SOUTH AFRICAN PRIMARY HEALTHCAREESSENTIAL MEDICINES LIST
PHC CHAPTER 8: KIDNEY AND UROLOGICAL DISORDERS
NEMLC RECOMMEDATIONS FOR MEDICINE AMENDMENTS (2020-2024 REVIEW CYCLE)

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG).

PROPOSED AMENDMENTS

SECTION	MEDICINE/ MANAGEMENT	ADDED/DELETED/AMENDED/NOT ADDED/ RETAINED
8.1 CHRONIC KIDNEY DISEASE (CKD)	Adjustment of medicine doses in renal impairment	Guidance amended
	Treatment and prevention strategies according to prognostic category	Guidance amended
	General measures	Editorial amendments to section made and guidance on low protein diet removed
	BP targets	Amended
	ACE-inhibitors, oral	Retained, indications for therapeutic class amended
	Furosemide, oral/IV	Dosing guidance amended
	Rehabilitation support	Added for referred stage 3-5 patients
8.2 ACUTE KIDNEY INJURY (AKI)	Medicine treatment	Guidance added on the principles of dosing medication in patients with AKI
8.4 URINARY TRACT INFECTION (UTI) *- Pregnant women*	Fosfomycin, oral	Added
	Nitrofurantoin, oral	Added
-Children	Acute pyelonephritis	Referral criteria for children amended
8.5 PROSTATITIS	Acute bacterial prostatitis	Guidance for treatment based on age thresholds removed
8.11 RENAL CALCULI	Referral criteria	Amended
PHC ESSENTIAL LABORATORY LIST (ELL)	Prostate specific antigen test	Not added

8.1. CHRONIC KIDNEY DISEASE

<u>Adjustment of medicine doses in renal impairment:</u> New guidance added

The principles of dosing medication in patients with chronic kidney disease (CKD) and acute kidney injury (AKI) have been added to the STG for clarity. The updated nomenclature includes "kidney disease" which encompasses both acute kidney injury and chronic kidney disease. The word “chronic renal disease” has been replaced with the word “chronic kidney disease” throughout the chapter.

The STG has been amended as follows:

CAUTION
Check all medicines for possible dose adjustment based on eGFR

The doses of many medicines need to be adjusted in renal impairment when there is impairment of kidney function. Close attention for dose adjustments should be made once the eGFR falls below 60ml/min/1.73m^2 and especially when <15mls/min/1.73m^2 or when the patient is on dialysis. ~~The doses of many medicines need to be adjusted in renal impairment.~~
Recommendations for medicines that require dose adjustment in renal impairment can be found in the South African Medicines formulary (SAMF), package insert, and from many online resources e.g.: http://www.globalrph.com/index_renal.htm

Treatment and prevention strategies according to prognostic category: Amended

The CKD Epidemiology Collaboration (CKD-EPI) equation has been included in the STG as the formula of choice in line with current practice[1,2]. The CKD-EPI measure of eGFR has acceptable performance characteristics and potential consequences that do not disproportionately affect any one group of individuals.

The STG has been amended as follows:

Treatment and prevention strategies according to prognostic category
Estimation of the degree of kidney damage is important to guide management to prevent adverse outcomes of ~~chronic kidney disease~~. CKD.
Use eGFR and albumin creatinine ratio to put patient into prognostic category - see table below.
The eGFR using the CKD-EPI (race neutral) equation is currently the formula of choice.

				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				ACR* <30 mg/g <3mg/mmol	ACR* 30–300 mg/g 3–30 mg/mmol	ACR* >300 mg/g >30 mg/mmol
eGFR categories (ml/min per 1.73m2) description and range	G1	Normal or high	≥90		Refer	Refer
	G2	Mildly decreased	60–89		Refer	Refer
	G3a	Mildly to moderately decreased	45–59		Refer	Refer
	G3b	Moderately to severely decreased	30–44	Refer	Refer	Refer
	G4	Severely decreased	15–29	Refer	Refer	Refer
	G5	Kidney failure	<15	Refer	Refer	Refer

