SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 7: NEPHROLOGICAL/ UROLOGICAL DISORDERS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2017 -2019)

Medicine amendment recommendations, with supporting evidence and rationale are listed below. Kindly review the medicine amendments in the context of this chapter.

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED
7.1 Nephrology disorders	Medicine information	Dose adjustment in renal impairment not added
7.1.1 Chronic kidney disease (CKD)	Staging of kidney disease	Amended (Prognosis of CKD by GFR and albuminuria categories)
- Proteinuria reduction	Enalapril, oral	Maximum dose retained as 40 mg per day
	ARB, oral	Retained the contra-indication following ACE-inhibitor-associated angioedema.
- Hypertension	Target BP	Guidance provided for co-morbid CKD, diabetes
- Hyperparathyroidism	Calciferol, oral	Added as a weekly dose
	Calcitriol, oral	Retained as a daily dose
- Anaemia associated with CKD in patients on dialysis programmes	Iron	Added with cross referral to section 2.2: Anaemia, iron deficiency
	Erythropoeitin IV/SC	Treatment protocol retained, but further described, dosing and directions for use added
7.2.2 Hypokalaemia: For severe symptomatic hypokalaemia	Potassium, IV	Directions for use amended
7.2.4 Hyponatraemia: In the absence of fluid overload	Sodium chloride 5% IV	Indications amended and caution added
7.3.1 Haematuria	Flow diagram for management	Amended
7.3.2 Urinary tract infection (UTI) - Uncomplicated community acquired cystitis	Ciprofloxacin, oral	Deleted
	Fosfomycin, oral	Added
	Gentamicin, IM	Added
	Nitrofurantoin, oral	Added
- For pregnant women	Fosfomycin, oral	Added
	Nitrofurantoin, oral	Retained
- *Complicated community acquired cystitis*	Ciprofloxacin, oral	Retained
7.3.3 Recurrent urinary tract infection - Prophylaxis	Ciprofloxacin, oral	Deleted
	Nitrofurantoin, oral	Deleted
	Cotrimoxazole, oral	Retained

7.1. NEPHROLOGY DISORDERS

Medicine information: *dose adjustment in renal impairment not added*

It was decided that a table on medicines requiring dose adjustment not be added as the list of medicines is large and the Standard Treatment Guideline (STG) text already provides the following hyperlink:

Check all medicines for possible dose adjustments. http://www.globalrph.com/index_renal.htm

7.1.1 CHRONIC KIDNEY DISEASE (CKD)

Staging of kidney disease: *amended (Prognosis of CKD by GFR and albuminuria categories)*

The STG was aligned with the KDIGO 2012 Guidelines, similar to the NEMLC approved PHC kidney chapter[1]. Following was included in the text of the STG:

				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 1.73m^2) - description and	G1	Normal or high	≥90			
	G2	Mildly decreased	60 –89			
	G3a	Mildly to moderately decreased	45–59			Refer
	G3b	Moderately to severely decreased	30–44		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

Proteinuria reduction

Enalapril, oral*: maximum dose retained as 40 mg per day*

Evidence: There is limited evidence in the published literature of the clinical significance of high dose of 40 mg enalapril, daily for management of chronic kidney disease. Comparative RCTs of enalapril 20 mg vs 40 mg could not be found in the published literature.

Clinical practice: High dose of enalapril (40 mg per day) is commonly used in clinical practice; and British National Formulary recommends a maximum dose of 40 mg enalapril.

Recommendation: Maximum daily dose of enalapril be retained for chronic kidney disease, aligned with British National Formulary, 2018[2] (i.e. 40 mg per day).

Level of Evidence: III Guidelines

Angiotensin II receptor blocker (ARB)

ARB, oral: *retained the caution following ACE-inhibitor-associated angioedema*

An external comment was received that in clinical practice patients with ACE-associated angioedema had been switched to ARBs without any problems. The Transcend RCT[3] was submitted as supporting evidence that showed no statistical difference between telmisartan versus placebo in terms of angioedema.

[1] Minutes of the NEMLC meeting of 1 February 2018

[2] Joint Formulary Committee. *British National Formulary.* London: BMJ Group and Pharmaceutical Press; 2018.

[3] Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators, Yusuf S, Teo K, Anderson C,Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet. 2008 Sep 27;372(9644):1174-83. https://www.ncbi.nlm.nih.gov/pubmed/18757085

	Telmisartan (n=2954)	Placebo (n=2972)	Relative risk	p value
Total number of discontinuations (temporary or permanent)	1090 (36·9%)	1143 (38·5%)	0·96	0·215
Number of patients with permanent discontinuations	639 (21·6%)	705 (23·7%)	0·91	0·055
Hypotensive symptoms	29 (0·98%)	16 (0·54%)	1·82	0·049
Syncope	1	0		
Cough	15 (0·51%)	18 (0·61%)	0·84	0·613
Diarrhoea	7 (0·24%)	2 (0·07%)	3·52	0·094
Angio-oedema	2 (0·07%)	3 (0·10%)	0·67	0·660
Renal abnormalities	24 (0·81%)	13 (0·44%)	1·86	0·067

*Most discontinuations were for non-specific reasons, with little difference between the two groups for any specific category.

Table 2: Discontinuation of study medications and selected reasons for permanent discontinuations*

The Adult Hospital Level Committee reviewed the evidence pertaining to the safety of ARBs in patients with previous ACE-induced angioedema.

