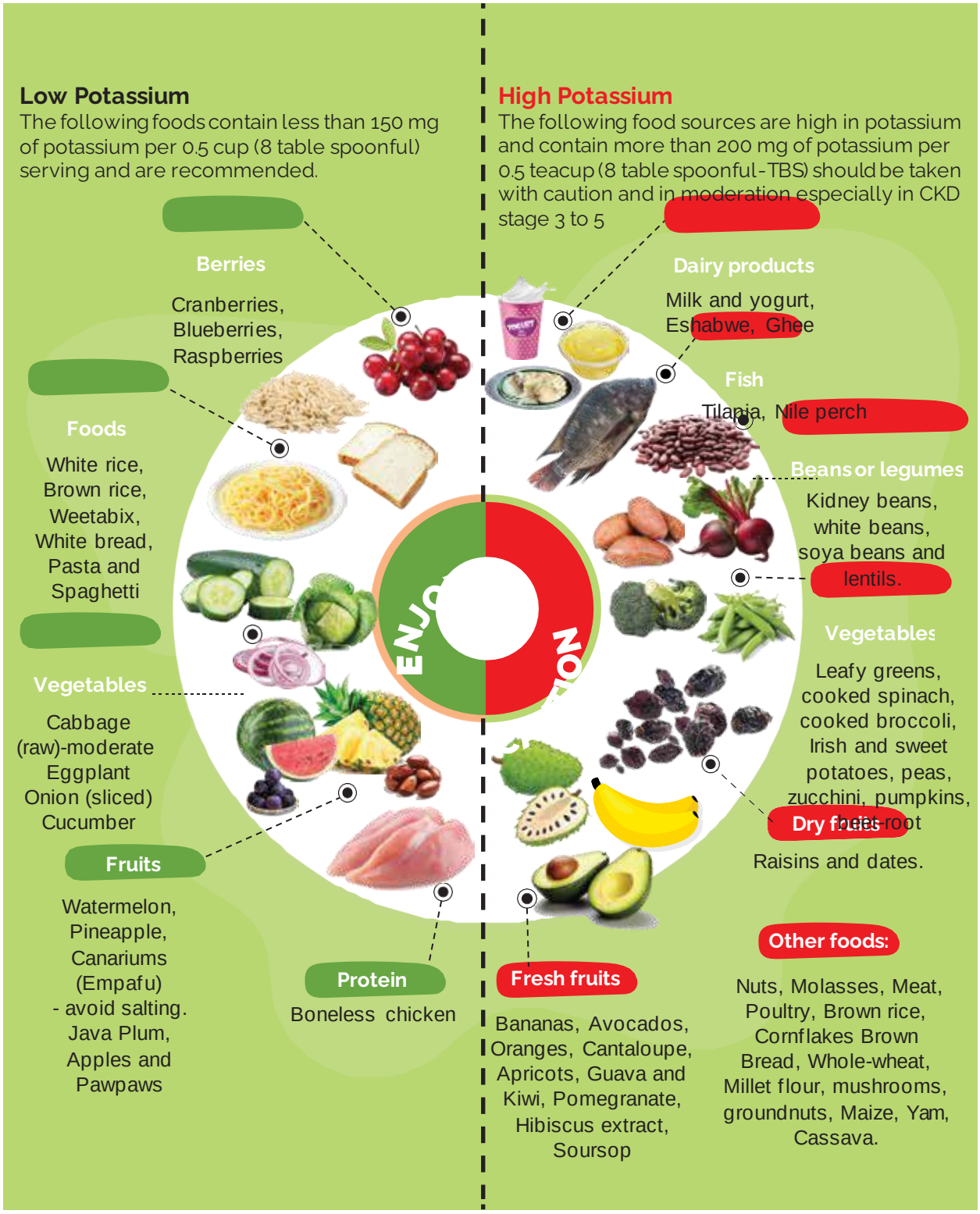


Figure 12: The foods recommended in patients with CKD.

In brief

- **Salt restriction** is recommended across the spectrum of disease.
- **High phosphate foods** like dairy products such as milk, ghee, yoghurt and eshabwe should be avoided in stage 4 CKD and 5.
- **Protein restriction** is recommended for moderate to high-risk CKD to slow progression. Plant-based proteins are preferred to animal-based proteins. [20] In patient with ESKD on dialysis, protein dietary restrictions may be exempted

- **Potassium rich foods** such as matooke, sweet banana, pumpkin, irish potatoes, avocado should be avoided in patients with CKD stage 4 and 5.
- **Boiling the matooke and irish potatoes and pouring away the water may remove the potassium to allow patients with CKD to eat them.** [21]
- **Alcohol**
- Avoid processed foods and beverages especially CKD stage 3-5 due high sodium and phosphorous content.

Physical activity:

Physical activity is beneficial in patients with CKD through slowing the development and progression of disease. Patients should have an individualized exercise program based on risk factors, comorbidities, and stage of disease. Before any exercise program, patients should be assessed for safety of the program. Table 6 shows the detailed physical activity recommendations in CKD patients.

Table 8. Detailed physical activity recommendations in patients with CKD

Type/Utility	Frequency	Intensity	Duration
Aerobic Exercise Increase cardiorespiratory fitness and physical function; reduce cardiovascular risk	≥ 5 days per week	Moderate – Hard (RPE 12–15; noticeable increases in heart rate and breathing)	≥ 30 minutes
Resistance Exercises Increase muscle mass and muscle strength	2 – 3 days per week (non consecutive days)	Moderate – Hard (RPE 12–15; 60 – 80% 1repetition maximum)	8 – 10 exercises targeting upper and lower body large muscle groups 10 – 15 repetitions
Flexibility Exercises Maintain habitual physical activity; increase range of motion; reduce exercise related injury risk	≥ 2 days per week (perform on the same days as aerobic or resistance exercises)		10 minutes targeting major muscle and tendon groups Hold each static stretch for 10–30s Repeat each stretch 3 – 4 times
Balance Exercises Fall prevention	≥ 3 days per week		

Adapted from Nelson ME, Rejeski WJ, Blair SN, et al. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc. 2007;39(8):1435 – 1445.

The healthcare workers in collaboration with patient should develop a personal action plan to address these lifestyle issues. The 5 A`s to facilitate effective behavior change (Figure 9). offers a framework for generating such a plan.

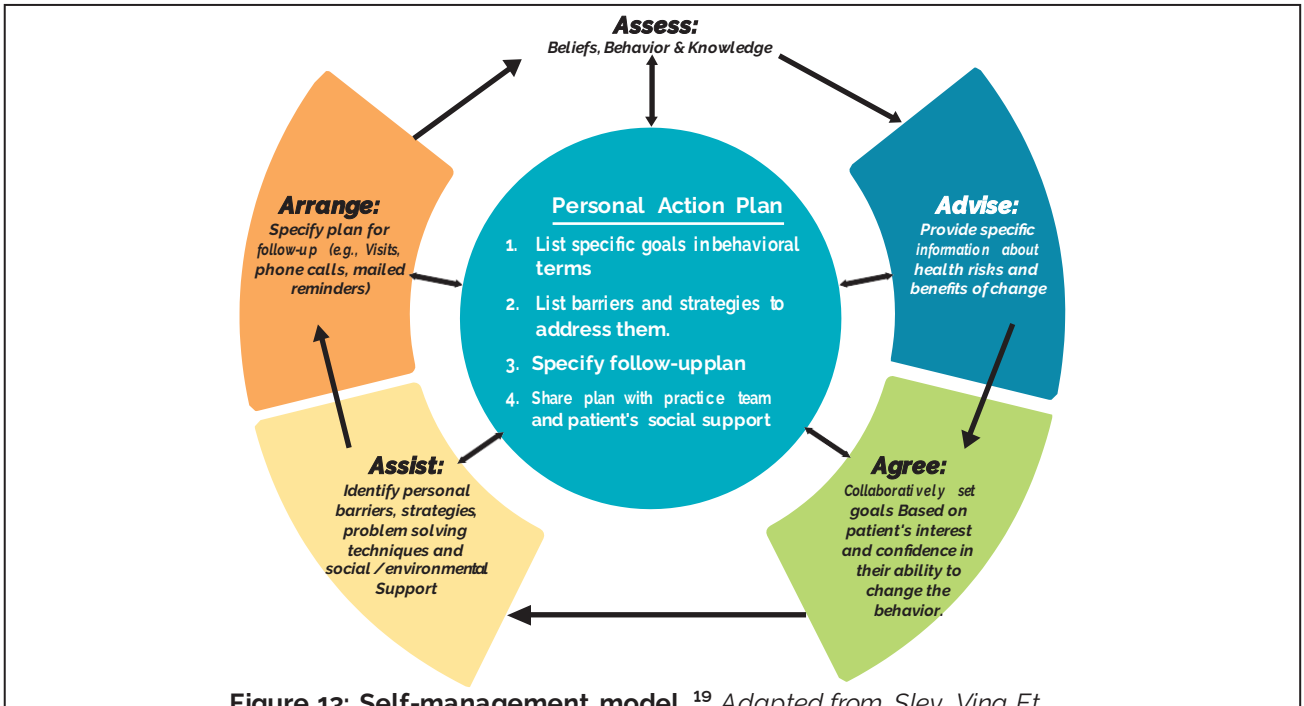


Figure 13: Self-management model. [19] *Adapted from Slev, Vina Et*

4.3.0 Principal 3: Slow progression of CKD

One of the main goals of management of CKD is to slow progression to ESRD. Approaches to slow progression of CKD include treatment of proteinuria and management of underlying causes / risk factors for CKD.

4.3.1 Treatment of Proteinuria

Proteinuria is an important marker of progression of kidney disease. Proteinuria is also correlated strongly with cardiovascular complications in CKD. Proteinuria also directly influences the worsening of kidney function. The control of proteinuria is key to preserving kidney function and prevention of cardiovascular complication.
The most important therapeutic agents used to manage proteinuria are ACEi or ACEi and SGLT2i. GLP-1 agonist is also suggested in management of proteinuria. Finerenone, a novel nonsteroidal MRA is also suggested as an add on medication for proteinuria and slowing CKD progression especially in type 2 DM.

Angiotensin converting enzyme inhibitor/ Angiotensin receptor blocker (ACEi / ARB)
Renin-angiotensin-aldosterone blockade has consistently been shown to reduce proteinuria through lowering the intraglomerular pressure and therefore reducing hyperfiltration. These class of drugs slows progression of CKD. [22]

We recommend the initiation or continuation of ACEI or ARBs in all CKD patients with proteinuria (greater than 1g/ 24 hours or proteinuria ++).

We do not recommend concurrent use of ACEi and ARB as they increase the risk of hyperkalemia and may make kidney function worsen.

If serum creatinine rises by >30% or eGFR falls by >25%, STOP ACEi/ARB and initiate referral to a nephrologist/ specialist physician.

Electrolytes should be assessed within 2 weeks after initiating therapy.
If K>6.0, stop ACEi/ARB and start low potassium diet.

Sodium-glucose cotransporter-2 inhibitors (SGLT2i)
Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are a class of oral anti-hyperglycemic agents which are increasingly used in clinical practice. SGLT-2 inhibitors improve glycemic control and cardio-renal outcomes, promote weight loss, and reduce blood pressure. Randomized controlled trials have demonstrated that SGLT-2 inhibitors reduce proteinuria and delay progression of kidney disease in patients with albuminuria. [23]

We recommend SGLT2i when CKD is diagnosed (eGFR<60ml/min/m3) regardless of level of proteinuria.

We suggest that SGLT2i can be used until dialysis is initiated.
Dapagliflozin and canagliflozin are the preferred SGLT2i. [24,25]

Glucagon-like peptide-1 receptor agonists (GLP-1RAs)

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are relative novel drugs which prevent albuminuria and slow the decline of renal function towards end stage kidney disease diabetic kidney disease. [26,27] These are still expensive and generally inaccessible.

GLP-1RA (especially semaglutide and liraglutide) can be added to ACEi and SGLT2i ,where, accessible for further reduction of albuminuria until GFR of 15ml/min/1.72m^2. [26,27]

4.3.2 Identify and manage the underlying cause / risk factors

Although CKD is generally progressive and irreversible, there are steps providers and patients can take to slow progression, enabling patients to live longer without complications or the need for renal replacement therapy.

Health workers should actively identify and manage the causes and risk factor of CKD

4.3.2.1 Hypertension

Hypertension is both a cause and a complication of CKD. The condition associated with increased risk of stroke and heart attack- the main complications of CKD; and accelerates the progression of CKD.

The health workers should manage hypertension to prevent cardiovascular disease and reduce risks of kidney disease progression.

Hypertension should be treated to a target of 130/80mmHg.[28]

Management of hypertension in CKD

The goal of treatment is reducing blood pressure to below lower than 130/80mmHg
Lifestyle changes (see the table 5) are integral to the management of hypertension in CKD and should be encouraged.
Multiple medications (2 or more drugs) are often needed to control hypertension adequately in most people with CKD. All groups of drugs should be considered with the aim being to reduce blood pressure to below target. Table 6 shows the considerations in the use of antihypertensive medication in patients with CKD.

We recommend, ACE inhibitors or ARB as first line class of drugs for BP lowering in hypertensive patients with proteinuria.

Additional antihypertensive agents can be chosen based on cardiovascular indications and comorbidities as shown in Table 7. The algorithm in Figure 10 offers guidance on approach to management of hypertension in CKD

Table 9: Considerations in the use on antihypertensive agents for BP lowering in CKD

DRUG CLASS	CONSIDERATION
ACEi/ ARB	Preferred for BP lowering especially in CKD patients with proteinuria ACEi and ARBs should not be combined Can be used in all stages of CKD. **CAUTION ⚠ : STOP if Serum Potassium> 5.5 mmol/L** **DO NOT INITIATE if eGFR<15** mL/min/1.73m^2
Thiazide diuretics	Effective in all stages of CKD as adjunct antihypertensive therapy especially in presence of fluid overload. They can be used if the eGFR is >45 mL/min/1.73m^2 but can be effective at low levels of eGFR, when sequentially combined with loop diuretics. Chlorthalidone and indapamide, the thiazide like diuretics are preferred over hydrochlorothiazide due to their longer half-lives and higher potency.
Loop diuretics	Should not be the preferred drug for the treatment of hypertension. Can be used as additional medicine in patients with fluid overload in all stages of CKD even when eGFR is severely reduced to <30 mL/min/1.73m^2 Doses of furosemide are 20-120 mg/day, but higher doses (up to 500 mg/day) may be required, especially at lower levels of eGFR.
β-blockers	Alternative agents after ACEi/ARBs for controlling hypertension in patients with CKD and systolic heart failure. Vasodilatory β-blockers (carvedilol, nebivolol) preferred in CKD
Calcium channel blockers	DHP CCBs such as amlodipine are used with ACEi or ARB (synergistic action in BP reduction) Non-DHP CCBs (e.g., verapamil and diltiazem) should be considered in CKD with proteinuria. Nifedipine should be avoided
Mineralocorticoid receptor antagonists	Preferred in resistant hypertension (failed BP control with>3 classed of drugs) Finerenone preferred in CKD with diabetes **CAUTION ⚠ :** Use with ACEi/ARB may be associated with hyperkalemia

Blood Pressure Monitoring in patients with CKD

Health workers should encourage CKD patient to acquire a home blood pressure measuring (HBPM) devices blood pressure monitoring. The values of HBPM correlate better with target organ damage and cardiovascular mortality and morbidity when compared to office BP measurements.