*ACR: albumin to creatinine ratio in urine specimen.
Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red: very high risk; A1, A2, A3 = categories of albuminuria; G1, G2, G3a, G3b, G4, G5 = categories of eGFR
Adapted from: Levin A, Stevens PE. Summary of KDIGO 2012 CKD Guideline: behind the scenes, need for guidance, and a framework for moving forward. Kidney Int. 2014 Jan;85(1):49-61. https://www.ncbi.nlm.nih.gov/pubmed/24284513

General measures: Amended
Dietary Protein limit: Guidance removed

[1] Delgado C, Baweja M, Crews DC, Eneanya ND, Gadegbeku CA, Inker LA, Mendu ML, Miller WG, Moxey-Mims MM, Roberts GV, St Peter WL, Warfield C, Powe NR. A Unifying Approach for GFR Estimation: Recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease. Am J Kidney Dis. 2022 Feb;79(2):268-288.e1. doi: 10.1053/j.ajkd.2021.08.003. Epub 2021 Sep 23. PMID: 34563581.

[2] Inker LA, Eneanya ND, Coresh J, et al., for the Chronic Kidney Disease Epidemiology Collaboration
New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race.N Engl J Med. 2021 November 4, 385 (19):1737-1749.

The recommendation to Limit dietary protein intake has been removed from the STG, A Systematic Review of 17 RCT's (n=2996) where 10 studies compared a low protein (0.5 to 0.6 g/kg/day) diet with a normal protein(≥ 0.8 g/kg/day) diet in participants with CKD categories 3a and 3b (9 studies) or 4 (one study), found that there was little or no difference in the numbers of participants who died from all causes (5 studies 1680 participants: RR 0.77, 95% CI 0.51 to 1.18; 13 fewer deaths per 1000). In addition, a low protein diet was found to make little or no difference in the number of participants who reached End-Stage Kidney Disease (ESKD) compared with a normal protein diet (6 studies, 1814 participants: RR 1.05, 95% CI 0.73 to 1.53; 7 more per 1000 reached ESKD)[3]. In addition,aminoglycosides have been included as an example of nephrotoxic medicines to avoid in patients with CKD[4]

The STG has been amended as follows:

~~Reduce salt intake – dietician consultation as required.~~
~~Low protein diet is indicated in the presence of CKD stage 4 and 5, dietician consultation as required.~~
Reduce cardiovascular disease risk factors. See Section 4.1: Prevention of ischaemic heart disease and atherosclerosis.
Avoid nephrotoxic drugs e.g. NSAIDs, tenofovir and aminoglycosides.

Hypertension

BP targets: *Amended*

Blood Pressure targets were aligned with the PHC cardiovascular and endocrine chapters for consistency, as follows:

Treat if present. See Section 4.7: Hypertension.
Target BP: Systolic < 140 mmHg and diastolic < 90 mmHg (See Sections 4.7: Hypertension, 9.1.2: Type 1 diabetes mellitus, in adults and 9.2.2: Type 2 diabetes mellitus, adults).

MEDICINE TREATMENT

ACE-inhibitors: Class retained, guidance amended

ACE-inhibitors in patients with eGFR < 30 mL/min/1.73m^2 may be nephroprotective[5] therefore, the STG has been amended to extend ACE-inhibitors for the management of patients with severe renal impairment in line with guidelines. A caveat has been included to highlight potassium level monitoring which is available at the PHC level of care.

The STG has been amended as follows:

ACE inhibitors can be used with an impairment (eGFR < 30 mL/min/1.73m2) if potassium can be monitored safely.

Monitor creatinine and potassium:

- 1–2 weeks after treatment initiation, if eGFR < 60 mL/min and after 4 weeks, if eGFR > 60 mL/min.
- If creatinine increases by > 20% from the baseline, stop ACE-inhibitor and refer.
- If stable, monitor thereafter at regular clinic visits.