Refer to the medicine review:

ARBs and AngioedemaCautior

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on this evidence review, the Adult Hospital Level Committee dose not recommend the removal of the caution of angioedema associated with ARBs in patients with a history of ACE-inhibitor induced angioedema.

Rationale: Low quality evidence of angioedema for safety of ARBs in patients with a history of ACE-inhibitor induced angioedema – excluded as outcome from other RCTs.

Replacing ACE-inhibitor with ARB does not preclude the risk of angioedema.

Level of Evidence: II Systematic reviews and meta-analyses[4] [5] [6]

The narrative of the STG, as follows:

- Replacing ACE-inhibitor with ARB does not preclude the risk of angioedema.

Hypertension

Target BP: *guidance provided for comorbid CKD, diabetes*

Text of the STG was editorially amended as follows for clarity purposes:

Optimise BP control with additional antihypertensive agents, BP control results in a lowering of proteinuria and slower decline in eGFR.
Target BP for patients with hypertension: <140/90 mmHg.
Target BP for patients with hypertension and confirmed CKD and/or diabetes: <130/80 mmHg.
See section 3.6: Hypertension.

Level of Evidence: III Guidelines[7]

[4] Caldeira D, David C, Sampaio C. Tolerability of angiotensin-receptor blockers in patients with intolerance to angiotensin-converting enzyme inhibitors: a systematic review and meta-analysis. Am J Cardiovasc Drugs. 2012 Aug1;12(4):263-77. https://www.ncbi.nlm.nih.gov/pubmed/22587776

[5] Haymore BR, Yoon J, Mikita CP, Klote MM, DeZee KJ. Risk of angioedema with angiotensin receptor blockers in patients with prior angioedema associated with angiotensin-converting enzyme inhibitors: a meta-analysis. Ann Allergy Asthma Immunol. 2008 Nov;101(5):495-9. https://www.ncbi.nlm.nih.gov/pubmed/19055203

[6] Makani H, Messerli FH, Romero J, Wever-Pinzon O, Korniyenko A, Berrios RS, Bangalore S. Meta-analysis of randomized trials of angioedema as an adverse event of renin-angiotensin system inhibitors. Am J Cardiol. 2012 Aug 1;110(3):383-91. https://www.ncbi.nlm.nih.gov/pubmed/22521308

[7] Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2018 Oct 23;138(17):e426-e483. https://www.ncbi.nlm.nih.gov/pubmed/30354655

Hyperparathyroidism

Calciferol, oral: *added as a weekly dose*

Calcitriol, oral: *retained as a daily dose*

External comment was received to consider weekly calciferol.

Evidence review

Malabanan et la[8]: Common practice to treat vitamin D deficiency is to treat with 50,000 IU (1250 mcg) of vitamin D_2 (ergocalciferol) or D_3 (cholecalciferol) orally once per week for six to eight weeks, and then 800 IU (20 mcg) of vitamin D3 daily thereafter. However, the efficacy of this practice compared with daily, weekly, or monthly dosing has not been rigorously established.

KDIGO Guidelines Supplement, 2017[9]*:* "Nutritional" vitamin D supplementation (cholecalciferol and ergocalciferol) is an alternative to calcitriol and its analogues – to suppress PTH in CKD and decrease hypercalcemia. However, an evidence review done for the KDIGO Guidelines found no studies of sufficient duration, and thus this therapy remains unproven[10].

Level of Evidence: III Standard of care

Price

Medicine	Tabs/caps for 28 day treatment course	Cost[11]
Calcitriol, oral 0.25-0.4 mcg daily	28 to 448 capsules (0.25 mcg caps)	R 124.01 to R 1984.19
Calciferol, oral 5000 iu weekly	4 tablets	R 8.08

Anaemia associated with CKD in patients on dialysis programmes

Iron: *added with cross referral to section 2.2: Anaemia, iron deficiency*

Erythropoietin IV/SC: *treatment protocol retained, but further described*

External comment was received from South African Medical Association recommending that recommendation to initiate iron and erythropoietin at the same time be reviewed, as 2012 KDIGO guidelines[12] recommend addressing all other sources or causes of anaemia (including iron replacement) before considering the addition of an erythropoiesis-stimulating agent.

Evidence review

Kuo et al (2015)[13]*:* A prospective cohort study was conducted based on the Taiwan National Health Insurance Research Database showed that iron supplementation were associated with a lower risk of all-cause death HR 0.85; 95% CI, 0.80 to 0.90 vs no iron supplementation (within 90 days after starting erythropoiesis-stimulating agent, ESA, therapy).

[8] Malabanan et al. Redefining Vit D deficiency. Section of Endocrinology, Nutrition, and Diabetes, Department of Medicine Boston University School of Medicine Boston, MA 02118, USA

[9] Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl (2011). 2017 Jul;7(1):1-59. https://www.ncbi.nlm.nih.gov/pubmed/30675420

[10] KDIGO Guidelines 2017 supplement: *"Oksa et al. reported an RCT of a high (20,000 IU/wk) versus low (5,000 IU/wk) dose of cholecalciferol supplementation in 87 adults with CKD. Serum vitamin D levels increased significantly in both groups and were significantly greater in the high-dose arm at the completion of the 12-month intervention. PTH levels decreased significantly in both groups; however, the PTH levels did not differ significantly between groups at the completion of the study".*

[11] Contract circular RT289-2019:

