HOW TO USE THESE GUIDELINES

Principles

The National Drug Policy[1] makes provision for an Essential Drugs Programme which is a key component in promoting rational medicines use.

The perspective adopted in the Adult Hospital Level Standard Treatment Guidelines (STGs) is that of a competent medical officer practicing in a public sector hospital. The STGs serve as a standard for practice, but do not replace sound clinical judgment. It is important to remember that the treatments recommended are guidelines only and are based on the assumption that prescribers can manage patients with the relevant conditions.
This includes rational prescribing in the elderly and palliative care, as the use of some medicines, especially as people get older or more ill, can cause more harm than good. Optimizing medication through targeted de-prescribing is a vital part of managing chronic conditions, avoiding adverse effects and improving outcomes. The goal of de-prescribing is to reduce pill burden and maintain or improve quality of life.

All reasonable steps were taken to align the STGs with Department of Health guidelines that were available at the time of review. Each treatment guideline in the Adult Hospital Level STGs and Essential Medicines List (EML) was designed as a progression in care from the current Primary Health Care (PHC) STGs and EML. Given that the PHC STGs and EML were reviewed prior to the Adult Hospital Level STGs, the two STGs are not always perfectly aligned. Where referral to a tertiary facility is recommended, the relevant medicines have either been reviewed or included in the tertiary level EML, or are in the process of being reviewed.

Each medicine was included or removed from the EML using an evidence based review of safety and effectiveness, followed by considerations of cost and other relevant practice factors, such as availability and storage requirements. Some recommendations might not be aligned with the SAHPRA registered label/package insert; but are guided by health needs assessment and the best available scientific evidence.

The dosing regimens provide the recommended doses used in usual circumstances. However, the prescribed dose should take into consideration drug-drug interactions and co-morbid states, notably renal or hepatic failure, critical illness, and morbid obesity.

Local formularies

The EML has been developed down to generic or International Non-Propriety Name (INN) level. Each Province is expected to review the EML and prevailing tenders and compile a formulary which:

» lists formulations and pack sizes that will facilitate care in alignment with the STGs and EML;

1NationalDrugsPolicy,1996.https://www.gov.za/documents/national-drugs-policy

» selects the preferred member of the therapeutic class based on cost;
» implements formulary restrictions consistent with the local environment; and
» provides information on medicine prices.

Therapeutic classes are designated in the "Medicine treatment" sections of the STGs which provide classes of medicines followed by an example of each class, such as 'HMGCoA reductase inhibitors (statins) e.g. simvastatin'. Therapeutic classes are designated where none of the members of the class offer any significant benefit over the other registered members of the class. It is anticipated that by listing a class rather than a specific medicine there is increased competition and hence an improved chance of obtaining the lowest possible price in the tender process. The designation of medicines into therapeutic classes may also assist with remedial actions to mitigate challenges to security of supply, by providing suggested alternatives which have already been approved by the ministerially appointed National Essential Medicines List Committee (NEMLC)[2].

Where therapeutic classes are listed in the STGs always consult your local formulary to identify the specific medicine that has been approved for use in your facility. A therapeutic interchange database has been developed that lists evidence-based reviewed medicines that have been grouped into each therapeutic class for a specific condition, as outlined in the policy for classifying medicines into therapeutic classes for purposes of therapeutic interchange. The database and policy are available on the National Department of Health website: http://www.health.gov.za/edp.php

Navigating the guidelines

It is important that you become familiar with the contents and layout of these guidelines in order to use the STGs effectively.

The STGs are arranged into chapters according to the organ systems of the body. Conditions and medicines are cross referenced in two separate indexes of these guidelines. In some therapeutic areas that are not easily amenable to the development of a STG, the section is limited to a list of medicines.

This edition of the Adult Hospital Level STG and EML provides additional information: Appendix III – guidance on the use of certain medicines in pregnancy; and Appendix IV – guidance on extemporaneous preparation of certain medicines using a standardised formula.

Revisions to previous recommendations are accompanied by the level of evidence that is cited and hyperlinked accordingly. All evidence is graded according to the Strength Of Recommendation Taxonomy (SORT) (a patient-centered approach to grading evidence in the medical literature), described in detail on page xli. To further promote transparency of medicine selection decisions, NEMLC reports, medicine reviews and costing reports are available

2 NEMLC is tasked to formulate and revise the Standard Treatment Guidelines (STGs) and Essential Medicines List (EML)usingapeerreviewconsultativeprocess.

on the National Department of Health website: http://www.health.gov.za/edp.php

The section on Patient Education in Chronic Conditions aims to assist health workers to improve patient adherence and health, generally. Information on the Central Chronic Medicines Dispensing and Distribution (CCMDD) programme is available at: nhiccmddadmin@health.gov.za

Diagnosis codes from the International Statistical Classification of Diseases and Related Health Problems (ICD-10) are included for each condition to facilitate accurate recording of diagnoses. The primary ICD-10 code may be accompanied by a secondary code that is bracketed to differentiate a secondary manifestation from the primary aetiology. (For example, uncomplicated broncho-pneumonia with severe penicillin allergy would be coded as: J18.0+(Z88.0)). All the rules and guidelines for the use of ICD-10 must be applied as per the World Health Organisation (WHO), the agreed South African Morbidity Coding Standards and Guidelines document, and the South African Master Industry Table (MIT).
Available at: http://www.health.gov.za/index.php/shortcodes/2015-03-29-10-42-47/2015-06-10-09-23-36/2015-06-10-09-26-11

Medicines safety
Provincial and local Pharmaceutical and Therapeutics Committees (PTCs) should develop medicines safety systems to obtain information regarding medication errors, prevalence and importance of adverse medicine events, interactions, and medicines quality. These systems should not only support the regulatory pharmacovigilance plan, but should also provide pharmacoepidemiology data that will be required to inform future essential medicines decisions as well as local interventions to improve safety.