LoE:IVb

ACE-inhibitors are contraindicated in, amongst others:

- hyperkalaemia
- known hypersensitivity to an ACE-inhibitor or an ARB
- bilateral renal artery stenosis
- pregnancy
- ~~severe renal impairment (eGFR < 30 mL/min)~~

Level of Evidence: Low certainty

Furosemide, oral/IV: Dose and directions amended

[3] Hahn D, Hodson EM, Fouque D. Low protein diets for non-diabetic adults with chronic kidney disease. Cochrane Database Syst Rev. 2020 Oct 29;10(10):CD001892. doi: 10.1002/14651858.CD001892.pub5. PMID: 33118160; PMCID: PMC8095031.

[4] Patel JB, Sapra A. Nephrotoxic Medications. 2023 Jun 21. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 31985937.

[5] Eknoyan G, Lameire N. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3(1):1-150.

For the management of fluid overload and oedema, the dose of furosemide, oral/IV has been amended to a dose of 20mg up to 160mg oral/IV in divided doses[6]. Additional guidance through an external comment has been added to first establish an effective dose of furosemide and ascertain that the prescribed dose results in urination within 1-2 hours of intake until urination ensues.

The STG has been amended as below:

•Furosemide, oral or IV, 20mg to 80mg daily, as a single or in divided doses, initiating at the lowest effective dose and titrating upwards. Dose may be increased to 160mg IV or oral daily in divided doses. •First establish an effective dose and ascertain if urination occurs within 1-2 hours of intake. If urination does not occur within 1-2 hours, the dose should be increased further until urination ensues. ~~•Furosemide, slow IV or oral, 40–80 mg, 12 hourly.~~

Level of Evidence: Low certainty

Referral

Rehabilitation support: *added for referred stage 3-5 patients*

Inspiratory muscle training shown to improve inspiratory and expiratory muscles and functional capacity.[7] Multidisciplinary care likely decreases rapid progression of renal disease[8] and exercise shown to improve sleep quality amongst adults and children with end-stage kidney disease.[9]

Level of Evidence: Low certainty evidence

The following text was added to the STG:

» In addition, patients with chronic kidney disease stages 3–5 may also require rehabilitation support for optimisation of function outcomes e.g., improved muscle strength and cardiovascular fitness, reduced blood pressure, weight management.

8.2. ACUTE KIDNEY INJURY

Medicine treatment: New guidance added

Additional guidance on the principles of dosing medication in patients with AKI has been added. Monitoring of the eGFR in AKI has been emphasized.

The STG has been amended as follows:

In the setting of kidney failure all prescribed medications should be reviewed regularly to ensure that they are safe and at the correct dose for the estimated glomerular filtration rate [eGFR]. Currently, the most reliable measure of eGFR is CKD-EPI (race neutral) in adults and Schwartz equation for children. Nephrotoxic drugs should be avoided in the setting of any kidney dysfunction. Prior to starting any medication review for previous drug allergies and adverse events. Monitoring of drug toxicity and levels is important where available (e.g. aminoglycoside). In acute kidney injury [AKI] the eGFR is not reliable as kidney function changes rapidly. Therefore, it is essential to monitor eGFR and doses of medications regularly.

8.4. URINARY TRACT INFECTION (UTI)

Pregnant women

[6] South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[7] de Medeiros AIC, Fuzari HKB, Rattesa C, Brandão DC, de Melo Marinho PÉ. Inspiratory muscle training improves respiratory muscle strength, functional capacity and quality of life in patients with chronic kidney disease: a systematic review. J Physiother. 2017 Apr;63(2):76-83. https://pubmed.ncbi.nlm.nih.gov/28433237/

[8] Hsu HT, Chiang YC, Lai YH, Lin LY, Hsieh HF, Chen JL. Effectiveness of Multidisciplinary Care for Chronic Kidney Disease: A Systematic Review. Worldviews Evid Based Nurs. 2021 Feb;18(1):33-41. https://pubmed.ncbi.nlm.nih.gov/33247619/

[9] Natale P, Ruospo M, Saglimbene VM, Palmer SC, Strippoli GF. Interventions for improving sleep quality in people with chronic kidney disease. Cochrane Database Syst Rev. 2019 May 26;5(5):CD012625. https://pubmed.ncbi.nlm.nih.gov/31129916/

Fosfomycin, oral: *added*
Nitrofurantoin, oral: *added*

Management was delineated to specifically provide guidance for pregnant women to minimise confusion.
The STG was updated as follows:

Uncomplicated cystitis
Adults
- Gentamicin, IM, 160 mg, as a single dose.
  - **Note:** Gentamicin should not be used in patients with known chronic kidney disease or pregnancy.