- Calciferol 5000 iu tabs (100) = R217.62
- Calcitriol 0.25 mcg caps (30) = R 132.87

[12] Kidney disease: improving global outcomes (KDIGO) anemia work group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl. 2012;2:279–335. https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-Anemia-Guideline-English.pdf

[13] Kuo KL, Hung SC, Liu JS, Chang YK, Hsu CC, Tarng DC. Iron supplementation associates with low mortality in pre-dialyzed advanced chronic kidney disease patients receiving erythropoiesis-stimulating agents: a nationwide database analysis. Nephrol Dial Transplant. 2015 Sep;30(9):1518-25. https://www.ncbi.nlm.nih.gov/pubmed/25829323

Shepshelovich et al (2016)[14]*:* Meta-analysis of 24 RCTs suggests that patients treated with IV iron were more likely to achieve Hb increase of >1 g/dL than patients treated with oral iron (CKD Stage 3-5: RR 1.61, 95% CI 1.39 to 1.87; CKD Stage 5: RR 2.14, 95% CI 1.68-2.72). Rates of mortality and serious adverse events found to be similar for the IV and oral iron groups, although IV iron associated with a higher risk of hypotension but less gastrointestinal effects.

REVOKE trial (2015)[15]*:* Open-label RCT in USA (n=136) showed no significant difference between oral and IV iron in improving Hb or rate of measured glomerular filtration (kidney function) in patients with CKD (stage 3/4), not on dialysis) and iron-deficiency anaemia. However, a higher incidence of serious adverse events (SAEs) (aIRR 1.60; 95% CI 1.28 to 2.00; p<0.0001), cardiovascular SAEs (aIRR, 2.51; 95% CI 1.56 to 4.04; p<0.001) and infection resulting in hospitalization (aIRR, 2.12; 95% CI 1.24 to 3.64; p<0.006) in the IV iron group resulted in early termination of the study.
PIVOTAL trial (2019)[16]*:* Subsequent open-labelled, RCT (n=2141) of patients on haemodialysis, randomised to **proactive high-dose IV iron** or **reactive low-dose IV iron;** targeting a Hb of 10–12 g/dl, median follow-up of 2.1 years. The high-dose IV iron approach was non-inferior with regard to the time to the primary composite of nonfatal myocardial infarction, nonfatal stroke, hospitalization, or death. There was no difference in serious adverse events, including infection. It is suggested that the dose-sparing effect of IV iron on ESAs may contribute to the cardiovascular safety profile of high-dose IV iron. In summary, proactive high-dose IV iron strategy (400 mg iron sucrose) shown to be safe, was superior to a low-dose regimen administered reactively and resulted in lower doses of ESA being administered.

Recommendation: Guidance provided to administer iron ***with*** ESA for anaemia associated with CKD in patients on dialysis programmes.
Rationale: Anaemia management in haemodialysis involves the administration of iron and ESAs – Iron treatment has also demonstrated to improve the erythropoietic response to ESA treatment, reducing the need for red blood cell transfusions[17]. Clinical practice is to correct iron deficiency prior to initiating erythropoietin; but there is evidence of mortality benefit when initiating iron and erythropoietin at the same time. However, correcting anaemia and maintenance of Hb levels to near normal levels with ESAs increased mortality and cardiovascular events without consistently improving quality of life[18] [19] [20]. Thus, KDIGO 2012 Guidelines recommend that ESA therapy should not be initiated where Hb concentration ≥ 10.0 g/dL; and that individualisation of therapy will be necessary because some patients may have improvements in QoL at Hb > 11.5 g/dL and will be prepared to accept the risks[21].
Level of Evidence: I Meta-analyses, RCT, Guidelines

[14] Shepshelovich D, Rozen-Zvi B, Avni T, Gafter U, Gafter-Gvili A. IntravenousVersus Oral Iron Supplementation for the Treatment of Anemia in CKD: An Updated Systematic Review and Meta-analysis. Am J Kidney Dis. 2016 Nov;68(5):677-690. https://www.ncbi.nlm.nih.gov/pubmed/27321965
[15] Agarwal R, Kusek JW, Pappas MK. A randomized trial of intravenous and oral iron in chronic kidney disease. Kidney Int. 2015 Oct;88(4):905-14. https://www.ncbi.nlm.nih.gov/pubmed/26083656
[16] Macdougall IC, White C, Anker SD, Bhandari S, Farrington K, Kalra PA, McMurray JJV, Murray H, Tomson CRV, Wheeler DC, Winearls CG, Ford I; PIVOTAL Investigators and Committees. Intravenous Iron in Patients Undergoing Maintenance Hemodialysis. N Engl J Med. 2019 Jan 31;380(5):447-458. https://www.ncbi.nlm.nih.gov/pubmed/30365356
[17] Palmer SC, Saglimbene V, Mavridis D, Salanti G, Craig JC, Tonelli M, Wiebe N, Strippoli GF. Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis. Cochrane Database Syst Rev. 2014 Dec 8;(12):CD010590. https://www.ncbi.nlm.nih.gov/pubmed/25486075
[18] Phrommintikul A, Haas SJ, Elsik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. Lancet. 2007 Feb 3;369(9559):381-8. https://www.ncbi.nlm.nih.gov/pubmed/17276778
[19] Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D; CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006 Nov 16;355(20):2085-98. https://www.ncbi.nlm.nih.gov/pubmed/17108343
[20] Skali H, Parving HH, Parfrey PS, Burdmann EA, Lewis EF, Ivanovich P, Keithi-Reddy SR, McGill JB, McMurray JJ, Singh AK, Solomon SD, Uno H, Pfeffer MA; TREAT Investigators. Stroke in patients with type 2 diabetes mellitus, chronic kidney disease, and anemia treated with Darbepoetin Alfa: the trial to reduce cardiovascular events with Aranesp therapy (TREAT) experience. Circulation. 2011 Dec 20;124(25):2903-8. https://www.ncbi.nlm.nih.gov/pubmed/22104547
[21] Kidney disease: improving global outcomes (KDIGO) anemia work group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl. 2012;2:279–335. https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-Anemia-Guideline-English.pdf