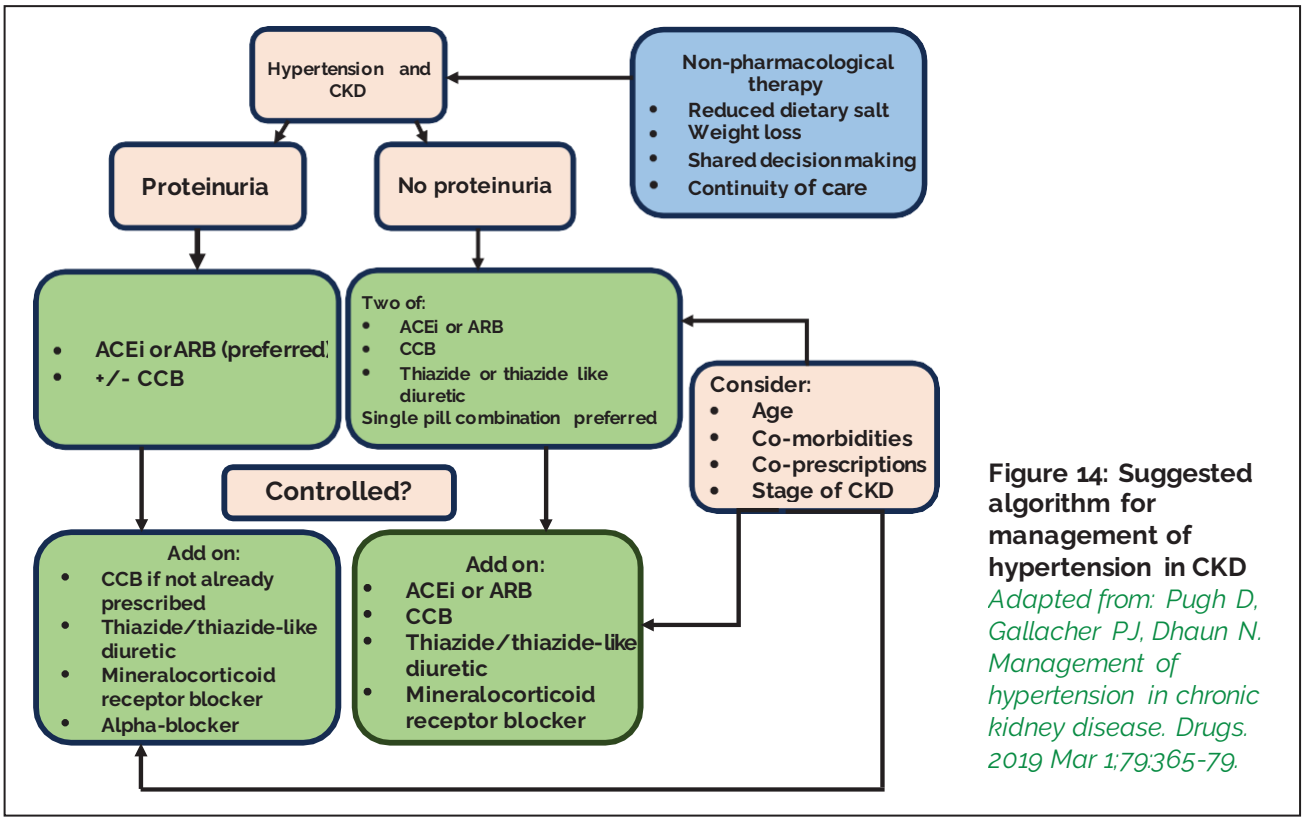


Figure 14: Suggested algorithm for management of hypertension in CKD
Adapted from: Pugh D, Gallacher PJ, Dhaun N. Management of hypertension in chronic kidney disease. Drugs. 2019 Mar 1;79:365-79.

4.3.2.2. Diabetes Mellitus

Up to 40% of people living with diabetes develop CKD - a key marker of cardiovascular risk in diabetes.[29] The presence of diabetes worsens the outcomes in all stages of CKD (cardiovascular outcomes, dialysis survival, and post-transplant survival).[30]

Health workers should detect diabetes early and manage it optimally to slow or stop the progression of chronic kidney disease and prevent cardiovascular disease in people with diabetes.

Screening and diagnosis

CKD in patient with DM is often diagnosed through routine screening. CKD screening should start at diagnosis of T2D because evidence of CKD is often already apparent at this time. For T1D, screening is recommended commencing 5 years after diagnosis, prior to which CKD is uncommon.[31]

SCREENING RECOMMENDATIONS IN PATIENTS WITH DIABETES
Type 1 diabetes Mellitus- Every year 5 years after diagnosis
Type 2 diabetes Mellitus- At diagnosis and every year after diagnosis

Diabetes management

Management of diabetes mellitus in CKD needs individualization according to patient circumstances (e.g. disease duration, life expectancy, comorbidities, and established vascular complications).
Optimal blood glucose control significantly reduces the risk of developing microalbuminuria, macroalbuminuria and/or overt nephropathy in people with type 1 or type 2 diabetes. [32]

Management of diabetes mellitus follows standard management practices that include lifestyle modification, structures health education, self-care aspects, self-monitoring of blood glucose and individualized drug therapy as shown in the algorithm in Figure 11.

Health workers should individualize the targets of treatment of diabetes based on patient preferences, severity of CKD, presence of macrovascular complications or comorbidities life expectancy, hypoglycemia burden, choice of glucose-lowering agents and availability of resources.

Drug therapy in diabetic patients with CKD

Table 8 shows the choice of antidiabetic agents that can be used in diabetic patients with CKD. Metformin remains the preferred agents in patients with eGFR> 30. In patient who fail to reach targets, we recommend addition of SGLT2i such as dapagliflozin until eGFR of 20 . In patients, who fail reach target GLP1 agonists are added. In our setting, where LP1 agonists are not readily available, we suggest the addition of insulin and DDP4 inhibitors and sulfonylureas

Algorithm for the management of diabetes in patients with chronic kidney disease

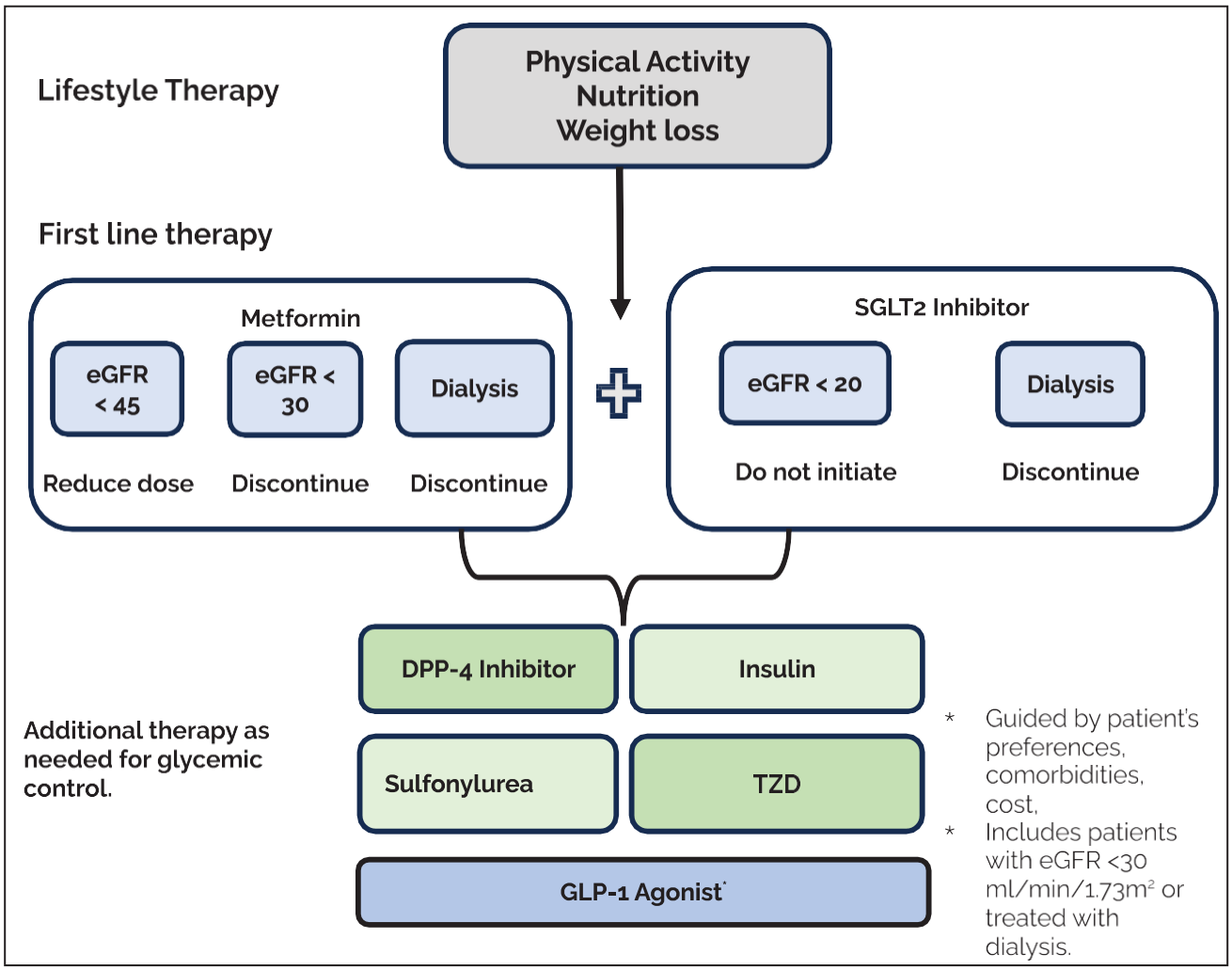


Figure 15: Treatment Algorithm for Selecting Antihyperglycemic Drugs for People with Type 2 Diabetes and CKD.

CKD: Chronic kidney disease rate; eGFR:estimated glomerular filtration (ml/min/1.73 m2); DPP-4:dipeptidyl peptidase-4; GLP-1: Glucagon-like peptide-1; SGLT2: sodium–glucose co-transporter-2; T2D:type 2 diabetes; TZD:thiazolidinedione Modified from Kidney Disease: Improving Global Outcomes. KDIGO 2020 clinical practice for diabetes management in chronic kidney disease. Kidney Int 2020; 98 (4): S1– S115. Reproduced with permission.

Table 10: Choice of antidiabetic agents used in diabetic patients with CKD.

DRUG CLASS	CONSIDERATION
Metformin	Preferred for glycemic control in T2DM Recommended for use in most patients with T2DM and CKD who have eGFR ≥30 mL/min/1.73 m^2, Reduced to 1,000 mg daily for patients with eGFR 30–44 mL/min/1.73 m^2 Avoid in eGFR < 30 or on dialysis, or in patients with high risk of lactic acidosis e.g. patients with volume depletion
SGLTi	Proven kidney and cardiovascular benefit- e.g. canagliflozin, dapagliflozin, Should be avoided in patients with eGFR >20 mL/min/1.73 m^2 or patients on dialysis Additional drug therapy as needed for glycemic control is guided by patient preference, cost, eGFR, comorbid conditions
GLP1- agonists	Proven benefit in CKD and CVD benefit (liraglutide, semaglutide), Recommended in patients not meeting glycemic target with metformin and/or an SGLT2i or who are unable to use these drugs. No dose adjustments in required CKD Not readily available in our setting
DPP IV inhibitors	Safe to use with dose reduction in renal impairment, Modest efficacy and no evident improvement in kidney or CV outcomes
Insulin	Only alternative in Type 1 DM eGFR> 50 mL/min/1.73 m^2 dose adjustments should be done, eGFR 15- 50 mL/min/1.73 m^2 dose adjustment by 25 %, below 15 mL/min/1.73 m^2 dose adjustment by 50%. Human insulins recommended

CKD: Chronic kidney disease; CVD: Cardiovascular disease; T2D:Type 2 diabetes; eGFR: estimated glomerular filtration rate; SGLT2: Sodium glucose co-transporter 2; GLP1: Glucose-like peptide-1; DPPIV:dipeptidyl peptidase-4

Glycemic targets in CKD

HbA1c target for CKD who are not on dialysis is <6.5 in patients with earlier stages of CKD, less comorbidities and better hypoglycemic awareness, while target of and <8.0% for more advanced disease, short life expectancy and impaired hypoglycemic awareness CKD as shown in figure 12.

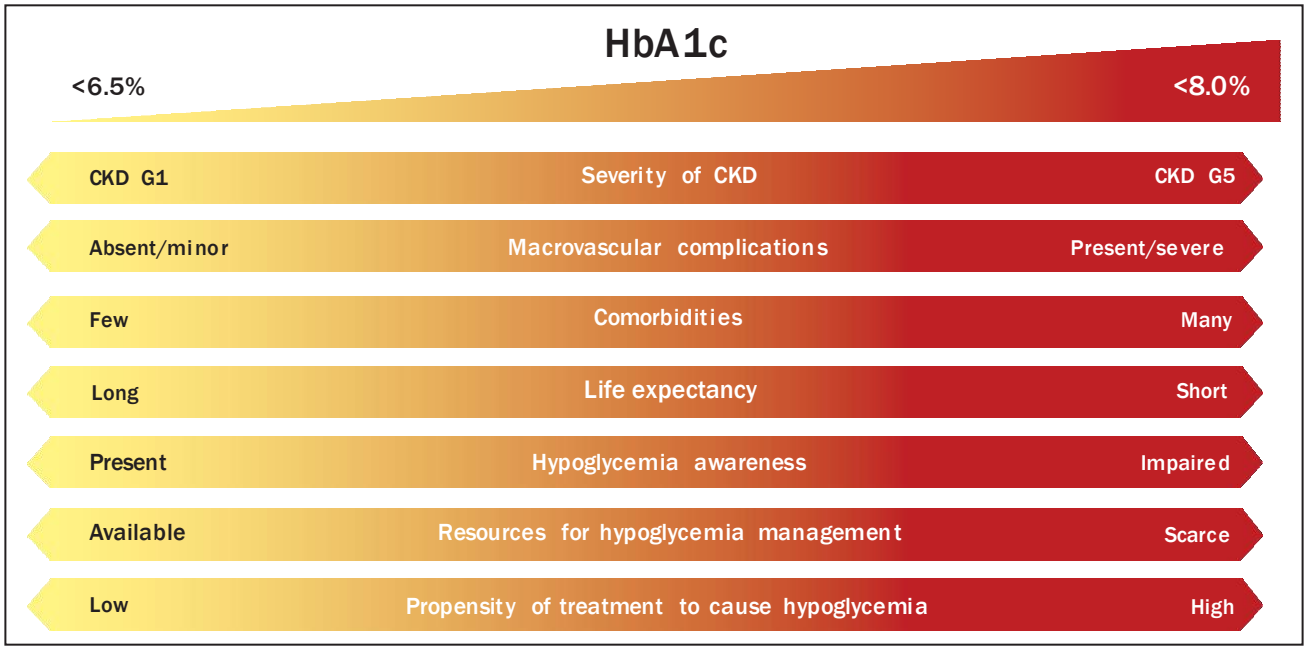


Figure 16: Targets for glucose control in CKD patients with diabetes mellitus

Adapted from Rossing P, Caramori ML, Chan JC, Heerspink HJ, Hurst C, Khunti K, Liew A, Michos ED, Navaneethan SD, Olowu WA, Sadusky T. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. Kidney International. 2022 Nov 1;102(5):S1-27.

Monitoring glycemic control

We recommend monitoring of glycemic control in patients with diabetes and CKD using glycated hemoglobin (HbA1c) twice a year in patients who are controlled to target; and every three months in patients above the target.

CAUTION: ⚠ HBA1C is not accurate in stage 4 and 5 of CKD. In these patients, Self-monitoring of blood glucose (SMBG) is used

Self-monitoring of blood glucose (SMBG) and use of continuous glucose monitoring (CBG) can help monitor for episodes of hypoglycemia.

For patients who do not have access to these modalities, glucose lowering therapies that pose lower hypoglycemic risks such as metformin, SGLT2i and DDP4i are preferred.

4.3.2.3 Heart failure

The heart and kidneys are closely related. The dysfunction of either of those organs leading to a functional deterioration of the other. Heart failure(HF) and CKD share risk factors, such as diabetes, hypertension, and coronary artery disease. Additionally, acute and chronic heart failure, lead to worsening of the kidney function.

Most drugs used in treatment of heart failure also have benefit in the management of CKD through BP reduction and control of albuminuria. However, the same drugs can lead to a deterioration in kidney function and expose the patient to complications, such as hyperkalemia leading to dialysis.

Health workers should anticipate worsening kidney functions and electrolyte abnormalities that may occur during heart failure treatment

Choice of antifailure therapies should be individualized depending on the Stage of CKD. Goal directed medical therapy (GDMT), the cornerstone of pharmacological therapy for patients with heart failure with reduced ejection fraction (HFrEF), should be used in patients with CKD. It consists of Angiotensin receptor neprilysin inhibitor (ARNI), evidence-based β-blockers, mineralocorticoid inhibitors and SGLT2i. Figure 13 shows the proposed algorithm for the management of heart failure in patients with CKD.