If gentamicin is unavailable/ contra-indicated:
- Fosfomycin, oral, 3 g as a single dose.

If fosfomycin is unavailable:
- Nitrofurantoin, oral, 100 mg 6 hourly for 5 days.

Complicated cystitis
Adults
- Ciprofloxacin, oral, 500 mg 12 hourly for 7 days.

For pregnant women:
- Fosfomycin, oral, 3 g as a single dose.

OR
- Nitrofurantoin, oral, 100 mg 6 hourly for 5 days.

Children
Acute pyelonephritis: Referral criteria for children amended

The indications for referral for children have been amended to provide better clarity on the age thresholds.
The STG has been amended as follows:

FROM:
» Children >3 months of age who appear ill.
» Children <3 months of age with any UTI.
TO:
Children ≥3 months of age who appear ill.
Children ≤3 months of age with any UTI.

8.5 PROSTATITIS

Acute bacterial prostatitis: Treatment according to age removed

Guidance on the management of bacterial prostatitis based on an age threshold has been removed. The STG is now aligned with the guidance included in the Adult Hospital Level Chapter 7: Nephrology/urological disorders.

The STG has been amended as follows:

FROM:

Acute bacterial prostatitis

In men ≤ 35 years of age or if there are features of associated urethritis (STI regimen):
Ceftriaxone, IM, 250 mg as a single dose.
AND
Azithromycin, oral, 1 g as a single dose.

In men > 35 years of age or if there is associated cystitis:
Ciprofloxacin, oral, 500 mg 12 hourly for 14 days.

TO:

Acute bacterial prostatitis

If there are features of associated urethritis (STI regimen):

- Ceftriaxone, IM, 250 mg as a single dose.

AND

- Azithromycin, oral, 1 g as a single dose.

If there are no features of associated urethritis:

- Ciprofloxacin, oral, 500 mg 12 hourly for 14 days.

8.11 RENAL CALCULI

Referral criteria: Amended

On receipt of an external comment, the referral section was updated from "*all patients"* to provide specific detail on patients to be referred, as follows:

» Referral, even with a single first stone episode:
  - All patients < 19 years of age.
  - Pregnant woman (refer postpartum).
  - Morbidly obese patients.
  - Patients known to have polycystic kidney disease.
  - Patients with inherited metabolic disorders of kidney function (e.g., Fanconi syndrome, and inherited conditions resulting in renal tubular acidosis or nephrolithiasis).

» Referral (for metabolic work-up to identify the cause and provide treatment in order to limit future episodes) to a nephrologist or paediatric nephrologist is indicated as follows:
  - Patients with first episode of multiple stones in both kidneys.
  - Patients with three or more kidney stone episodes within 2-3 years.

PRIMARY HEALTH CARE AND ESSENTIAL LABORATORY LIST (ELL)

Prostate-specific antigen (PSA) test: *not added*

Screening for prostate cancer using PSA tests is not included in the PHC STGs and EML. The National Health Laboratory Services (NHLS) reported and recently published findings of irrational PSA testing in clinical practice.[10] PSA tests are therefore not included in the PHC Essential Laboratory List (ELL).

[10] Cassim N, Rebbeck TR, Glencross DK, George JA. Retrospective analysis to describe trends in first-ever prostate-specific antigen (PSA) testing for primary healthcare facilities in the Gauteng Province, South Africa, between 2006 and 2016. BMJ Open. 2022 Mar 21;12(3):e050646. https://pubmed.ncbi.nlm.nih.gov/35314469/