The text of the STG was amended as follows:

Patients on chronic haemodialysis or peritoneal dialysis are often anaemic due to iron deficiency and deficiency of erythropoietin (EPO). Simultaneous administration of iron and EPO is recommend, as EPO should be administered in a patient with normal iron stores. Adequate iron stores are required to assist with red blood cell production immediately after EPO administration (see section 2.2: Anaemia, iron deficiency).

Erythropoietin, IV/SC: *amended - dosing and directions for use added*

Aligned with the SAMF, 2016[22] and KDIGO Guidelines[23], as well as the evidence of mortality and cardiovascular risk when Hb levels are maintained to near normal levels[24]:

- Erythropoietin, 40–50 IU/kg/dose, IV/SC 2–3 times weekly and assessed at 4 weekly intervals.
  - Administer IV dose over 1–5 minutes.
  - If necessary, dose may be increased by 25 IU/kg.

Note: There is an increased risk of cardiovascular events with Hb > 12g/dL.

Level of Evidence: I Metaanalysis, III Guidelines

7.2.2 HYPOKALAEMIA

For severe symptomatic hypokalaemia:

Potassium chloride, IV: *dosing; directions for use amended*

Dosing: Guidance amended to include a maximum allowed daily dose of K+ is 3 mmol/kg/day (or 400 mmol/day), aligned with the SAMF, 2016.

Monitoring: Continuous cardiac monitoring and frequent estimations of serum K^+ levels is required[25] [26].

Central access: If higher doses of potassium is required, a central IV line would be required.

Directions for use: Guidance provided that potassium ampoules should not to be administered as IV bolus doses and that hat potassium chloride ampoules must be diluted before infusion.

Text was updated as follows, with a cross reference to Appendix II, for individual dosing and monitoring for response and toxicity:

- Potassium chloride, IV by peripheral line, 40 mmol in 1 L of 0.9% or 0.45% sodium chloride, mixed thoroughly.
  - Administer at a maximum rate of 20 mmol per hour over 3 hours. Beware of volume overload. (See Appendix II, for individual dosing and monitoring for response and toxicity).
  - Repeat as required, monitoring potassium serum levels after each replacement dose.
  - Potassium chloride 15%, 10 mL ampoule contains 20 mmol potassium.
  - Maximum allowed daily dose of K^+ is 3 mmol/kg/day (or 400 mmol/day).

CAUTION
Potassium chloride ampoules must always be diluted before infusion.

Reduce the rate of intravenous potassium repletion or change to oral therapy once the hypokalaemia is no longer severe. Continue treatment until the serum potassium concentration is persistently above 3.5 mmol/L and symptoms or signs have resolved.

Level of Evidence: III Guidelines[27]

[22] SAMF, 2016

[23] Kidney disease: improving global outcomes (KDIGO) anemia work group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl. 2012;2:279–335. https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-Anemia-Guideline-English.pdf

[24] Phrommintikul A, Haas SJ, Elsik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. Lancet. 2007 Feb 3;369(9559):381-8. https://www.ncbi.nlm.nih.gov/pubmed/17276778

[25] Tsuji H, Venditti FJ Jr, Evans JC, Larson MG, Levy D. The associations of levels of serum potassium and magnesium with ventricular premature complexes (the Framingham Heart Study). Am J Cardiol. 1994 Aug 1;74(3):232-5. https://www.ncbi.nlm.nih.gov/pubmed/7518645

[26] Hoes AW, Grobbee DE, Peet TM, Lubsen J. Do non-potassium-sparing diuretics increase the risk of sudden cardiac death in hypertensive patients? Recent evidence. Drugs. 1994 May;47(5):711-33. https://www.ncbi.nlm.nih.gov/pubmed/7520854

[27] SAMF, 2016

A hyperlink to an appropriate tool to calculate potassium deficit was added to the STG:

Link to calculating potassium deficit can be found here: http://www.medicinehack.com/2011/07/hypokalemia-potassium-replacement.html

7.2.4 HYPONATRAEMIA

In the absence of fluid overload:

Sodium chloride, IV infusion: *indications amended and caution added*

One litre of NaCl infusate	Total Na (mmol/l)	Indication	Fluid	Aim
5% NaCl Expect an increase of 2-3 mmol/L for every 60mL	855	» Sodium level < 120 mmol/L **and** » Severe symptoms ~~(i.e. seizures, obtundation, coma, and respiratory arrest)~~ (see above). **or** » Acute hyponatraemia due to water intoxication.	• Hypertonic sodium chloride, 5%, 60 mL as an IV bolus over 15 min. ○ If symptoms persist/ worsens or sodium is not improving, consult a specialist.	» Symptom relief. » Correct hyponatraemia: – 4-6 mmol/L immediately **AND** – Maximum 8 mmol/L in 1st 24 hrs.