Detail of the drugs of used in the treatment of heart failure and how they may be used in in different stages of CKD are shown in Table 9

Table 11: Considerationof Pharmacotherapy in heart failure patients with CKD

Agents	CKD St ages 1 – 3	CKD Stages 4 and 5
Angiotensin receptor and neprilysin inhibitor (sacubitril-valsartan)	Should be used in patients with HFrEF instead of ACEis/ ARBs	May be used in HFrEF, with monitoring of creatinine and potassium. Dose modification may be necessary
Sodium -glucose cotransporter 2 inhibitor	Should be used in patients with HFrEF with or without diabetes	Should be used in patients with HFrEF with or without diabetes until a GFR of 20ml/ min/ 1.73m ^{2} Can also be used in HFpEF
ACEis/ ARBs	Maybe used in all patients with HFrEF instead of ARNI, with monitoring of creatinine and potassium	May be used in HFrEF, with monitoring of creatinine and potassium. Dose modification may be necessary.
β-Blockers	Should be used in all patients with HFrEF	May be used in HFrEF. Among patients with ESKD on dialysis, bisoprolol, nebivolol and metoprolol preferred

Mineralocorticoid receptor antagonists	Should be used in HFrEF, with careful monitoring of potassium	May be used in HFrEF, with caution and monitoring of potassium
Ivabradine	May be used in patients with HFrEF with sinus rhythm in whom β-blockers fail to control heart rate or where there is intolerance to β-blockers	Evidence for use is lacking; but may be used with expert guidance
Hydralazine and isosorbide dinitrate	Should be considered in patients with HFrEF who are intolerant to ACEis/ ARBs/ ARNi or as add on inHFrEF who are less responsive to back bone GDMT	May be considered in patients with HFrEF who are intolerant to ACEis/ ARBs r an add on inHFrEF who are less responsive to back bone GDMT .
ACEi, angiotensin-converting enzyme inhibitor; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with reduced ejection fraction; ARB, angiotensin receptor blocker; ARNI, Angiotensin receptor and neprilysin inhibitor; GDMT: Goal directed medical therapy,		

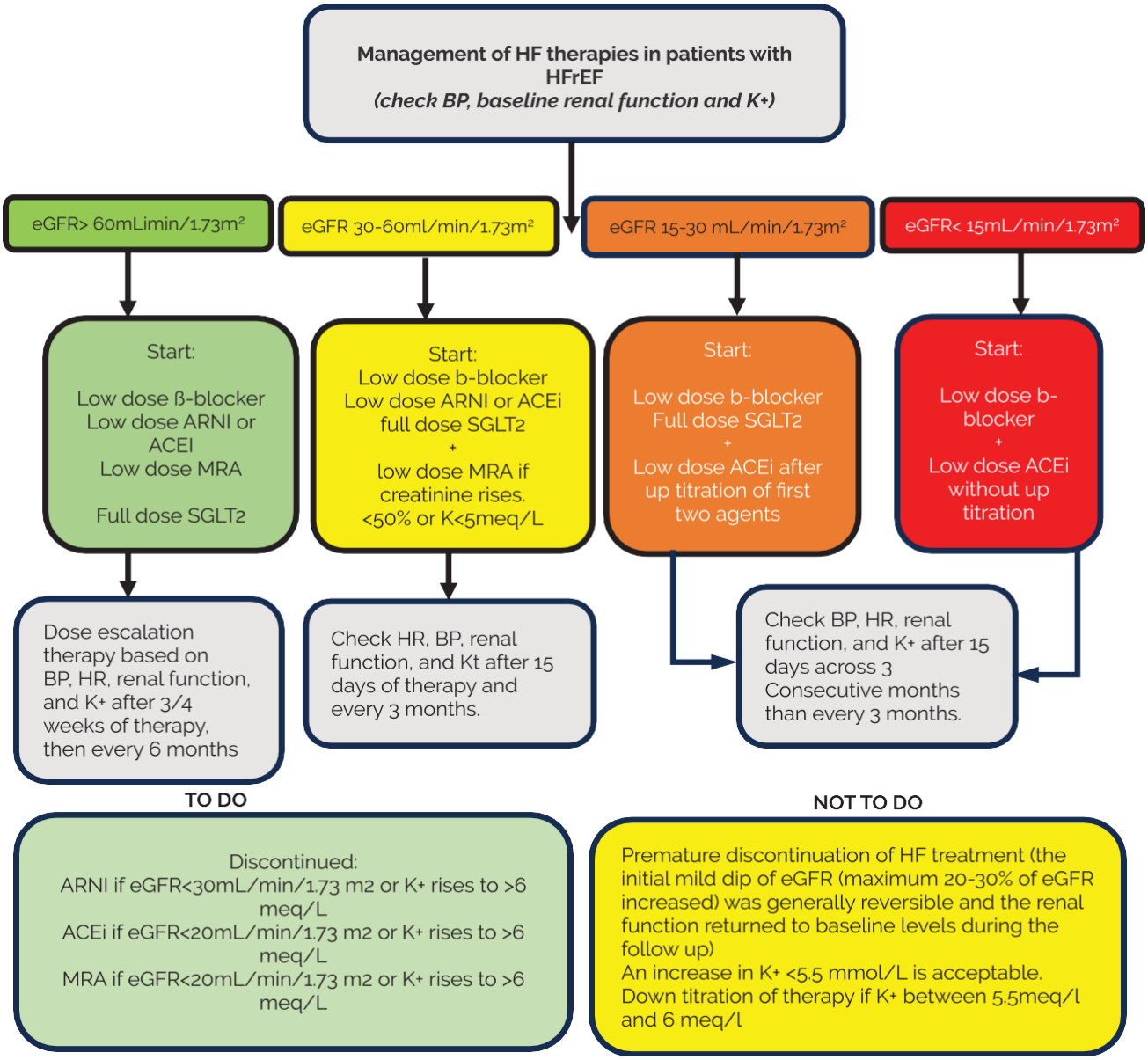


Figure 17: Algorithm for the management of heart failure in CKD

HFrEF: Heart failure with reduced ejection fraction; ARNI : Angiotensin receptor- neprilysin inhibitor; MRA: Mineralocorticoid receptor antagonist; ACEi: Angiotensin converting enzyme inhibitor;

Adapted from Beltrami, Matteo, Massimo Milli, Lorenzo Lupo Dei, and Alberto Palazzuoli. 2022. "The Treatment of Heart Failure in Patients with Chronic Kidney Disease: Doubts and New Developments from the Last ESC Guidelines" Journal of Clinical Medicine 11, no. 8: 2243. https://doi.org/10.3390/jcm11082243

4.3.2.4 Lipid metabolism abnormalities in CKD

Chronic kidney disease is commonly associated with substantial abnormalities of lipid metabolism, including increased LDL, triglycerides, very low-density lipoproteins, and lipoprotein(a), and reduced levels of HDL cholesterol.

Dyslipidemia is more severe in individuals with albuminuria, particularly those with nephrotic syndrome; and is more common as kidney dysfunction progresses. Lipid abnormalities in CKD are associated with increases cardiovascular risk and worsening of kidney function. [33]

Management of dyslipidemia in CKD

In adults with newly identified CKD, evaluation with a standard fasting lipid profile panel (total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides) is recommended.[34] Follow-up measurements are not recommended.

Dyslipidemia classification should then follow the National Cholesterol Education Panel for levels as shown in Table 10.

Table 12: ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dl)

LDL Cholesterol	
<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
≥190	Very high
Total Cholesterol	
<200	Desirable
200-239	Borderline high
≥240	High
HDL Cholesterol	
<40	Low
≥60	High

Adopted from National Cholesterol Education Program (US). Expert Panel on Detection, Treatment of High Blood Cholesterol in Adults. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). The Program; 2002.

The management of dyslipidemia should be individualized. Table 11 gives guidance on approach of management of dyslipidemia.

Table 13 Management of dyslipidemia in CKD

STAGE OF CKD/ ESRD	CONSIDERATIONS	
	18-49 years	>50 years
G1-2	Statin suggested in high-risk individuals*	Statin recommended
G3a-5	Statin suggested in high-risk individuals*	Statin or statin/ezetimibe recommended
Dialysis	Starting lipid lowering therapy not recommended, Continue therapy of already started	Starting lipid lowering therapy not recommended, Continue therapy of already started
Kidney transplant	Statin recommended	Statin recommended

*High risk individual: known coronary artery disease (with previous myocardial infarction or revascularization), diabetes mellitus previous ischemic stroke, diabetes or estimated 10-year incidence of cardiovascular death or non-fatal myocardial infarction> 10%. [30]

We recommend specialist evaluation if fasting lipid levels are severely elevated (very high LDL cholesterol, high cholesterol and).
Lifestyle advice if hypertriglyceridemia is present.
Examples of statins include Atorvastatin, rosuvastatin, simvastatin

4.3.2.5 Sickle cell disease in CKD

Sickle cell disease (SCD) is a major risk factor for CKD. The major pathophysiological mechanism leading to kidney disease in SCD is hypoxia that results from ischemia and hemolysis.[34]
Risk factors associated with progression of CKD to ESKD in SCD include: Hypertension, proteinuria, severe anemia, vaso-occlussive crisis, acute chest syndrome, stroke, pulmonary hypertension, βS- gene haplotype and Parvovirus.[34]

Children with sickle cell disease commonly get episodes of AKI especially during vaso-occlusive events and these recurrent episodes of AKI may increase their risk for CKD. In addition, the prevalence of mineral bone disease is significantly high among children with sickle cell disease .

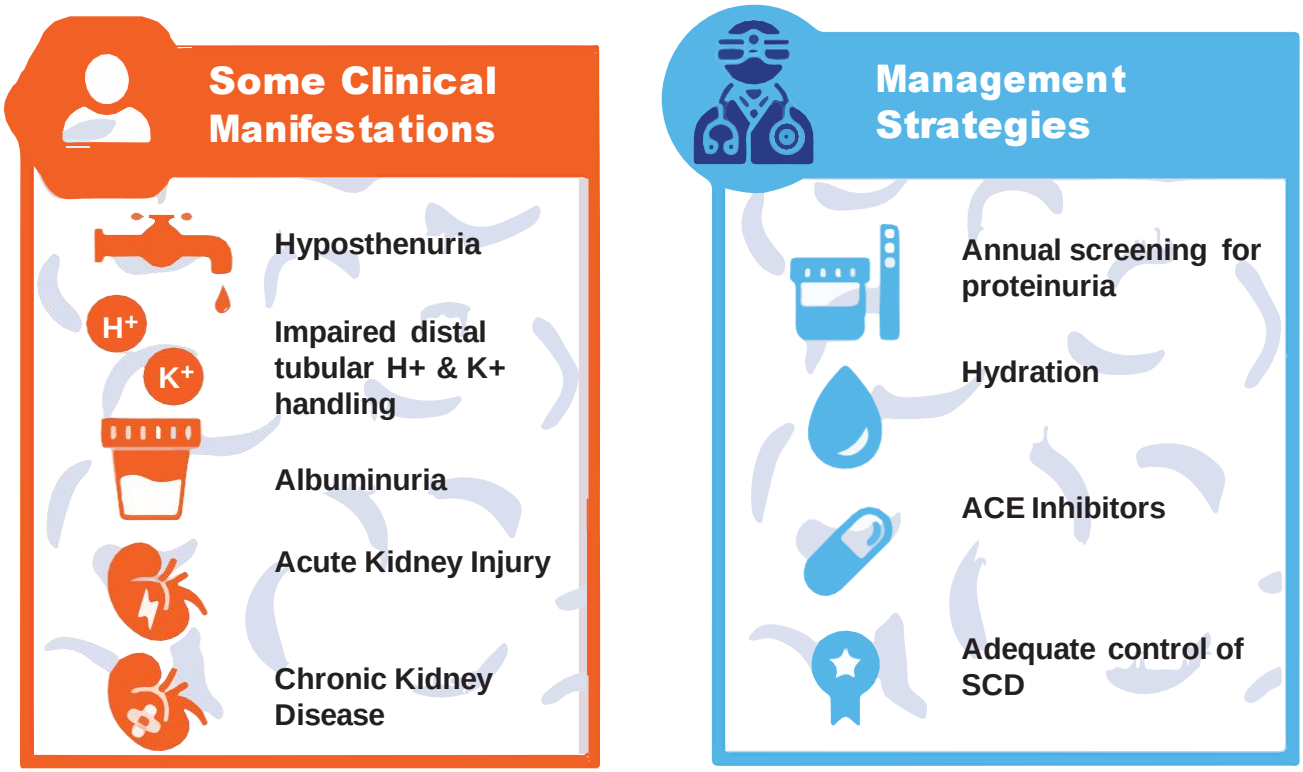


Figure 18: Clinical manifestations and management strategies of sickle cell disease in CKD. *Adapted from Amarapurkar P, Roberts L, Navarrete J, El Rassi F. Sickle cell disease and kidney. Advances in Chronic Kidney Disease. 2022 Mar 1;29(2):141-8.*

Approach to prevention and management of CKD in SCD

Annual screening for CKD persons with SCD in patients aged 10 years and above.
Screening tests include: urine dipstick proteinuria, UACR, and creatinine.
In the treatment of SCD with CKD, we recommend the following measures in treatment of sickle cell nephropathy:

- Adequate control SCD using hydroxyurea, Use renal dose of 7.5- 15mg/kg/day for SCD patients with eGFR <60 mL/min per 1.73 m^2. [36]
- Giving ACEI/ARB in proteinuria of 2+ and above; ACEI/ARB safety needs to be monitored as discussed in previous chapters and these can be temporarily withheld in children with diarrhea, vomiting and/or dehydration.
- Continuing routine treatments- antimalarials, vaccinations, folate

CAUTION: ⚠ For pain control: avoid NSAIDS in eGFR <60 mL/min per 1.73 m2 e.g. - diclofenac, ibuprofen, Preferably use opioids and paracetamol

- Morphine dose should be adjusted according to the CKD stage
- With GFR < 30mL/min per 1.73 m2 consider nephrologists/ specialists review once a year
- Target hemoglobin in SCD patients with kidney disease should be between 10 to 10.5mg/dl to avoid hyper viscosity which would precipitate crises

4.3.2.6 Infections

Infections are a major cause of kidney injury either directly by invasion, indirectly by immune mediated mechanisms, or through their treatment. Common subacute and chronic viral infections (such as hepatitis B virus, hepatitis C virus and HIV) induce glomerular disease which can progress to ESKD.
In individuals with CKD, infections and their treatments can cause worsening of kidney function and pose a significant source of morbidity and mortality.

HIV Infection

HIV associated kidney disease is a common complication of HIV infection and results from direct viral invasion of the glomerular visceral and parietal epithelial cells. Other causes of kidney dysfunction in HIV infection due immunocomplex formation, other coinfections and HIV treatment,.
HIV causes accelerated kidney dysfunction and there is need for close evaluation of HIV patients to avoid progression to ESKD

We recommend the screening, monitoring and treatment algorithm in figure 15 for CKD in people living with HIV.

In treatment of PLWHIV and CKD, there is need for appropriate adjustment of antiretroviral therapy doses according to eGFR. Tenofovir, the backbone of HAART treatment, requires dose adjustment when eGFR <50.
Refer to supplemental table S1 for antiretroviral adjustment for CKD.