Text was amended from "or" to "and" as the mentioned severe symptoms can be from any cause, and a low sodium value must accompany these severe symptoms to warrant treatment with 5% NaCl[28].

The following caution box was added to the narrative of the STG:

CAUTION
Hypertonic sodium chloride should be reserved for severe acute hyponatraemia (sodium level < 120 mmol/L with severe symptoms) and exceptional circumstances.

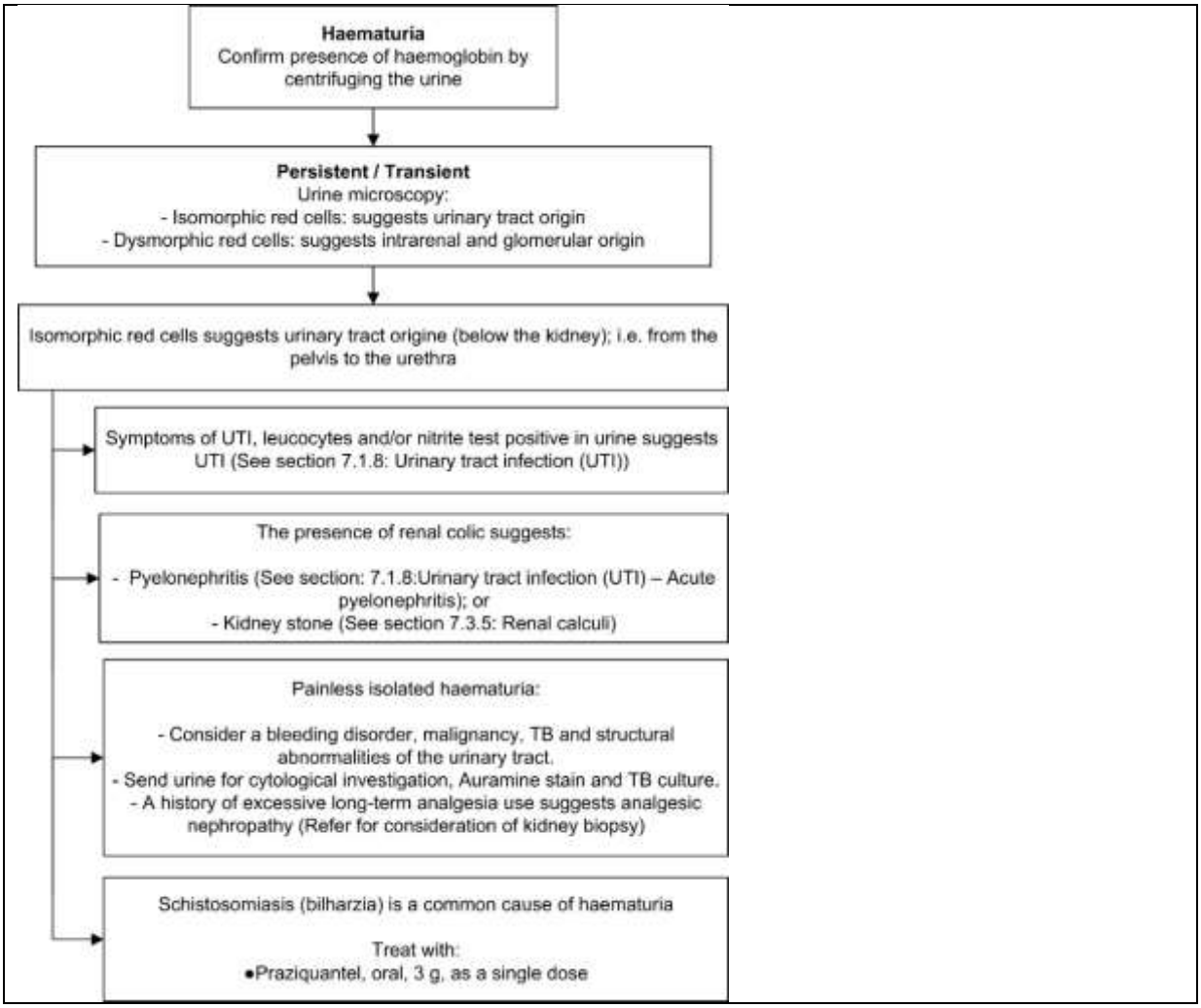
Level of Evidence: III Guidelines, Expert opinion

7.3.1 HAEMATURIA

Flow diagram was updated for correctness, as for transient haematuria, urine microscopy to assess the red cell morphology is also required.

Level of Evidence: III Expert opinion

[28] Adrogué HJ, Madias NE. Hyponatremia. N Engl J Med. 2000 May 25;342(21):1581-9. https://www.ncbi.nlm.nih.gov/pubmed/10824078



7.3.2 URINARY TRACT INFECTION

Uncomplicated community acquired cystitis:
Ciprofloxacin, oral*: deleted*
Fosfomycin, oral: *retained and indications extended to all uncomplicated UTI patients*
Nitrofurantoin, oral: *retained and indications extended to all uncomplicated UTI patients*
Gentamcin, IM: *added, but not indicated in pregnancy and renal impairment*