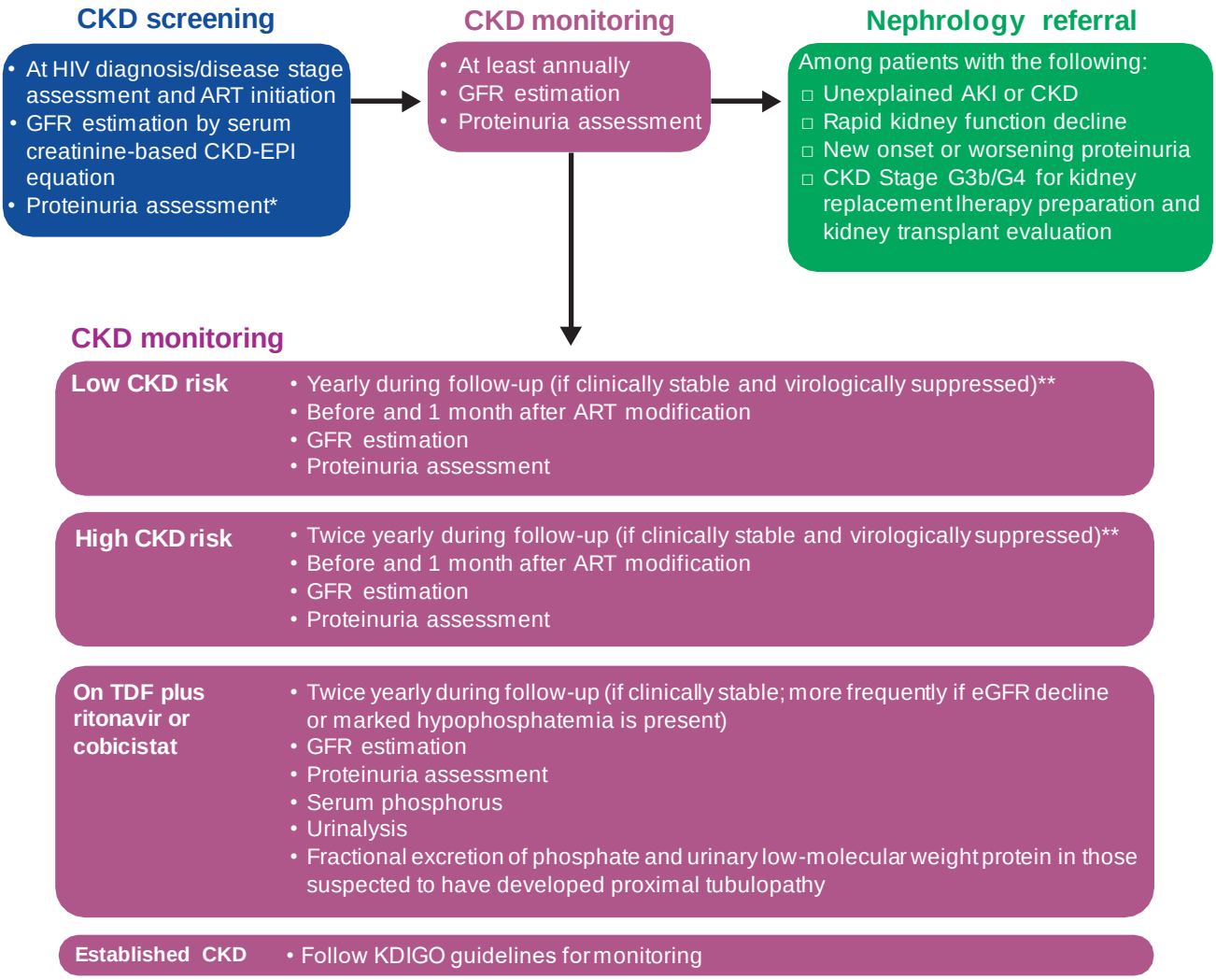


Figure 19: Recommendations for kidney disease screening and monitoring in HIV-positive adults. AKI, acute kidney injury; ART, antiretroviral therapy; CKD, chronic kidney disease; CKD-EPI, CKD Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; TDF, tenofovir disoproxil fumarate.

Adapted from: Swanepoel, C. R. et al. Kidney disease in the setting of HIV infection: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int 93, 545–559 (2018).

WE RECOMMEND:

- Urinalysis all newly diagnosed HIV patients (with UACR estimation where feasible)
- Annual monitoring of e-GFR if low risk of CKD, bi-annual if high risk of CKD
- More frequent monitoring is recommended in persons who are clinically unstable, severely immunocompromised, or viremic.
- Control of traditional risk factors e.g DM, hypertension
- Avoidance of nephrotoxic ART (tenofovir, indinavir, atazanavir, lopinavir) in patients at high risk of CKD progression (TDF in eGFR <50, diabetes mellitus, uncontrolled HTN, history of CVD).
- Dose adjustment for HAART

Tuberculosis

Tuberculosis and CKD relationship is bidirectional as both are immunosuppressive illness. Patients with CKD are more susceptible to TB infection or reactivation of latent TB infection (LTBI) due to their immunosuppression. The risk of TB increases especially among patients with late-stage CKD (stage 3 and above). [37]

High mortality is noted among CKD patients with TB; and arises from delayed diagnosis and side-effects of TB drugs. Typical symptoms of TB (cough and hemoptysis) are less frequent in CKD patients compared to the general population; and the clinical features of TB such as poor appetite and weight loss are similar to those found in late-stage CKD. Additionally, extrapulmonary TB presentations are common, all of which make the diagnosis difficult. Anti-TB medications, some of which are nephrotoxic, also lead to worsening of the stage of kidney failure. [38]

The evaluation CKD patients with TB is complex because of the immunosuppressive nature of both conditions. Health workers should have a high index of suspicion for TB infection in CKD especially among patients with fever, lack of appetite, weight loss night sweats and a high ESR.

After confirmation of TB infection in CKD, renal dose adjustments of antiTB therapy is recommended to increase effective while minimizing toxicity. In patients with eGFR between 30 and 60, lower doses of the anti-TBs medications are recommended while monitoring. Suggested adjustments of anti-TB medications are shown in Supplementary table S2

KEY CONSIDERATIONS

- Renal failure is a risk factor for developing tuberculosis (TB)
- High index of suspicion for extrapulmonary tuberculosis necessary
- Dose adjustments required because of increased toxicity of the anti-TB medicines
- For patients with MDR TB with CKD should be managed in consultation with nephrologist
- Of the first line agents (EHRZ), ethambutol is excreted via the kidneys – accumulation in CKD may lead to can lead to irreversible ocular toxicity. while Pyrazinamide can lead to accumulation of uric acid due to impaired urate excretion.
- In patients with GFR >30, first line drugs RHZE should be given every other day- ref tables
- 2ND LINE drugs-Aminoglycosides e.g Kanamycin and quinolones, doses should be adjusted according to the GFR

HBV and HCV infection

Kidney disease is an important extra-hepatic manifestation of HBV and HCV infection. HCV associated renal disease can either be an immune-complex glomerulonephritis such as membranous glomerulonephritis (MGN), membranoproliferative GN (MPGN), cryoglobulinemic GN and IgA nephropathy (IgAN), or immune-mediated vasculitis (Polyarteritis nodosa).
The disease can present as either nephritic syndrome (hypertension, hematuria, proteinuria, edema), or nephrotic syndrome (high level proteinuria, edema, hyperlipidemia, hypoalbuminaemia and lipiduria).

We recommend screening of all patients with CKD for hepatitis B (HepBSAg) and hepatitis C (Anti-HCV) infection to determine if these are the cause of kidney disease and to plan further management.

Treatment

We recommend referral of patients with CKD found with hepatitis B or hepatitis C infection to hepatologist to manage with nephrologist

Treatment for of HBV related GN and vasculitis involves the use of interferons (conventional IFN-α, or pegylated IFN-α-2a) or oral antiviral agents that consist of either one of nucleotides (adefovir dipivoxil, tenofovir disoproxil fumarate, tenofovir alafenamide) or nucleoside (lamivudine, entecavir, and telbivudine) reverse transcription inhibitors for treatment

WE RECOMMEND:

1. Dose adjustments of drugs according to creatinine clearance.
2. Monitoring for nephrotoxicityin patients on Adefovir and Tenofovir.
3. Use of entecavir in patients with advanced kidney disease.This may be associated with lactic acidosis and may require dose adjustments according to the GFR

Treatment for HCV infection in CKD: relies on the use directly acting antivirals (DDAs) e.g Sofosbuvir (renal dose at GFR < 30).
Interferon therapy should be avoided due to prolonged therapy, poor tolerance, an unsatisfactory sustained viral response.

Infection and vaccination

Patients with CKD are at increased risk for infection. The risk of bacterial infection (particularly pulmonary and genitourinary) increases with the decline in kidney function. According to the 2012 KDIGO guidelines:

- Adults with all stages of CKD should be offered annual vaccination with influenza virus unless contraindicated.
- Adults with stage 4 and 5 CKD who are at high risk of progression ofCKD should be immunized against hepatitis B and the response confirmed by immunologic testing.
- Adults with CKD stages 4 and 5 should be vaccinated with polyvalent pneumococcal vaccine unless contraindicated. Patients who have received pneumococcal vaccination should be offered revaccination within five years.

4.3.2.7 Autoimmune Diseases

Autoimmune conditions are a common cause of chronic kidney disease and ESKD. Kidney damage occurs because of immune-mediated damage to the glomerulus. Immunosuppressive therapies are key to the management of autoimmune kidney conditions.

We recommend that patients with suspected autoimmune disorders are referred for specialist evaluation and management

4.4.0 Principal 4 Screen and manage complications

4.4.1 Anemia in CKD

Anemia is a common complication in CKD occurring in about 40% of patients with CKD.[39] The prevalence of anemia increases with advancing stages of CKD.

The main causes of anemia include low production of erythropoietin, a hormone that helps to support the bone marrow to make more blood. Other causes include reduction in production of red blood cells due to nutritional deficiencies mainly iron, folate and vitamin B12, reduced red blood cell survival from intravascular or extravascular hemolysis, and blood loss from multiple venipunctures, GIT uremia and sometimes dialysis.

Signs and symptoms of anemia in CKD

The clinical presentation of anemia of CKD is like that of anemia due to other causes. Symptoms include shortness of breath, GBW, fatigue, dizziness, headaches, easy fatigability. Signs on physical examination include pallor, tachycardia and respiratory distress.

Evaluation

The aim of evaluation is to find the cause of anemia. The important investigations include Complete blood count (CBC) with differential (RBC, HB, HCT, MCV). An assessment for nutritional deficiencies like iron, Vitamin B, and folate) is important as initial work up. Other tests may include: fecal occult blood, abdominal ultrasound scan, Gastro-intestinal endoscopy etc.

Management:

The goal of management is to increase the RBC production and improve renal function if possible. Erythropoietin stimulating agents (ESAs) together with iron supplementation are the treatment of choice.

Erythropoietin stimulating agents (ESAs)

Erythropoietin (EPO) deficiency is the leading cause of anemia in patients with CKD. Deficiency of EPO retards maturation of red blood cells; and decreases the survival of these immature red blood cells. The anemia of EPO deficiency in CKD is usually normocytic normochromic. Therefore, other forms of anemia should trigger investigating for additional causes of anemia.
Treatment with ESA is effective in raising the mean hemoglobin and reduces the need for blood transfusions and its attendant complications in patients with stage 3 to 5 CKD

WE RECOMMEND

1. **Treatment with an erythropoiesis-stimulating agent (ESA) such as epoetin alfa or darbepoetin alfa when the hemoglobin level is below 10 g/dL.** [40–42]
2. **ESAs are not started at hemoglobin level greater than 10 g/dL.** [40]
3. **Target hemoglobin level NOT more than 12 g/dL in CKD patients on ESAs.** [41]

Target hemoglobin levels of greater than >11.0 gm/dl after initiating ESA therapy confer an increased risk of adverse side effects, especially of hypertension and stroke without attendant improvement in quality of life. [40]

Caution should be exercised in patients with malignancy; alternatively, consider Roxadustat or daprodustat, which stabilizes hypoxia-inducible factor (HIF) by inhibiting prolyl hydroxylase (PH) enzymes

Iron deficiency anemia in CKD

Iron deficiency is common in patients with CKD for a variety of reasons. Bleeding (e.g., menstrual, GI, operative) and medications that may decrease intestinal iron absorption, such as phosphate binders or gastric acid inhibitors, may contribute to iron depletion. In addition, patients with CKD are at increased risk of inflammation, resulting in elevated hepcidin levels, which may also contribute to poor GI absorption of iron and decreased iron release from macrophages.

Iron deficiency anemia usually co-exists with EPO deficiency. Before starting erythropoietin, patients should have their iron stores checked. The aim is to keep iron saturation at 30-50% and ferritin at 200-500 ng/mL.

For treatment of iron deficiency anemia injectable forms of iron such as irons sucrose or iron carboxymaltose are preferred because anemia because oral iron is poorly absorbed. However, the use of injectable forms is limited by their higher cost, and the need for infusion capabilities. The injectable forms also have a high risk of anaphylaxis and hypotension, which is less with newer IV iron preparations (e.g., iron sucrose, sodium ferric gluconate, ferric carboxymaltose, ferumoxytol)

We suggest initiation of oral iron therapy to support iron requirements in patients with chronic kidney disease.

SUMMARY OF MANAGEMENT OF ANEMIA IN CKD

1. Iron therapy- functional iron deficiency (TSAT less than 20% and a ferritin level less than 100 ng/ml)
2. Erythropoiesis stimulating agent.(ESA)- started at Hb (9-10),stopped when Hb >11.5g/dl due risk of stroke ,worsening HTN,Vascular access thrombosis etc.
3. Blood transfusion in severely anemic patients - However, it has a risk for alloimmunization.
4. Hypoxia-inducible factor (HIF) Stabilizers (prolyl hydroxylase inhibitors)

Note:

- Management should be individualized to patients' needs and access.
- Investigate, treat and rule out all the other causes of anemia in CKD.

4.4.2 Chronic kidney disease and mineral and bone disorder (CKD-MBD)

With progressive reduction in kidney function among patients with CKD, there is deterioration in mineral homeostasis, the normal serum and tissue concentrations of phosphate and calcium are disrupted leading to a rise in levels of parathyroid hormone (PTH) and reduction of 1,25(OH)2D (calcitriol). These events called bone mineral disorder (BMD) are associated with associated with bone complications and vascular calcification, which are associated with increased disease progression, morbidity, and mortality in patients with CKD. [43]

Management of CKD-MBD

According to KDIGO guidelines, the decision to treat for CKD-MBD among patients with CKD Stages G3a–G5D should be based on serial assessments of Phosphorous, Calcium and Parathyroid hormone (PTH) levels considered together. [39]

The management of CKD-MBD involves management of hyperphosphatemia, hypocalcemia, lowering parathyroid hormone levels and providing osteoporosis prophylaxis. In these patients, phosphate levels should be lowered toward normal range. Although highly recommended, dietary restriction of phosphates often fails in most patient. As a result, the use of phosphate binders (eg, calcium acetate, sevelamer carbonate, lanthanum carbonate) has been proposed as a means of reducing elevated phosphorus levels in patients with CKD. The use of aluminum-based phosphate binders should be avoided due to associated complications. The benefits of phosphate binders on mortality in CKD has not been demonstrated in clinical trials.

In patients with hypocalcemia, we recommend treatment with calcium supplements with or without calcitriol

In patients with CKD G5D with hyperparathyroidism, we recommend the use calcimimetics, calcitriol, or vitamin D analogues, or a combination of calcimimetics and calcitriol or vitamin D analogues

4.4.3 Metabolic acidosis in CKD

Metabolic acidosis is common complication of advanced CKD and leads to poor outcomes, such as bone demineralization, muscle mass loss, and worsening of renal function. [44] Metabolic acidosis is assessed by measuring serum bicarbonate concentration and PH where feasible.

We recommend alkali therapy to maintain the serum bicarbonate concentration above 22 mEq/L.

Oral sodium bicarbonate 500mg given three times a day should be used to slow progression to end-stage renal disease. Refer for hemodialysis if acidosis persists despite sodium bicarbonate.

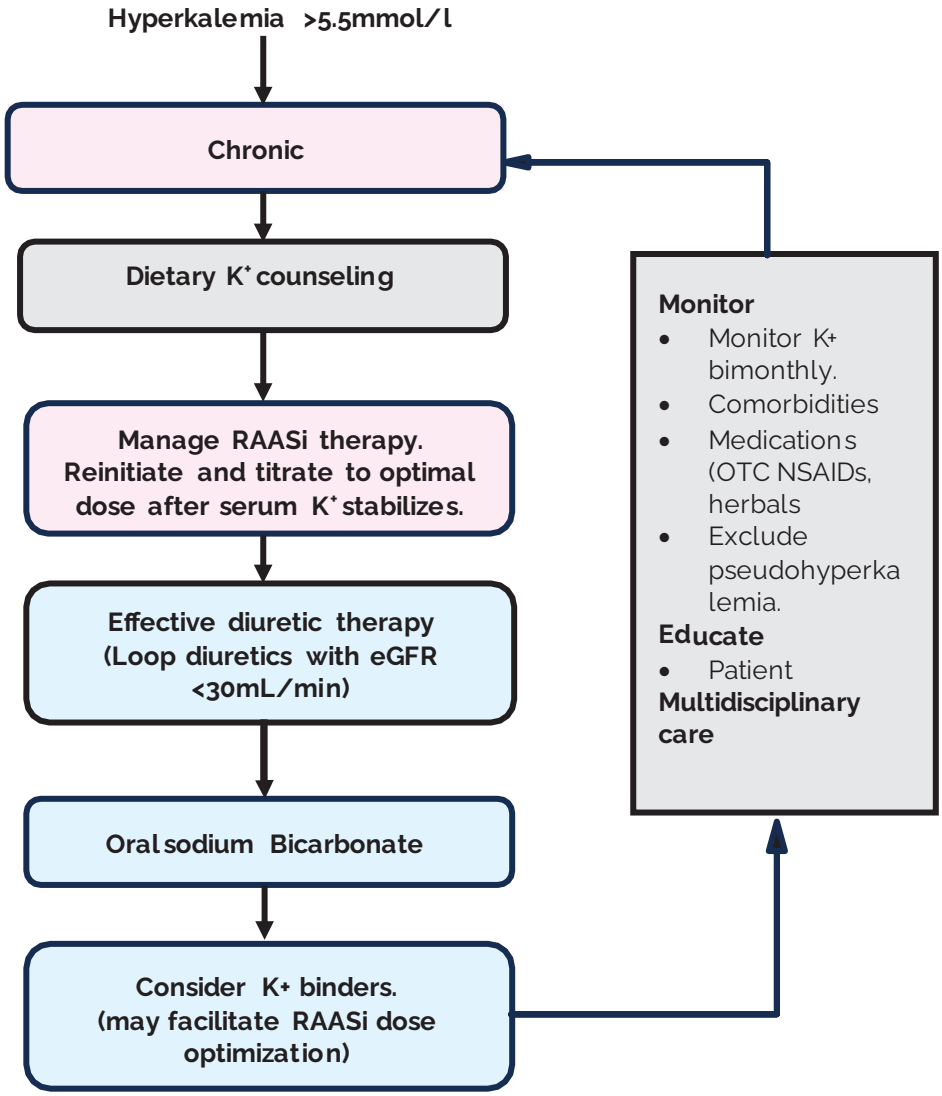
NB: caution should be taken with long term use of sodium bicarbonate due to its fluid retention effects leading to peripheral and pulmonary oedema, weight gain and increased blood pressure.

4.4.4 Hyperkalemia

Hyperkalemia is a common complication in advanced CKD because of reduced urinary potassium excretion with progressive reduction in eGFR. The risk of hyperkalemia is also increased among patient with congestive heart failure, diabetes mellitus, and those on medications such as RAAS inhibitors and mineralocorticoid receptor blockers. Hyperkalemia increases mortality among patients with CKD.

Figure 16 shows our recommendations for the management of chronic hyperkalemia > 5.5mmol/L

In patients with severe acute hyperkalemia, the management considerations in Table 12 are recommended.



[a]In patients with metabolic acidosis
[b]Hypervolemic patients (non-oliguric)
[c]Oliguria or ESRD

Figure 20. Management of chronic hyperkalemia in CKD. ECG: electrocardiography; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; NSAIDs: nonsteroidal anti-inflammatory drugs; OTC: over the counter; RAASi: renin-angiotensin-aldosterone system inhibition.

Table 14. Management of severe hyperkalemia (K> 6.5mmol/l)

Mechanism	Therapy	dose	Onset	Duration
Antagonize membrane depolarization	Calcium	Calcium gluconate, 10% solution, 10ml IV over 10min	1-3 minutes	30-60 minutes
Increase cellular potassium intake	Insulin	Regular insulin, 10IU IV; add dextrose, 50%, 50 ml IV if Plasma glucose < 250 mg/ dl	30 minutes	4-6 hours
	ß2 – Adrenergic agonist	Nebulized albuterol (salbutamol), 10mg	30 minutes	2-4 hours
Remove Potassium	Sodium polystyrene sulphonate	Kayexalate, 20g orally, 8hourly	1 – 2 hours	4-6 hours
	Hemodialysis	Blood flow and dialysate flow as tolerated, avoid excessive K gradient which can cause cardiac ectopy and hypokalemia.	Immediate	Until dialysis completed

4.4.5 Volume overload

Fluid retention and overload may become a problem with worsening CKD severity and usually manifests as oedema. Oedema is rarely caused by early-stage CKD alone (except in nephrotic syndrome) and is more a feature of advanced stage CKD.

The potential causes of oedema in patients with CKD include reduced water excretion and reduced urine output in advanced CKD, Sodium retention and/or excess sodium intake, urine protein loss and low blood albumin in nephrotic syndrome; and medication (amlodipine, nifedipine, steroids).

The clinical assessment should include measurement of blood pressure and respiratory examination. Hypertension is common in fluid overload; and pulmonary oedema may be a feature of more advanced CKD. Ascites may be seen in severe fluid overload.

Management

Mild ankle oedema that is not symptomatic does not usually need to be treated; and may managed conservatively with raising legs, using stockings and moderate sodium restriction.

Diuretic therapy with loop and thiazide diuretics should be used for treating ankle oedema only after assessment of volume status has occurred.

Diuretic resistance may occur in stages of CKD necessitating diuretic doses may need to increase. Refractory oedema in advanced CKD is usually an indication to commence dialysis.

Other management considerations

- Reduction of fluid intake-to less than 1.5L/ day
- Restriction of salt intake to less than 2g/day (half tea spoonful/day)
- Monitoring of weight daily- daily weight loss should depend on the degree of fluid overload however aim at weight loss of 0.5L/day
- Diuretics are given concurrently with above measures.
- Loop diuretics- furosemide- 20- 80mg/day but can be increased every 6 hours, do not exceed 600mg/day
- Torsemide- 10- 20mg/day increased to maximum daily dose of 40mg
- Consider referral for dialysis in acute pulmonary edema or fluid overload not responding to above therapies.

4.4.6 Management of Uremic Complications in CKD

With deterioration of ESKD (kidney failure with eGFR <15mls/min/1.73m2), patients get a number of signs and symptoms related to uremia. These symptoms include nausea, vomiting, fatigue, sexual dysfunction, malnutrition, pericarditis, platelet dysfunction and neuropathy.

4.4.6.1 Malnutrition

Protein malnutrition is common in patients with advanced chronic kidney disease (CKD) and end-stage kidney disease (ESKD) due to lower food intake (principally due to anorexia), decreased intestinal absorption and digestion, and metabolic acidosis. All these derangements can further worsen kidney function leading to poor patient outcomes. Among participants presenting to Mulago Referral Hospital Renal clinic, the prevalence of malnutrition was higher 47.3% of 198 participants compared to 21.3% in those without malnutrition. [45]

A low plasma concentration of serum albumin concentration may indicate a state of malnutrition.

We suggest measurement of serum albumin every 3 months among patients with eGFRs <20 mL/min/1.73 m^2

The management of malnutrition in CKD must be individualized and based on degree of kidney dysfunction, comorbid condition, baseline nutritional status and physical functional capacity. Close nutritional counselling and supervision is recommended,

We recommend referral for kidney replacement therapy in patients whose malnutrition is refractory to individualized nutritional interventions.

4.4.6.2 Uremic neuropathy

Dysfunction of the central and peripheral nervous system including encephalopathy, polyneuropathy and mononeuropathy are important complications of kidney failure. Sensory dysfunction, characterized by the restless leg or burning feet syndromes, are frequent presentations of uremic neuropathy. These complications are absolute indications for the initiation of dialysis.

We recommend initiation of dialysis in patients with uremic neuropathy.

4.4.6.3 Pericarditis

Advances in management have decreased the incidence of pericarditis in patients with CKD, but this problem is still associated with significant morbidity and occasional mortality.

Fever, pleuritic chest pain, and a pericardial friction rub are the major presentations of uremic pericarditis. It is not associated with ST, T elevations because it is metabolic without injury to the pericardium.

The development of unexplained pericarditis in a patient with ESKD is an indication for dialysis (providing there is no circulatory compromise or evidence of impending tamponade). Most patients with uremic pericarditis respond rapidly to dialysis, with resolution of chest pain as well as a decrease in the size of the pericardial effusion.

We recommend initiation of dialysis in patients with uremic pericarditis.

4.5.0 Principle 5: Identify and prepare patients for kidney replacement therapy and/or comprehensive conservative care.

Once a patient has been identified as having stage 5 CKD, considerations for kidney replacement therapy need to be initiated. It is best to initiate discussions for the initiation of KRT early so that the patient is psychologically and physically prepared for the lifestyle changes that this brings. Financial preparation is also necessary since these therapies involve significant out of pocket costs. These discussions should ideally occur at higher level healthcare centers, led by a Nephrologist.

4.5.1 When to refer patients to a nephrologist or regional and national referral hospitals.

Patients who are referred to nephrologists have been shown to have better outcomes. Since we have a few nephrologists, we believe that referral to the higher levels of health care will help improving outcomes for the patients. We do not have any local data to validate this at the time of this guideline.

1. eGFR <30 mL/min/1.73 m2 to facilitate education and planning for RRT (dialysis or kidney transplant)
2. Kidney function that is rapidly worsening without obvious cause
3. Metabolic complications of CKD (e.g., anemia, secondary hyperparathyroidism)
4. CKD of unclear etiology after initial work up, or known or suspected kidney condition requiring specialized care (e.g., autosomal dominant polycystic kidney disease [ADPKD], renal vasculitis)
5. Non-diabetics with heavy proteinuria (24 hr urine protein >500 mg, uPCR >0.5, uACR >300)
6. Diabetics with >3 g proteinuria (uPCR >3) or hematuria

4.5.2 Preparation for kidney replacement therapy

Patients with ESKD may require KRT. The preparation of these patients involves;

1. Extensive health education to help patients make informed decisions about the most appropriate type of KRT for them. This decision may be individualized based on various patient characteristics such as frailty status, extent of cormobidities, accessibility and affordability of care.
2. Identifying a kidney donor, for patients aiming to receive a pre-emptive kidney transplant.
3. Getting an arterio-venous fistular created, for patients aiming to start hemodialysis
4. Learning about home care and referral systems for patients opting for Comprehensive conservative care.

In cases where patients present with advanced disease, lifesaving urgent hemodialysis may need to be initiated to allow time for the patient and family to have the discussion about the definitive option of care.

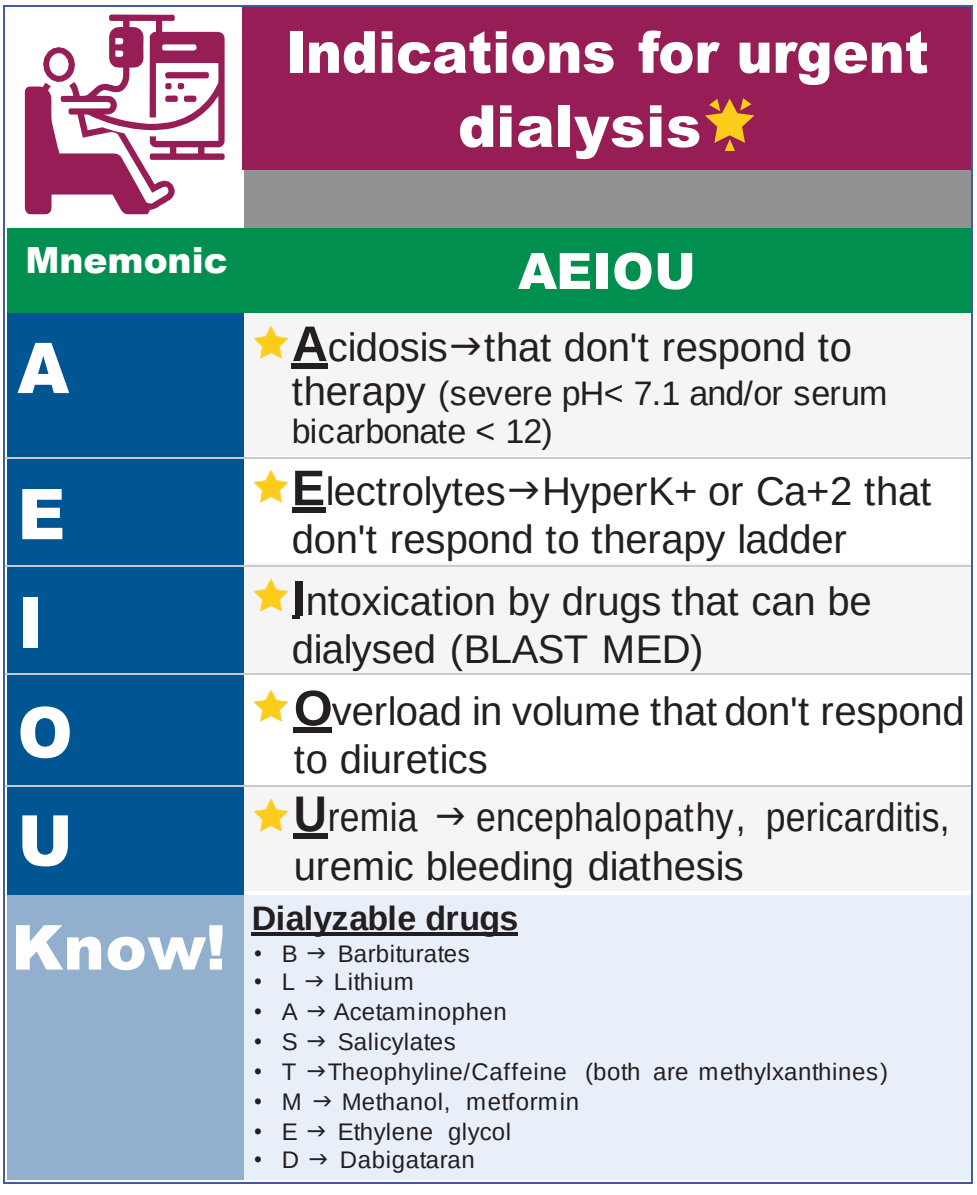


Figure 21: Indications for urgent initiation of Hemodialysis.

Adapted from: http://youtube.com/@pgmedicine2023

4.5.4 Comprehensive conservative care

This is initiated by a nephrologist after extensive discussion with the patient and family and may then be maintained and monitored at lower level healthcare facilities by trained multidisciplinary teams of healthcare workers including medical officers, palliative care teams, VHTs, spiritual and social workers, and family care givers. Training and accreditation is carried out by the Uganda Kidney Foundation (UKF) based on the core curriculum for CCC. The training provides the competencies needed to ensure that the five domains of CCC (Figure 18) are aptly provided as required by the patient. Table 13. summarises which members of the team may be called upon to support these domains of care.

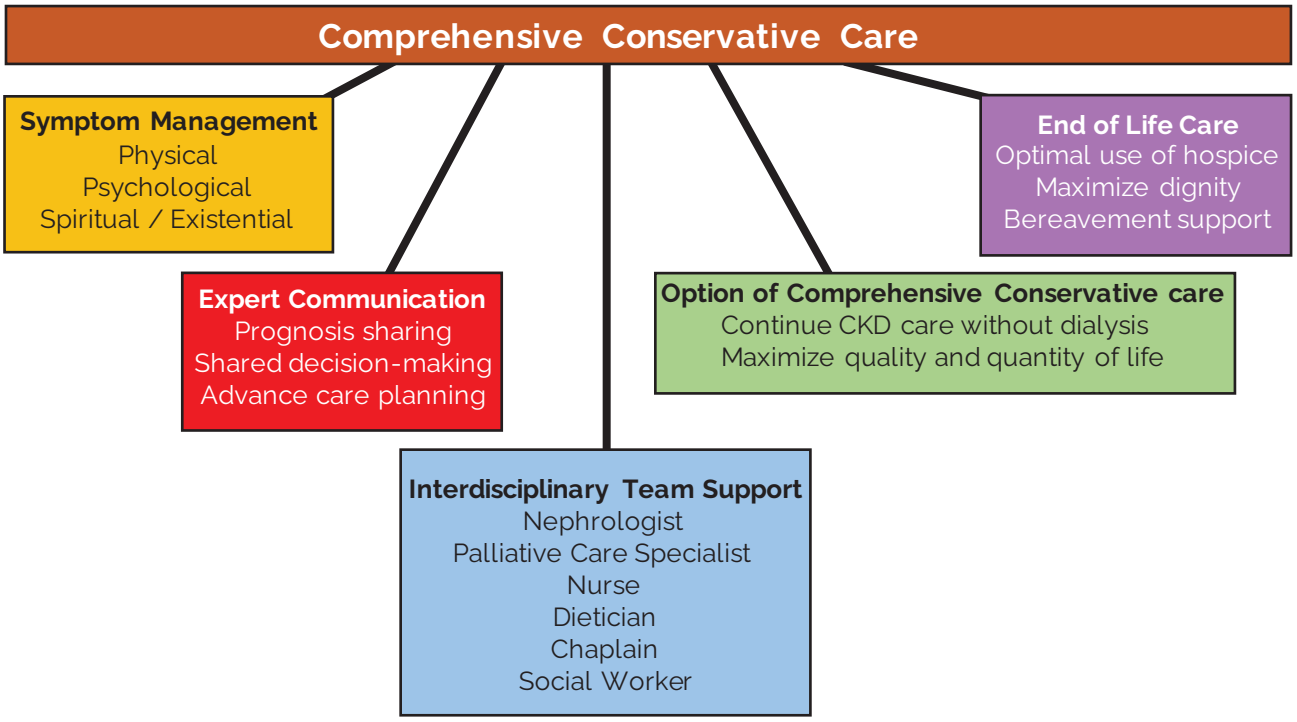


Figure 22: Domains of comprehensive conservative care. CKD- Chronic Kidney Disease
Adapted from, Gelfand, S.L., Scherer, J.S. and Koncicki, H.M., 2020. Kidney supportive care: core curriculum 2020. American Journal of Kidney Diseases, 75(5), pp.793-806.