Background: Whilst globally, Medicines Regulatory Authorities[29] [30] announced safety warnings and recommended the restricted use of fluoroquinolone antibiotics. A safety review[31] showed rare but serious, disabling and potentially serious adverse effects associated with fluoroquinolones (i.e. *musculoskeleta*l: tendonitis, tendon rupture, myalgia, muscle weakness, arthralgia, joint swelling; *nervous system*: peripheral neuropathy, psychosis, anxiety, insomnia, depression, hallucinations, suicidal thoughts, confusion, impairment of vision, hearing, smell and taste; *cardiac*: aortic aneurysm and dissection; *endocrine*: hypoglycaemic coma).
Restrictions for the use of systemic fluoroquinolones include:

[29] FDA report of safety signals associated with fluoroquinolones.
[30] EMEA report of safety signals associated with fluoroquinolones.
[31] European Medicines Agency: Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics, 16 Nov 2018. https://www.ema.europa.eu/documents/press-release/disabling-potentially-permanent-side-effects-lead-suspension-restrictions-quinolone-fluoroquinolone_en.pdf

- Self-limiting or non-severe infections
- Non-bacterial infections
- Prophylaxis of traveller's diarrhoea or complicated urinary tract infections
- Mild to moderate bacterial infections, where other antibiotics are effective
- Avoid with concomitant corticosteroid therapy
- Previous SAEs experienced with fluoroquinolones

NEMLC REVISION:

Indication: Following the communication of the above-mentioned safety alert regarding the rare serious side effects (including nervous system, cardiac and endocrine-related ADRs) associated with fluoroquinolones; as well as stewardship concerns of extensive use of empirical fluoroquinolone therapy (fluoroquinolone resistance appears to be increasing); STG recommendations for fluoroquinolones in **non-severe uncomplicated bacterial infections** were revised.

Local NICD/NHLS surveillance:

Local surveillance for community acquired urinary tract infections is lacking in South Africa. NICD/NHLS has indicated lack of funding for this to occur.

Fosfomycin and nitrofurantoin

Lewis et al[32]*:* Local susceptibility study done in Gauteng Province (2013) showed that fosfomycin and nitrofurantoin had a reasonable susceptibility profile –see table below:

Table 3. Antimicrobial susceptibility profiles for the antimicrobial agents tested against UTI pathogens by Gram-stain morphotype

Antimicrobial agent (*N*=9)	GNB (*N*=181)* Susceptibility *n*	GNB (*N*=181)* Susceptibility % (95% CI)	GNB MIC_{50} (mg/l)	GNB MIC_{90} (mg/l)	GPC† (*N*=22)‡ Susceptibility *n*	GPC† (*N*=22)‡ Susceptibility % (95% CI)	All (*N*=203) Susceptibility *n*	All (*N*=203) Susceptibility % (95% CI)
Ciprofloxacin	170	93.9 (90.4 - 97.4)	0.012	0.19	21	95.5 (86.0 - 100.0)	191	94.1 (90.8 - 97.4)
Levofloxacin	170	93.9 (90.4 - 97.4)	0.023	0.38	21	95.5 (86.0 - 100.0)	191	94.1 (90.8 - 97.4)
Norfloxacin	170	93.9 (90.4 - 97.4)	0.064	0.75	21	95.5 (86.0 - 100.0)	191	94.1 (90.8 - 97.4)
Cefixime	172	95.0 (91.8 - 98.2)	0.25	0.75	7	31.8 (10.7 - 53.0)	179	88.2 (83.7 - 92.6)
Cefuroxime	169	93.4 (89.7 - 97.0)	3	4	14	63.6 (41.8 - 85.5)	183	90.1 (86.0 - 94.3)
Fosfomycin§	176	98.3 (96.4 - 100.0)	0.5	4	16	72.7 (52.5 - 92.9)	195	95.5 (92.6 - 98.4)
Nitrofurantoin¶	155	90.6 (86.2 - 95.1)	12	32	22	100.0 (100.0 - 100.0)	177	91.7 (87.8 - 95.6)
Amoxicillin/clavulanic acid	146	80.7 (74.9 - 86.5)	6	16	22	100.0 (100.0 - 100.0)	168	82.8 (77.5 - 88.0)
Trimethoprim/sulphamethoxazole	75	41.4 (34.2 - 48.7)	>32	>32	15	68.2 (47.0 - 89.3)	90	44.3 (37.4 - 51.2)

MIC = minimum inhibitory concentration; GNB = Gram-negative bacilli; GPC = Gram-positive cocci.
* One plate, containing a GNB, was discarded in error before species identification and antimicrobial susceptibility testing.
† MIC_{50}/MIC_{90} values are not presented for GPC due to the heterogeneous nature of this group.
‡ Two isolates (*K. kristinae*, *P. pentosaceus*) were excluded from the antimicrobial susceptibility analysis as they were deemed to be commensal contaminants rather than true UTI pathogens.
§ Two Gram-negative strains (*E. coli* and *P. mirabilis*) were unavailable for fosfomycin susceptibility testing.
¶ Ten Gram-negative strains (*E. coli* (*n*=8) and *P. mirabilis* (*n*=2)) were unavailable for nitrofurantoin susceptibility testing.