Domain of Care	Primary conservative care by the internal medicine or nephrology teams	Specialty conservative care by palliative care team consultation
Symptom management	Routine symptom assessment and treatment	Refractory symptom treatment, including pain, neuropathy, itch, nausea, and anxiety/depression
Decision making	Communication about patient priorities, prognosis, dialysis modality options	Assistance with navigation of complex clinical situations or interpersonal dynamics
Interdisciplinary team support	Screening for social, spiritual, or nutritional distress	Access to dieticians, chaplains, and social workers trained in palliation
Conservative care	Medical CKD management with focus on quality of life	Assistance with advance care planning and end of life care

Table 15: Primary providers of various domains of care in the multidisciplinary team management during comprehensive conservative kidney failure care.
CKD, chronic kidney disease.
Adapted from Quill, T.E. and Abernethy, A.P., 2013. Generalist plus specialist palliative care—creating a more sustainable model. New England Journal of Medicine, 368(13), pp.1173-1175.

CHAPTER 5 – MANAGEMENT OF CKD IN WOMEN AND CHILDREN

5.1 Special consideration in women

Women are at an increased risk of CKD. Some risk factors such as recurrent urinary tract infections, autoimmune conditions such as systemic lupus erythematosus, rheumatoid arthritis and Sjogren's syndrome for CKD are more common in women. They may also suffer hypertensive disorders (pregnancy induced hypertension and pre-eclampsia) and AKI in pregnancy. [46]

UNIQUE RISK FACTORS OF CKD IN WOMEN

1. Hypertensive disorders in pregnancy
2. Pregnancy conditions that cause AKI – Puerperal sepsis, hyperemesis gravidarum, post - partum hemorrhage
3. Autoimmune disorders
4. Recurrent UTIs

Identification and management of these unique factors can prevent CKD in women.

A. Sexual and reproductive health of women with CKD

Women with CKD have sexual and reproductive health issues that must be considered during their management. These include contraception, pregnancy and its related complications and post-partum care. These issues must be handled in a multidisciplinary team with a Nephrologist/ Specialist Physician, Obstetrician, and midwife at the core.

The affected women experience disorders of sexual function, menstruation and fertility as shown in the figure below

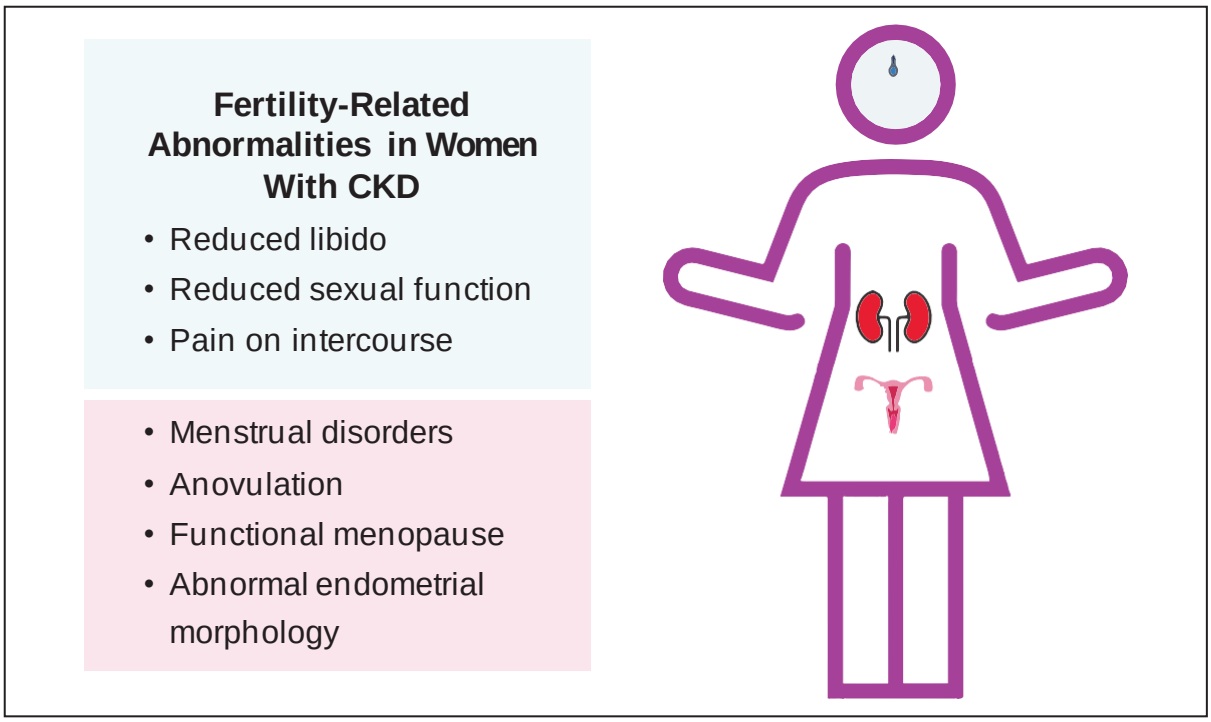


Figure 23: Fertility-Related Abnormalities in Women With CKD

Adapted from Oliverio et al, AJKD © National Kidney Foundation

1. Contraception uses in CKD

Women of childbearing age with CKD can get pregnant. Pregnancies present challenges in management of patients with CKD.

- Health care workers should provide counselling about contraception use (family planning) to all women in child bearing age with CKD.
- Counselling should include information on the increased risk of intrauterine growth retardation, low birthweight, pre - eclampsia and worsening of kidney function.

Recommended family planning methods in CKD.

Barrier methods and progesterone containing contraception (Depo-Provera injections, intra-uterine device, and sub-dermal implants) are recommended.

Permanent contraception methods are encouraged in those who have completed their families because they offer a more durable option for pregnancy prevention.

Estrogen containing contraception (such as combined oral contraception, vaginal rings, and transdermal patches) should be avoided due to increased risk of hypertension and venous thromboembolism.

Pregnancy should be discouraged in women with CKD that are on teratogenic medication (ACE inhibitors, MMF and cyclophosphamide) and during flare up in lupus nephritis. In case of desire for pregnancy, planning with an obstetrician and a nephrologist is recommended.

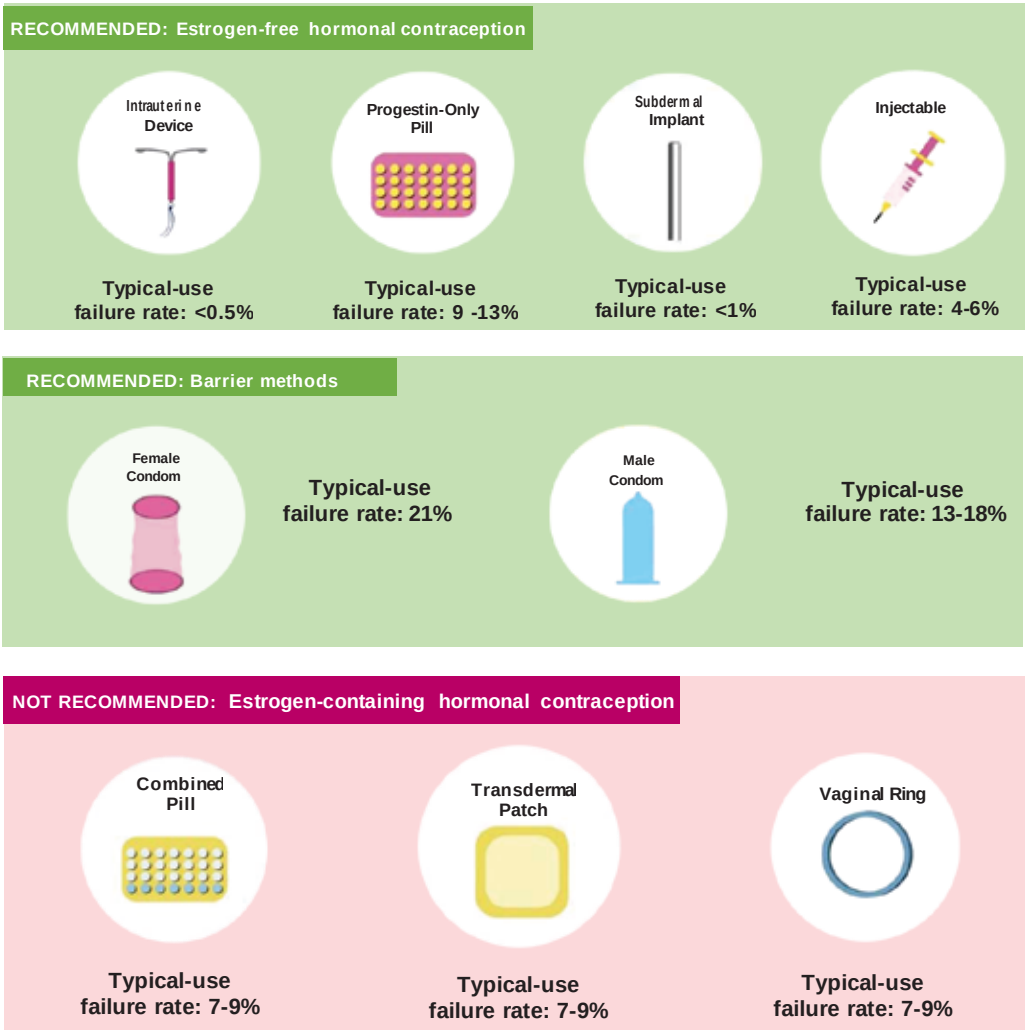


Figure 24: Recommended contraception methods in women with CKD

Adapted from Chang DH et al Kidney International Reports. 2022 Feb 1;7(2):152-64.

B. Pregnancy in women with CKD

Pregnancy presents unique challenges among women with CKD. In early stages of CKD, episodes of AKI arising out of peripartum volume changes, pre-eclampsia, puerperal sepsis, hyperemesis gravidarum, peripartum hemorrhage and severe malaria in pregnancy may lead to worsening of the CKD and progression to ESKD.
More advanced stages of CKD are associated with adverse maternal and fetal outcomes including preterm delivery, low birth weight and worsening of kidney disease.

1. Estimating GFR in pregnancy

Estimating eGFR using creatinine-based equations is inaccurate. Health workers should monitor kidney function using serial creatinine measurements and AUCR to detect reduction in kidney function in pregnancy. Patients with rising creatinine and protein should be referred to nephrologists.

2. Diagnosis of pre-eclampsia in CKD

The diagnosis of pre-eclampsia without CKD is premised on the presence of proteinuria and hypertension, which are identical to the features of CKD. This makes the diagnosis of the conditions difficult especially if the follow-up is not adequate.
Health workers should consider the diagnosis pre-eclampsia if there is worsening proteinuria and hypertension at 20 weeks of pregnancy or later.
Uterine artery doppler measurements where available, may be used monitor placental flow; and diagnose pre-eclampsia superimposed on CKD.

We recommend monitoring fetal wellbeing using ultrasound in pregnant women with CKD.
We suggest the use of umbilical artery Doppler to help predict fetal distress where available.

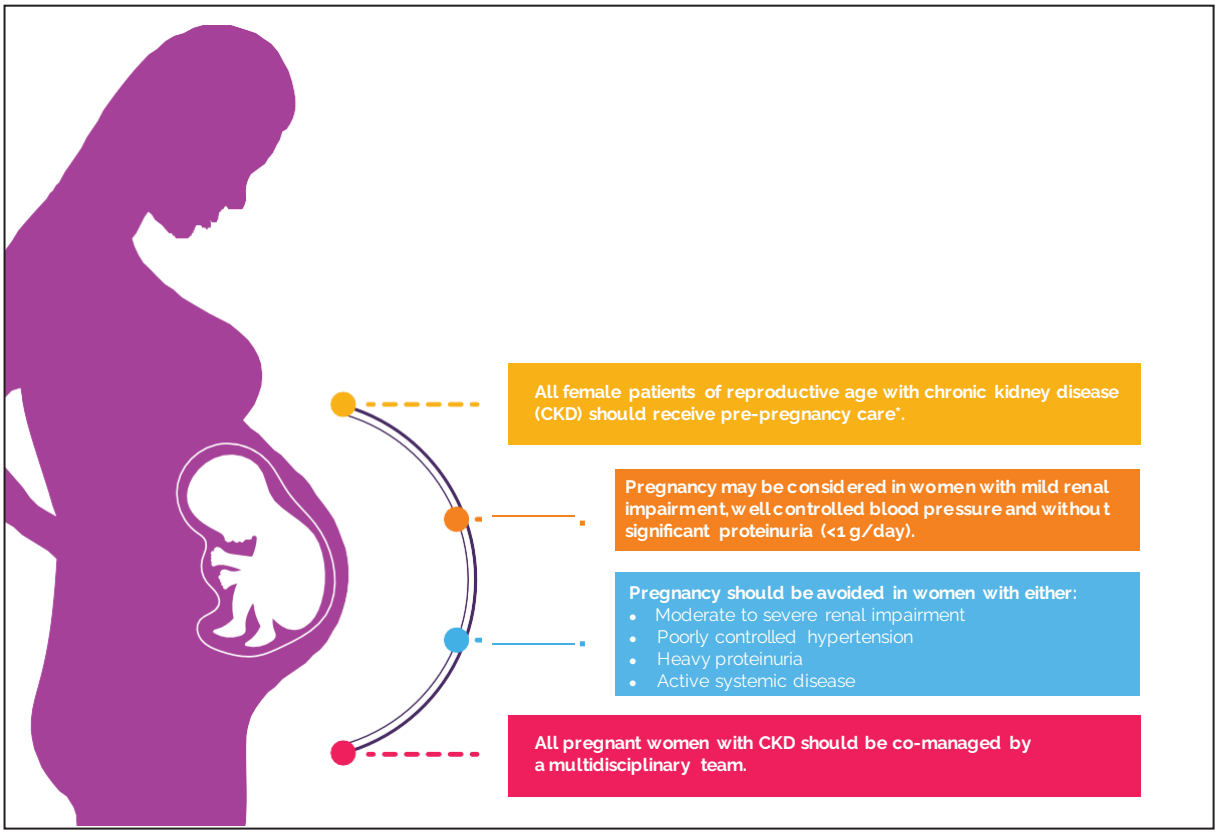


Figure 25: Management of pregnant women with Chronic Kidney Disease

C. Medications in women with CKD in pregnancy

Patients with CKD are usually on multiple drugs and some of these may be contraindicated in pregnancy. Table 13 offers guidance on how some commonly used medications should be utilized in pregnancy

Table 16 Fetal Risks of Common Kidney Medications in Pregnancy and Suggested Alternatives

	Associated adverse pregnancy outcomes	**When to stop relative to pregnancy**	**Potential alternatives**
Conservative Therapies			
ACEIs and ARBs	Renal tubular dysplasia, postnatal kidney failure, oligohydramnios, growth restriction, pulmonary hypoplasia, hypocalvaria if exposure in second and /or third trimesters	For women with non-proteinuric kidney disease, consider stopping before attempts to conceive; for those with progressive proteinuric kidney diseases, can stop in early first trimester	Labetalol, nifedipine, and methyldopa and commonly used antihypertensives in pregnancy with little to no fetal risks
Mineralocorticoid receptor antagonists	Similar to ACEI/ARB; additional concerns regarding feminization of male fetuses due to antiandrogenic properties of spironolactone	Stop before trying to conceive	
SGLT2 inhibitors	No safety data in humans; animal data suggest it may affect kidney development and maturation in utero	Currently advised to stop 6 weeks before conception	
Immunosuppression			
Mycophenolate mofetil	Increased miscarriage rate, microtia, orofacial clefts, ocular defects, micrognathia, congenital heart defects, agenesis of corpus callosum, esophageal atresia, digital hypoplasia	Discontinue ≥ 6 weeks before conception	Glucocorticoids may be used at lowest effective dose, but pulse therapy safe when needed; azathioprine, cyclosporine, tacrolimus, IVIg and PLEX also compatible with pregnancy; switch from mycophenolate mofetil to azathioprine typically occurs ~ 3 months before conception to ensure disease stability
Cyclophosphamide	Teratogenicity risk is highest in first trimester: growth restriction , ear and facial abnormalities , hypoplastic limbs; in later pregnancy, neurologic damage with developmental delays and fetal demise can occur	Discontinue ≥ 6 months before conception	
Rituximab	Neonatal B-cell depletion and other cytopenias when administered in second or third trimester	Can consider if no options available, but best before 16 weeks	

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; IVIg, intravenous immunoglobulin G;PLEX,plasmapheresis;SGLT2,sodium/glucose co-transporter 2

5.2.0 Special consideration in children

5.2.1 Etiology of CKD in children

The causes of CKD in children are different from those in adults. CKD in children is caused by congenital anomalies of the kidney and urology tract (CAKUT). Other causes include glomerular causes which are more common in older children; and genetic disorders.