Huttner et al:[33] meta-analysis showed comparable clinical resolution rates, at 28 days, with nitrofurantoin, oral (5 day course) vs fosfomycin, oral (single dose):

Systematic review and meta-analysis results:

[32] Lewis DA, Gumede LY, van der Hoven LA, de Gita GN, de Kock EJ, de Lange T, Maseko V, Kekana V, Smuts FP, Perovic O. Antimicrobial susceptibility of organisms causing community-acquired urinary tract infections in Gauteng Province, South Africa. S Afr Med J. 2013 Mar 15;103(6):377-81

[33] Huttner A, Verhaegh EM, Harbarth S, Muller AE, Theuretzbacher U, Mouton JW. Nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials. J Antimicrob Chemother. 2015 Sep;70(9):2456-64. https://www.ncbi.nlm.nih.gov/pubmed/26066581

- Clinical resolution through day 28 was achieved in 171 of 244 patients (70%) receiving nitrofurantoin vs 139 of 241 patients (58%) receiving fosfomycin (difference, 12%, 95% CI 4 to 21%); p=0.004". NNT 9 (95% CI 5 to 25)
- Microbiologic resolution occurred in 129 of 175 (74%) vs 103 of 163 (63%), respectively (difference, 11%; 95% CI 1 to 20%), p=0.04 - statistically not significant.

Prices:

NEMLC had indicated that the preferred agent for uncomplicated cystitis was fosfomycin; and if this was not available, a 5-day course of nitrofurantoin. However, fosfomycin, oral is currently on tender; and a price comparison follows:

Medicine	Treatment Regimen	Price*
Fosfomycin, oral	3 g as a single dose	R 103.26
Nitrofurantoin, oral	100 mg 6 hourly for 5 days	R 99.61

*Contract circular HP02-2019AI: Nitrofurantoin 100 mg, 50 capsules = R 249.01; Fosfomycin 3g, sachet = R 103.26

Nitrofurantoin safety in pregnancy:

NEMLC had previously reviewed the safety of nitrofurantoin in the 1st trimester of pregnancy with the review of the 2018 PHC STGs and EML, 2018 edition – extract from the NEMLC report for the PHC obstetrics and gynaecology chapter follows below [accessible at: http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/497-national-essential-medicine-list-committee-nemlc]

EXTRACT FROM THE NEMLC REPORT FOR THE PHC STG: SECTION 6.4.5.1 CYSTITIS

A registry study[34](that included 180 120 pregnancies with 5 794 nitrofurantoin exposures) showed no increased risk of fetal malformations when used in the first trimester (compared to other antibiotics or infants not exposed to any antibiotics). The same study showed an increased risk of neonatal jaundice when compared to infants who were not exposed to antibiotics, but this was not significant when compared to those exposed to other antibiotics: OR 1.31 (95% CI 1.02 to 1.70) and 1.25 (95% CI 0.93 to 1.69) respectively, both adjusted for prematurity, sex, year of birth, neonatal antibiotic treatment and maternal oxytocin treatment, age, parity, and smoking.

Gentamicin

Refer to the medicine review, gentamicin for uncomplicated UTI (November 2019):

Gentamicin for UTI-Adults Review_N

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation

Based on this evidence review, is the Adult Hospital Level Committee recommends that gentamicin, IM 5mg/kg as a single dose as an alternative to ciproflxacin; whilst in pregnancy and renal impairment, fosfomycin and nitrofurantoin may be considered.

Rationale: Meta-analysis[35] of RCTs investigating upper or lower UTI, as well as initial or recurrent infections showed acceptable microbiological cure rate of single dose aminoglycosides for uncomplicated UTI with minimal toxicity. Single dose gentamicin considered to be a more pragmatic option, as amikacin is preferred

[34] Nordeng H, Lupattelli A, Romøren M, Koren G. Neonatal outcomes after gestational exposure to nitrofurantoin. Obstet Gynecol. 2013 Feb;121(2 Pt 1):306-13. http://www.ncbi.nlm.nih.gov/pubmed/23344280

[35] Goodlet KJ, Benhalima FZ, Nailor MD. A Systematic Review of Single-Dose Aminoglycoside Therapy for Urinary Tract Infection: Is It Time To Resurrect an Old Strategy? Antimicrob Agents Chemother. 2018 Dec 21;63(1). pii: e02165-18. https://www.ncbi.nlm.nih.gov/pubmed/30397061

for nosocomial infections. It is acknowledged that uncomplicated UTI has a substantial spontaneous cure rate, but morbidity is being managed in this setting.

Local susceptibility data from NICD/NHLS, though sourced from antenatal care centre at a tertiary institution (Charlotte Maxeke Hospital), showed resistance of *E.Coli* to ciprofloxacin[36]; similar to results of susceptibility study of community acquired UTI also done in Gauteng.[37]

Level of Evidence: I Systematic review and meta-analysis , Antibiotic susceptibility study and data, Expert opinion

NEMLC RECOMMENDATION:

Therapeutic alternative for ciprofloxacin be recommended for uncomplicated UTI in adults as either nitrofurantoin, fosfomycin or single dose gentamicin, IM; whilst in pregnancy and renal impairment, fosfomycin and nitrofurantoin may be considered.

Rationale: There is comparable evidence of efficacy and comparative prices for nitrofurantoin vs fosfomycin treatment courses for uncomplicated UTI. Despite the concern regarding non-adherence of the nitrofurantoin treatment course, it was accepted that both treatment options (i.e. fosfomycin and nitrofurantoin) be included, to ensure sustainable supplies of treatment for uncomplicated UTIs.

There is evidence of low to moderate quality, suggested that aminoglycosides have good microbiological cure rate with low number of report ADRs associated with single IM dose for uncomplicated UTI. Single dose gentamicin considered to be a more pragmatic option, as amikacin is preferred for nosocomial infections.
NEMLC acknowledged that uncomplicated UTI has a substantial spontaneous cure rate, but morbidity is being managed in this setting.

Level of Evidence: II Meta-analyses of low to moderate quality RCTs[38], Local Susceptibility study[39], Expert opinion

ACE-inhibitor/angiotensin receptor inhibitor: *caution with concomitant use of fluoroquinolones added*

Caution was updated following the safety alert for concomitant use of ACE-inhibitors and fluoroquinolones causing acute kidney injury. WHO Uppsala Pharmacovigilance Monitoring Centre receipt of an increased number of individual case safety reports (ICSRs)[40] and a nested case-control study[41] suggests a risk of developing acute kidney injury with concomitant use of fluoroquinolones and renin-angiotensin receptor blockers, which appears to be a class effect.

The following was added to the STG:

» Concomitant use of fluoroquinolones with ACE-inhibitor/angiotensin receptor blocker is contraindicated in moderate to severe renal impairment (Creatinine Clearance ≤ 30 ml/min) and in the elderly. Assess renal function before initiating treatment and monitor during treatment.

Level of Evidence: III Observational studies

[36] NICD susceptibility data submitted per e-mail and on file.

[37] Lewis DA, Gumede LY, van der Hoven LA, de Gita GN, de Kock EJ, de Lange T, Maseko V, Kekana V, Smuts FP, Perovic O. Antimicrobial susceptibility of organisms causing community-acquired urinary tract infections in Gauteng Province, South Africa. S Afr Med J. 2013 Mar 15;103(6):377-81

[38] Huttner A, Verhaegh EM, Harbarth S, Muller AE, Theuretzbacher U, Mouton JW. Nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials. J Antimicrob Chemother. 2015 Sep;70(9):2456-64. https://www.ncbi.nlm.nih.gov/pubmed/26066581

[39] Lewis DA, Gumede LY, van der Hoven LA, de Gita GN, de Kock EJ, de Lange T, Maseko V, Kekana V, Smuts FP, Perovic O. Antimicrobial susceptibility of organisms causing community-acquired urinary tract infections in Gauteng Province, South Africa. S Afr Med J. 2013 Mar 15;103(6):377-81.http://www.ncbi.nlm.nih.gov/pubmed/23725955

[40] Savage R. Ciprofloxacin, enalapril and acute kidney injury: Strengthening of a drug Interaction signal. WHO Pharmaceuticals Newsletter : 16-21, No. 1, 201. http://www.who.int/medicines/publications/WHO-Pharmaceuticals_Newsletter_No1-2018.pdf?ua=1

[41] Bird ST, Etminan M, Brophy JM, Hartzema AG, Delaney JA. Risk of acute kidney injury associated with the use of fluoroquinolones. CMAJ. 2013 Jul 9;185(10):E475-82. https://www.ncbi.nlm.nih.gov/pubmed/23734036

7.3.3 RECURRENT URINARY TRACT INFECTION

Prophylaxis

Cotrimoxazole, oral: *retained*

Ciprofloxacin, oral: *deleted*

Ciprofloxacin: Deletion of ciprofloxacin is aligned with recommendations for uncomplicated UTI, and the signal of associated harm with fluoroquinolones (see section 7.3.2: Urinary tract infection, above).

Nitrofurantoin, oral: *deleted*

Nitrofurantoin: There is a paucity on data for safety (only data on short-term use of less than 14 days[42]). The risk of obtaining permanent irreversible and possibly fatal pulmonary fibrosis outweighs benefit of possibly preventing cystitis.

Danish Pharmacovigilance Update 2015[43] reported that there is still inadequate evidence on long-term treatment with nitrofurantoin and the risk of pulmonary fibrosis. Long-term treatment with nitrofurantoin could cause irreversible pulmonary fibrosis and routine spirometry and symptom screening are recommended.

Systematic review and meta-analysis[44] suggests that nitrofurantoin is effective in the prevention of UTI. Its use may be associated with increased non-severe adverse effects, whilst severe adverse effects occur infrequently. The risk of severe toxicity seems to increase with the duration of nitrofurantoin prophylaxis. However, overall quality of studies was poor, with all studies at increased risk for various biases.

Level of Evidence: II Systematic review and meta-analysis of RCTs of low methodological quality, Pharmacovigilance report

Report prepared by TD Leong: Secretariat to the Adult Hospital Level Committee (2017-2020)

- ***Note:*** *Information was sourced from NEMLC ratified minutes and NEMLC-approved documents.*

[42] Huttner A, Verhaegh EM, Harbarth S, Muller AE, Theuretzbacher U, Mouton JW. Nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials. J Antimicrob Chemother. 2015 Sep;70(9):2456-64. https://www.ncbi.nlm.nih.gov/pubmed/26066581

[43] Danish Pharmacovigilance Update, Volume 6 February 2015. https://laegemiddelstyrelsen.dk/en/news/danish-pharmacovigilance-update,-archive/danish-pharmacovigilance-update,-february-2015/~/media/2D8B01D232124E1DB1B21378AEDAE5EE.ashx

[44] Muller AE, Verhaegh EM, Harbarth S, Mouton JW, Huttner A. Nitrofurantoin's efficacy and safety as prophylaxis for urinary tract infections: a systematic review of the literature and meta-analysis of controlled trials. Clin Microbiol Infect. 2017 Jun;23(6):355-362. https://www.ncbi.nlm.nih.gov/pubmed/27542332