Table 17 common cause of kidney disease in children

Congenital anomalies of the kidney and urinary tract (CAKUT) - 19%	kidney aplasia/hypoplasia/dysplasia, reflux nephropathy, obstructive uropathy anomalies (eg, posterior urethral valves) and polycystic kidney disease.
Glomerular diseases	Postinfectious Glomerulonephritis Parasitic infections such as schistosomiasis HIV-related nephropathy, Sickle cell disease APOL1 gene mutation Acute kidney injury following severe acute infections (diarrhea, malaria, pneumonia} Protein-energy malnutrition Prematurity, low birth weight and birth asphyxia
Others	Genetic disorders: Alport syndrome, cystinosis, oxalosis, and Interstitial nephritis Unidentified or unknown primary underlying etiology

5.2.2 Diagnosis of CKD in children

A diagnosis of **CKD in children is made if one of these** criteria is present

- GFR of less than 60 mL/min per 1.73 m2 for greater than three months regardless of whether other CKD markers are present.
- GFR greater than 60 mL/min per 1.73 m2 that is accompanied by evidence of structural damage or other markers of kidney function abnormalities, including proteinuria, albuminuria, renal tubular disorders, or pathologic abnormalities detected by histology or inferred by imaging.

Adapted from [K/DOQI clinical practices for chronic kidney disease: evaluation, classification, and stratification. AU National Kidney Foundation SO Am J Kidney Dis. 2002;39(2 Suppl 1):S1.]

5.2.3 Risk stratification of CKD in children

KDIGO clinical practice s risk stratification criteria; like that used in adults is applied for patients greater than 2 years

Children below 2 years:

The KIDGO clinical practice risk stratification criteria cannot be used in children below 2 years because their GFR is normally lower than the values in older individuals and would overestimate the stage of disease.

Kidney impairment can be detected by comparing creatinine derived eGFR based on serum creatinine and comparing it with normative age-appropriate values (see table below).

- **Moderate reduction is defined as an age specific GFR value between 1 to 2 SD below the mean**
- **Severe reduction is defined as an age specific GFR value >2 SD below the mean**

Table 18. Plasma pediatric creatinine reference intervals (2.5th to 97.5th percentiles)

Enzymatic creatinine			Jaffe creatinine		
Age group	mg/dL	micromol/L	Age group	mg/dL	
0 to 14 days	0.32 to 0.92	28 to 81	0 to 14 days	0.42 to 1.05	37 to 93
15 days to <2 years	0.10 to 0.36	9 to 32	15 days to <1 year	0.31 to 0.53	27 to 47
2 to <5 years	0.20 to 0.43	18 to 38	1 to <4 years	0.39 to 0.55	34 to 49
5 to <12 years	0.31 to 0.61	27 to 54	4 to <7 years	0.44 to 0.65	39 to 57
12 to <15 years	0.45 to 0.81	40 to 72	7 to <12 years	0.52 to 0.69	46 to 61
15 to 19 years (male)	0.62 to 1.08	55 to 95	12 to 15 years	0.57 to 0.80	50 to 71
15 to <19 years (female)	0.49 to 0.84	43.3 to 74	15 to < 17 years (male)	0.65 to 1.04	57 to 92
			15 to <17 years (female)	0.59 to 0.86	52 to 76
			17 to < 19 years (male)	0.69 to 1.10	61 to 97
			17 to <19 years (female)	0.60 to 0.88	53 to 78

Adapted from Colantonio DA et al, Clinical chemistry. 2012 May 1;58(5):854-68.

Creatinine pediatric reference values measured by 2 different laboratory assays: enzymatic reaction by isotope dilution mass spectrometry (IDMS) and the Jaffe reaction. Creatinine values are based on age, and, for adolescent patients, reference values are also based on sex.

Data from: Colantonio DA, Kyriakopoulou L, Chan MK, et al. Closing the gaps in pediatric laboratory reference intervals: a CALIPER database of 40 biochemical markers in a healthy and multiethnic population of children. Clin Chem 2012;58:854.

Calculation of glomerular filtration rate — The Schwartz formula was devisedin the mid-1970s to estimate GFR in children. Estimation of GFR in children with CKD uses serum creatinine-based formulas which consider the height of the child, serum creatinine, and a constant "k" that is based on the creatinine assay that has been used. eGFR= 41.3xheight/Scr. (height in cm, SCr in umol/l); (note: CREAT in umol/l divide by 88.4 = creat in mg/dl)

The online calculator below can be used:
https://www.kidney.org/professionals/kdoqi/gfr_calculatorped

5.2.4 Management of CKD in children

The goals of CKD management in pediatric patients include (A) slowing disease progression, (B) prevention and treatment of complications, and (C) optimizing growth, development, and quality of life.

Achievement of these goals requires a multi-disciplinary team as illustrated in figure 16

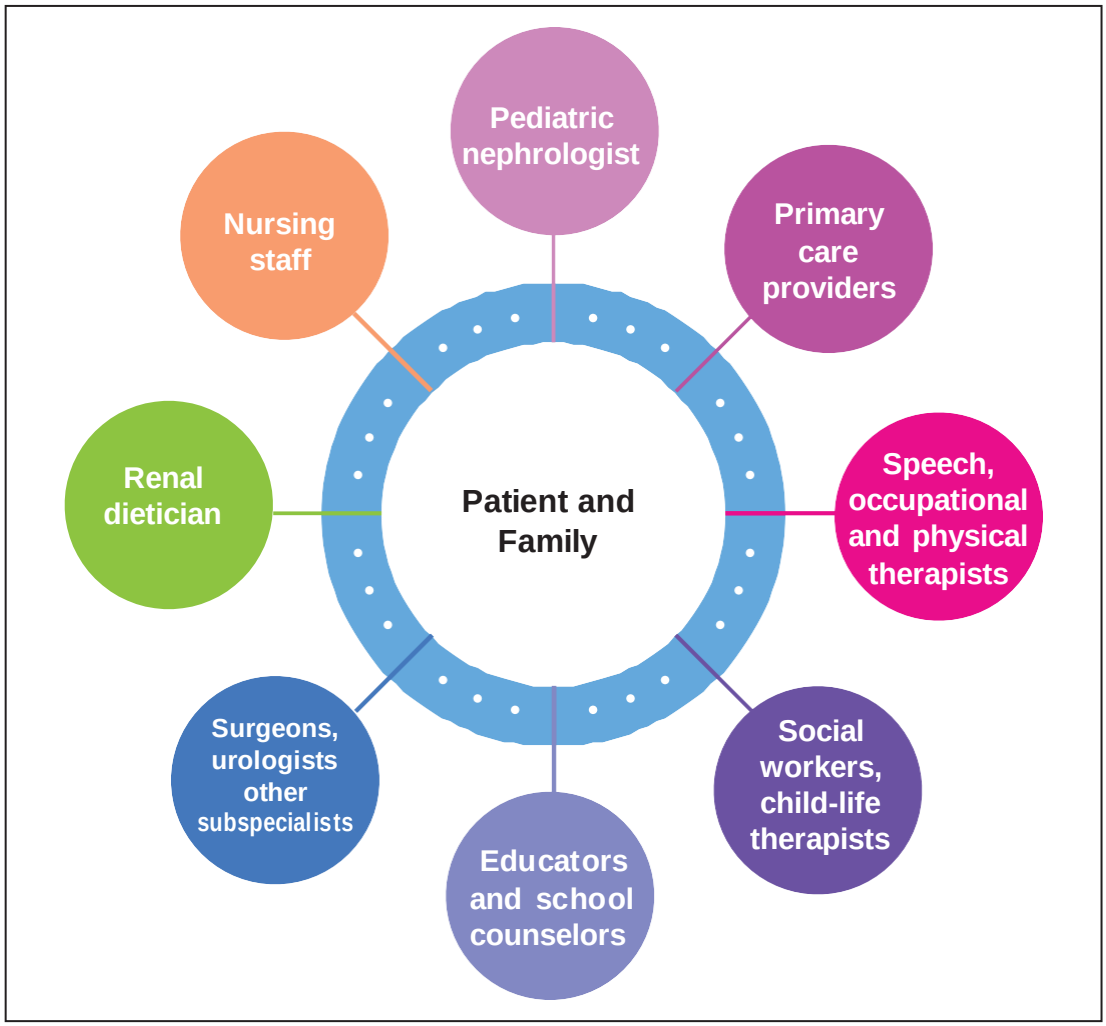


Figure 26: Multi-disciplinary team required in management of CKD in children

A. Slowing progression of disease

1. Treat underlying cause
2. Correct anatomical defects of the genital urinary system (such as obstructive uropathy)
3. Manage nephrotic syndrome and glomerulonephritis with immunomodulators
4. Prevent and aggressively manage conditions that may cause acute kidney injury such as malaria, diarrheal diseases. Adequate rehydration is recommended in such patients.
5. Avoid or cautiously use nephrotoxic agents such as nonsteroidal anti-inflammatory drugs, contrast agents, aminoglycosides, amphotericin B, cyclosporine, and tacrolimus.
6. Control blood pressure with ACEI/ ARB – based regimen. (please refer to safety text in previous sections when using ACEIs/ ARBs)
7. Update immunizations
8. Reduce proteinuria with ACEI/ARB
9. Manage sickle cell disease.

B. Manage complications

1. Fluid and electrolytes abnormalities
2.. Bone mineral diease
3. Growth abnormalities
4. Anemia
5. Hypertension

Early asymptomatic CKD: Stages G1 and G2 –

- Close follow-up deterioration of kidney function.
- Treatment of any reversible cause of kidney dysfunction and prevent or slow the progression of CKD.
- Avoidance risk factors that can accelerate the progression of CKD (eg, avoidance of nephrotoxic drugs, recurrent infections, dehydration, obesity, smoking, and use of illicit drugs in adolescents)
- Institution of measures that may slow progression to more advanced stages (eg, strict blood pressure [BP] control and/ or reducing proteinuria)

Mild to moderate CKD: Stages G3a and G3b –

In addition to the above, prevent and manage complication of CKD that may occur (hypertension, fluid and electrolytes abnormalities, anemia, bone mineral disease endocrine abnormalities and growth impairment in children.

Severe CKD and kidney failure: Stages G4 and G5 –

Early identification of children with progressive disease who may require KRT for patients with eGFR less than 30 mL/min per 1.73 m2.
Preparation and education of the patient and family.

Adapted from: Kidney Disease: Improving Global Outcome (KDIGO) Clinical Practice Guideline and the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines

5.2.5 Management of complications of CKD in Children

1. Fluid and electrolytes abnormalities

Salt and water

- Manage salt wasting and inability to concentrate urine (isosthenuria) in children with dysplastic kidneys and obstructive uropathy which may dehydration and recurrent acute kidney injury.
- Adequate rehydration and especially during acute infection is recommended. Salt supplementation may be required. (We recommend supplemental free water and sodium supplements for children with CKD and polyuria to avoid chronic intravascular depletion and to promote optimal growth (KDIGO 2012)
- Salt and water restriction may be required in advanced disease, and in glomerular diseases. However, these restrictions need to be based on the clinical evaluation, electrolyte results, needs for feeding and growth.

Potassium

- Hypokalemia may occur in children with polyuria, and tubular abnormalities and acute severe malnutrition. Potassium supplementation may be required.
- Hyperkalemia is common in advanced disease: Low-potassium diets are advised Potassium binders should be used in hyperkalemia- For infants or children dependent on milk, kayexalate is mixed in the cup or tin containing the expressed breast milk, infant formula or cow's milk. Repeated stirring is done and after repeated stirring for about 5 minutes, this mixture is left to stand for about 10 minutes. The kayexalate will settle down in the cup with the extracted potassium. This can be decanted and the child is fed on this milk which will have had potassium extracted.

2. Bone mineral disease

Bone mineral disease presents as growth failure, rickets and increased risk of fractures and extra-skeletal calcification in children. Children with CKD Stage G2 should be monitored for BMD through annual measurement of serum calcium, phosphorus, PTH, total ALP, and 25-hydroxyvitamin D.

Treatment is instituted to prevent and treat secondary hyperparathyroidism through
1) dietary phosphate restriction and
2) use of calcium containing phosphate binders such as calcium gluconate given with meals, sevelamer and other interventions as listed in the previous sections of these guidelines.

3. Growth abnormalities

Children with CKD have retardation in growth. Growth velocity declines with more progressive CKD, but impairment is observed at all levels of CKD. This is more severe when CKD occurs during the first year of life; and in advanced stages of CKD.
Untreated CKD in infancy results in profound growth retardation, with a severe loss in relative height. Poor nutrition is the most important factor contributing to growth impairment in younger children.

The cause of stunting in children with CKD include intrauterine growth restriction, metabolic acidosis, malnutrition, CKD-BMD, uremic toxins, steroid use and salt wasting. Prolonged use of steroids for in children with SRNS leads to stunting. Disturbances in the growth stimulating hormone- insulin- like growth factor -I axis also occur and are characterized by decreased efficiency of growth hormone to initiate and sustain growth. Recombinant human GH (rhGH)has been shown to improve growth among children CKD especially those on dialysis but this should be initiated when feeding is optimized.[47,48]

Management of growth reduction includes correction of metabolic acidosis, CKD-BMD and nutritional deficiencies. Optimizing caloric and protein intake in younger children with CKD and ESKD is the most effective strategy to enhance growth velocity…fortify/supplement/concentrate feeds; consider NG feeding when needed, and Gastrostomy feeding when feasible. Breast milk is preferred in infants. There is need for a dietician as part of the management team.

4. Anemia

Anemia in children with CKD is common. Causes of anemia is multifactorial but in advanced disease is mainly due to erythropoietin deficiency. Annual testing for anemia is recommended. The approach in the figure 17 is suggested

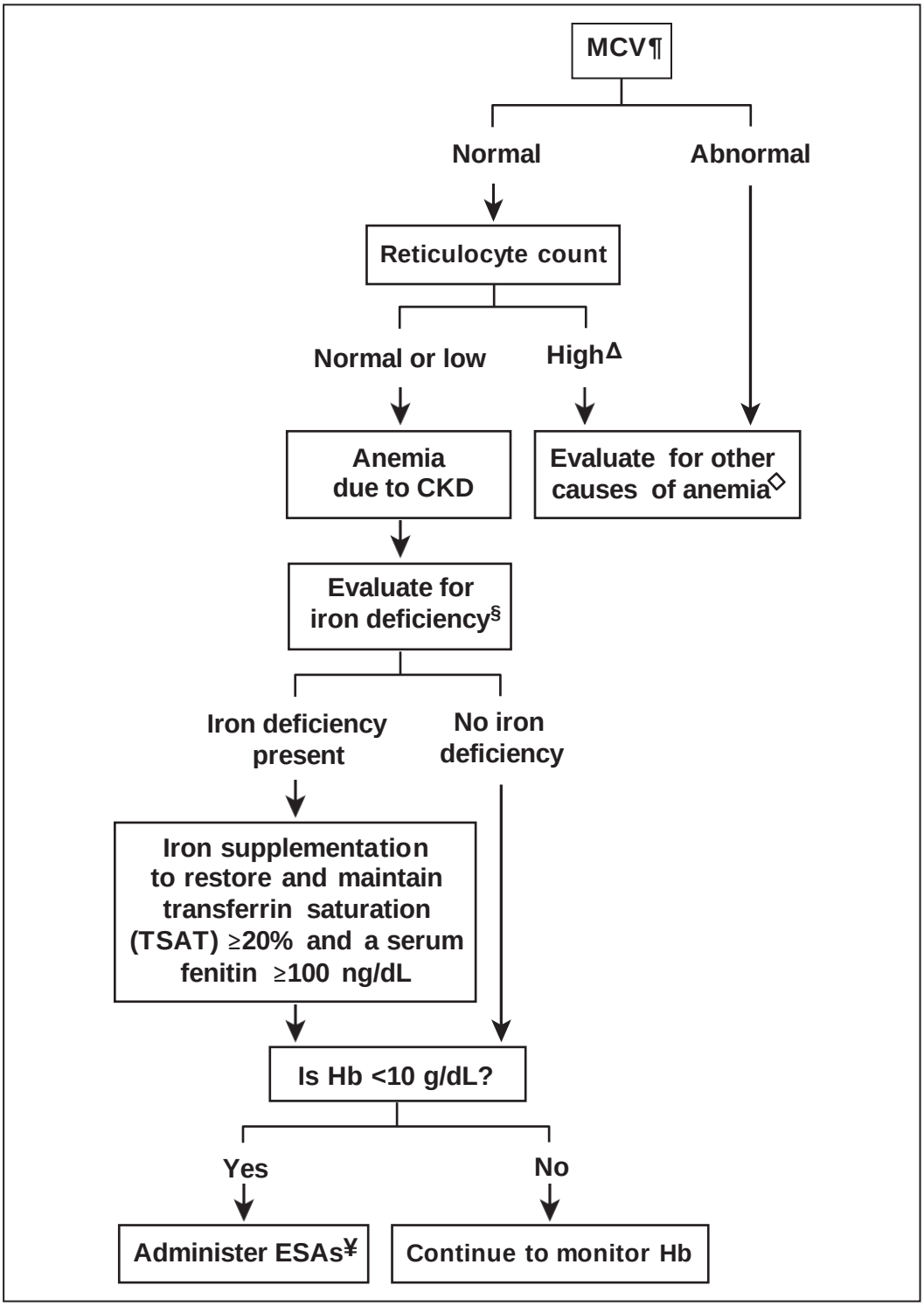


Figure 27: Approach to diagnosis andmanagement of anaemia in chidren with CKD

We recommend

Annual testing of hemoglobin (Hb): A diagnosis of anemia should be made when the Hb is below the 2.5th percentile of normal, adjusted for age and sex

If the child is anemic; investigate the cause of anemia

Treat anemia according to the cause with iron supplementation (if necessary) and erythropoietic stimulating agent (EPO/ESA). Initiate ESA at 50-100u/kg/week. To achieve and maintain target haemoglobin levels, young children require higher rHuEPO doses than adults, ranging from 275 U/kg to 350 U/kg per week for infants, to 200–250 U/kg per week for older children (NAPRTCS data).

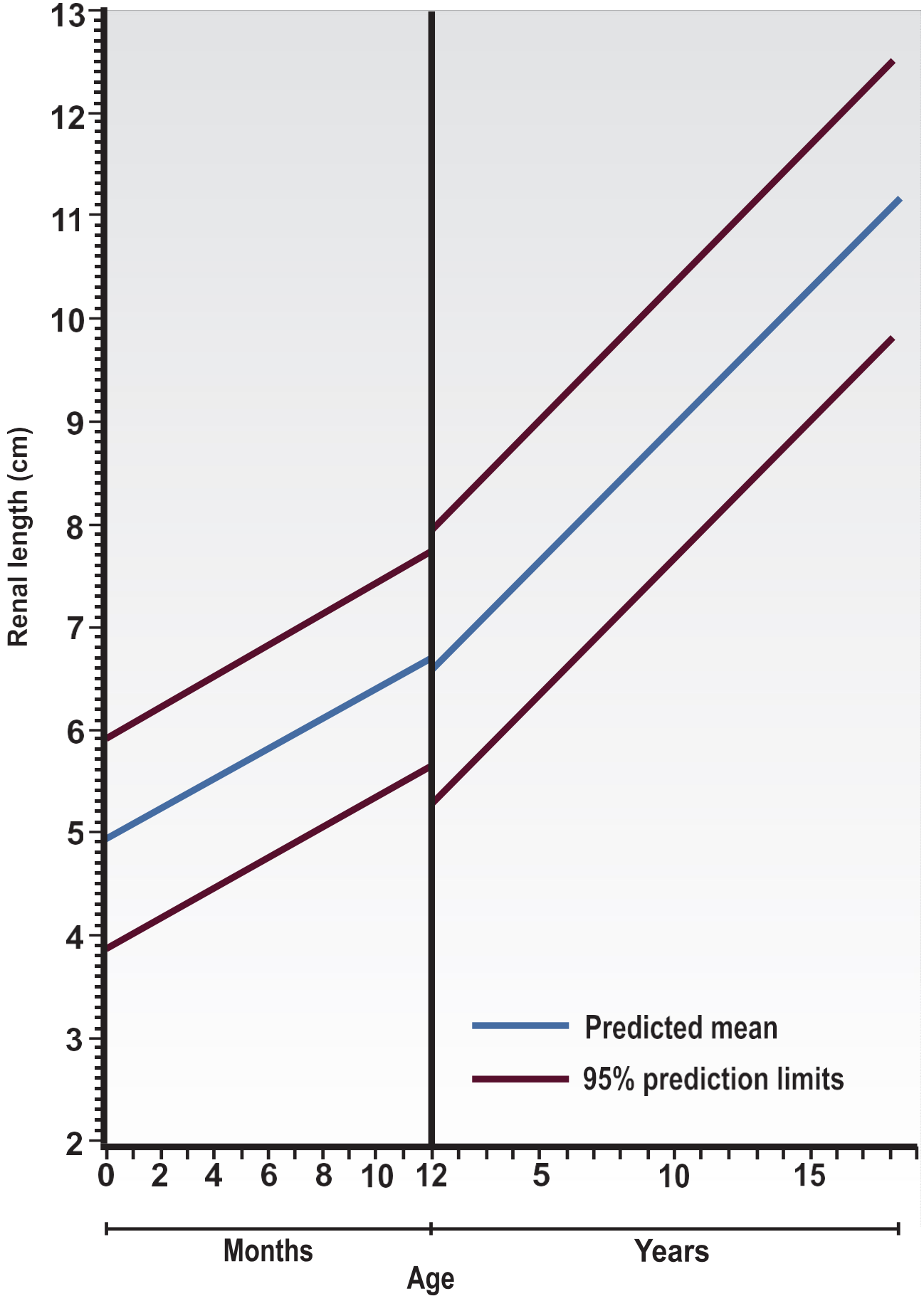
The target Hb in children is 11-12g/dl

5. Hypertension

Hypertension = systolic/diastolic BP>/= 95th centile for age, sex and height percentile. (Refer to childhood BP charts). Hypertension is present in about 54% of CKD children. Tight blood pressure control slows CKD progression as in adults.
During treatment, it is best to target BP < 50th centile as these have better outcomes than those in 50th-90th centile BP target [49]

When measuring blood pressure to diagnose hypertension there is need to take adequate care ensuring that arm-size appropriate blood pressure cuffs are used, multiple blood pressure measurements are taken (at least 3 measurements) and that the child is calm during blood pressure measurement.

Supplementary material –ultrasound kidney size centile charts for children (Guide in diagnosing CKD as kidney size reduces with progressive CKD).



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Supplementary Table S1. Antiretroviral dose adjustments in chronic kidney disease according to creatinine clearance (CrCl)

Generic name	Dosage form	Standard adult dose	CrCl 30-50 ml/min	CrCl 10-29 ml/min	CrCl <10 ml/min
Nucleoside Reverse Transcriptase Inhibitors (NRTI)					
Abacavir (ABC)	300 mg tablet	600 mg daily	Standard dose		
	ABC 600 mg +3TC 300 mg	1 tablet daily	Not recommended		
	ABC 300 mg + AZT 300 mg + 3TC 150 mg	1 tablet twice daily	Not recommended		
Didanosine (ddI)	Powder: 100, 167, 250 mg	<60 kg: Powder 250 mg daily or 125mg twice daily	<60 kg: 150mg daily or 75mg twice daily	<60 kg: 100mg daily	<60 kg: 75mg daily
		>60 kg: Powder 400mg daily or 200mg twice daily	>60kg: 200mg daily or 100mg twice daily	>60kg: 150mg daily	>60kg: 100mg daily
	Enteric coated (EC) capsule: 125, 200, 250, 400 mg	<60kg: EC capsule: 250mg daily	<60 kg:125 mg daily	<60 kg:125 mg daily	Not recommended
		>60kg: EC capsule: 400 mg daily	>60kg: 200mg daily	>60kg: 125mg daily	>60kg: 125mg daily
		With TDF 250 mg daily 200 mg daily	Not recommended		
Emtricitabine (FTC)	200 mg	200 mg daily	200 mg every 48 hours	200 mg every 72 hours	200 mg every 96 hours; administer after dialysis
	10 mg/ml solution	24 ml (240 mg) daily (liquid)	120 mg daily (liquid)	80 mg daily (liquid)	60 mg daily (liquid)
	FTC 200 mg + TDF 300 mg	1 tablet daily	Not recommended		
	FTC 200 mg + TAF 25 mg	1 tablet daily	1 tablet daily	Not recommended	
Lamivudine (3TC)	100, 150, 300 mg tablet, 5 mg/ml solution	300 mg/day	150 mg daily	150 mg stat then 100mg/d	150 mg stat then 50 mg/d
	3TC 150 mg + AZT 300mg +	1 tablet twice daily	Not recommended		
	3TC 300 mg + ABC 600 mg	1 tablet daily	Not recommended		
	3TC 150 mg + ABC 300 mg + AZT 300 mg	1 tablet twice daily	Not recommended		
Stavudine (d4T)	15,20,30,40mg, 1 mg/ml solution	<60 kg: 30 mg twice daily	<60 kg: 15 mg twice daily	<60 kg: 15 mg daily	<60 kg: 15 mg daily
		>60kg: 40 mg twice daily	>60 kg: 20 mg twice daily	>60 kg: 20 mg daily	>60 kg: 20 mg daily
Tenofovir Disoproxil Fumarate (TDF)	300 mg tablet	300 mg daily	300 mg every 48 hours	300mg 2 days/week	300mg every 7 days
	TDF 300 mg + FTC 200 mg	1 tablet daily	Not recommended		
Tenofovir Alafenamide (TAF)	TAF 10 or 25mg + FTC 200 mg	1 tablet daily	Standard dose	Not recommended	
Zidovudine (AZT)	100 capsule, 300 mg tablet, 10mg/ml IV solution	300 mg twice daily or 200mg three times daily	Standard dose		300 mg once daily
	AZT 300mg+3TC 150mg	1 tablet twice daily	Not recommended		
	AZT 300 mg +3TC 150 mg +ABC 300 mg	1 tablet twice daily	Not recommended		

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)				
Delavirdine (DLV)	100, 200 mg tablet	400 mg three times daily	Standard dose	
Efavirenz (EFV)	50, 100, 200 mg capsule, 600 mg tablet	600 mg at night	Standard dose	
	EFV 600 mg + FTC 200mg + TDF 300mg	1 tablet daily	Not recommended	
Nevirapine (NVP)	200 mg tablet; 50 mg/5ml suspension	200 mg daily x 14 days, then 200 mg twice daily	Standard dose	
	NVP 200 mg + d4T 30mg + 3TC 150mg	1 tablet twice daily	Not recommended	
Etravirine (TMC125)	100 mg tablet	200 mg twice daily	Not established but likely standard dose. (only 1.2% is excreted in urine)	
Rilpivirine (RPV)	25 mg tablet	25 mg daily	Standard dose	
	RPV 25mg + FTC 200mg + TDF 300mg	1 tablet daily	Not recommended	
	RPV 25mg + FTC 200mg + TAF 25mg	1 tablet daily	Standard dose	Not recommended
Protease inhibitors: ritonavir-boosted (PI/r) or cobicistat-boosted (PI/c)				
Atazanavir (ATV)	100, 150, 200, 300 mg	ATV 400 mg daily or ATV/r 300/100 mg daily	Standard dose but best avoided in people with CrCl <60 ml/min	
	ATV/c 300/150 mg	1 tablet daily	Standard dose but best avoided in people with CrCl <60 ml/min	
Darunavir (DRV)	800 mg, 600 mg, 400 mg, 300 mg tablet	DRV/r 800/100 mg daily or 600/100 mg twice daily	Standard dose	
	DRV/c 800/150 mg	1 tablet daily	Standard dose	
Fosamprenavir (FPV)	700 mg tablet	FPV/r 1400/200 mg daily or 700/100 mg twice daily	Standard dose	
Indinavir (IDV)	100, 200, 333, 400 mg capsule	IDV 800 mg q 8h or IDV/r 800/100 mg twice daily	Standard dose but best avoided in people with CrCl <60 ml/min	
Lopinavir + Ritonavir (LPV/r)	LPV/r 200/50 mg tablet; LPV/r 80/20 mg/ml solution	LPV/r 400/100 mg twice daily or 800/200 mg daily	Standard dose but best avoided in people with CrCl <60 ml/min	
Nelfinavir (NFV)	250 mg, 625 mg tablet	1250 mg twice daily or 750 mg three times daily	Standard dose	
Ritonavir (RTV)	100 mg tablet	100-400 mg/day to boost concentrations of other PIs	Standard dose	
Saquinavir (SQV)	200 mg capsule, 500 mg tablet	SQV/r 1000/100 mg twice daily	Standard dose	
Tipranavir (TPV)	250 mg capsule	TPV/r 500/200 mg twice daily	Standard dose	
Integrase strand transfer inhibitors (INSTI)				
Raltegravir (RTG)	25 mg, 100 mg, 400 mg tablet + 100 mg/packet powder	400 mg twice daily	Standard dose	Dialysis: Dose after hemodialysis on dialysis days
	RTG 300 mg + 3TC 150 mg	1 tablet twice daily	Not recommended	
Elvitegravir/ cobicistat (EVG/c)	EVG/c 150/150 mg + FTC 200 mg + TDF 300 mg	1 tablet daily	Not recommended	
	EVG/c 150/150 mg + FTC 200 mg+ TAF 10 mg	1 tablet daily	1 tablet daily	
Dolutegravir (DTG)	50 mg tablet	1 tablet daily	Standard dose	
	DTG 50mg + ABC 600 mg + 3TC 300 mg	1 tablet daily	Not recommended	
Entry Inhibitors				
Enfuvirtide (T20)	90 mg single-dose vial	90 mg subcutaneously twice daily	Standard dose	
Maraviroc	150, 300 mg tablet	150, 300 or 600 mg twice daily	Dose reduction at CrCl <80 ml/min; not recommended in individuals with renal impairment who are taking potent CYP3A4 inhibitors	

Sources: AIDS info for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.[46-84]

Supplementary Table S2. Antituberculous medication dose adjustments in chronic kidney disease.

Drug	eGFR ≥60ml/min	eGFR 30-59ml/min	eGFR <30ml/min	Intermittent Haemodialysis	Peritoneal dialysis
Rifampicin	10mg/kg q24h		No dose adjustment required		
Isoniazid	5mg/kg q24h		No dose adjustment required		
Pyrazinamide	25-35mg/kg q24h	25-35mg/kg q24h	25-35mg/kg 3 times a week	25-35mg/kg 3 times a week after haemodialysis	No dose adjustment required
Ethambutol	15-25mg/kg q24h	15-25mg/kg q24h	15-25mg/kg 3 times a week	15-25mg/kg 3 times a week after haemodialysis	15mg/kg q48h
Moxifloxacin	400mg q24h	No dose adjustment required			
Prothionamide	15-20mg/kg/d in divided doses	No dose adjustment required	eGFR ≥10 to 30: No dose adjustment eGFR <10: 250mg q12h	250mg q12h	250mg q12h
Cycloserine	10-15mg/kg/d in divided doses	250mg q12h	250mg q24h	250mg q24h given after dialysis	250mg q24h
Bedaquiline	400mg q24h for 2 weeks then 200mg thrice weekly	No dose adjustment required	Use with caution and consider therapeutic drug monitoring		
Linezolid	600mg q24h	No dose adjustment required			
Para- aminosalicylic acid	8-12g/d in divided doses	No dose adjustment required	4g q12h	4g q12h	4g q12h
Streptomycin, Amikacin, Capreomycin	15mg/kg/d	15mg/kg individual doses with dosing interval extended to achieve an undetectable plasma trough level prior to each dose			
Clofazimine	*100mg q 24h*	*No dose adjustment required*			

Table 3 Legend Further details on anti TB drug dosing can be accessed from the listed sources that were used to compile this table:

i https://www.health.qld.gov.au/ data/assets/pdf_file/0024/444507/tb-guideline-renal.pdf

i https://pubmed.ncbi.nlm.nih.gov/27516382/ Official ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis.

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