In accordance with SAHPRA's guidance on reporting adverse drug reactions in South Africa, the medical officer with the support of the PTC should report the relevant adverse reactions to the National Adverse Drug Event Monitoring Centre (NADEMC). To facilitate reporting, a copy of the form and guidance on its use has been provided.

Feedback
Comments that aim to improve these treatment guidelines will be appreciated. The submission form and guidance for completing the form are included with these guidelines. Motivations will be accepted from Provincial PTCs only.

THERAPEUTIC DRUG MONITORING (TDM)
Medicines with narrow therapeutic indices and those with variable pharmacokinetics should be monitored regularly to optimise dosing, obtain maximum therapeutic effect, limit toxicity, and assess compliance. Appendix II provides detailed information for specific medicines.
TDM sampling for all drugs is to be done only once steady state has been reached (i.e. after 4–5 half-lives).

Lithium
Measure serum concentrations at about 12 hours after the last dose – i.e.

immediately prior to the next dose. Concentrations should be less than 1 mmol/L and should be monitored 6-monthly while on therapy, with more frequent monitoring in the elderly (see Appendix II for guidance on prescribing lithium).

Aminoglycosides

Peak concentrations will generally be adequate if dosing is adequate (e.g. gentamicin 5 mg/kg/day in a single daily dose) and measuring peak concentrations is not recommended unless the organism has a high minimum inhibitory concentration (MIC) or if the patient is critically ill. Trough concentrations, taken immediately before the next dose, are valuable for identifying potential toxicity. Toxicity may manifest as deafness or renal impairment. Aminoglycosides are relatively contraindicated in renal impairment. Audiology assessment and renal function monitoring is indicated in all patients who develop aminoglycoside toxicity (see Appendix II for guidance on prescribing amikacin and gentamicin).

Anti-epileptics

Measuring concentrations may be helpful to confirm poor adherence or to confirm a clinical suspicion of toxicity. Routine measurement in patients with well-controlled seizures and no clinical evidence of toxicity, is not appropriate. Individual concentrations may be difficult to interpret – if in doubt, seek assistance from a clinical pharmacologist.

PRESCRIPTION WRITING

Prescribers may initiate and/or maintain treatment with medicines as per the STGs in accordance with their scope of practice.

Medicines should be prescribed only when they are necessary for treatment following clear diagnosis. Not all patients or conditions need prescriptions for medication. In certain conditions simple advice and general and supportive measures may be more suitable.

In all cases carefully consider the expected benefit of a prescribed medication against potential risks. This is especially important during pregnancy where the risk to both mother and fetus must be considered.

All prescriptions must:

- be written legibly in ink by the prescriber with the full name, identification number and address of the patient, and signed with the date on the prescription form;
- specify the age and, in the case of children, weight of the patient;
- have prescriber details including contact details i.e. name, qualification, registration number, address and contact telephone number;
- indicate the diagnosis on the prescription, where there patient has provided consent.

In all prescriptions:

- State the treatment regimen in full:
    - medicine name, strength and formulation,
    - dose or dosage,

- dose frequency,
- dose route
- duration of treatment,
- e.g. amoxicillin 250 mg capsules, 8 hourly orally for 5 days.

» Write the name of the medicine/preparation in full using the generic name.
» Avoid abbreviations to reduce the risk of misinterpretation. Avoid the Greek mu (ų): write mcg as an abbreviation for micrograms.
» Avoid unnecessary use of decimal points. If necessary, write a zero in front of the decimal point only, e.g. 2 mg not 2.0 mg; or 0.5 mL not .5 mL.
» Avoid Greek and Roman frequency abbreviations that cause considerable confusion (qid, qod, tds, tid, etc). Instead either state the frequency in terms of hours (e.g. '8 hourly') or times per day in numerals (e.g. '3x/d').
» In the case of "as required", a minimum dose interval should be specified, e.g. 'every 4 hours as required'.
» Most monthly outpatient scripts for chronic medication are for 28 days; check that the patient will be able to access a repeat before the 28 days are completed.
» Prescriptions for schedules 6 medicines are not repeatable, requiring to be issued monthly; and the quantity to be issued should be expressed in words.

After writing a prescription, check that the dose, dose units, route, frequency, and duration for each item is stated. Consider whether the number of items is too great to be practical for the patient, and check that there are no redundant items or potentially important drug interactions. Check that the script is dated, that the patient's name, identification number and diagnosis/diagnostic code are on the prescription form. Only then should you sign the prescription and provide some other way for the pharmacy staff to identify the signature if there are problems (print your name, use a stamp, or use a prescriber number from your institution's pharmacy).

Notes on specific medicines

ACE-inhibitor	Angioedema is a potentially serious complication of ACE-inhibitor treatment and if it occurs it is a contraindication to continued therapy or to re-challenge.
ACE-inhibitors and ARBs	ACE-inhibitors and ARBs can cause or exacerbate hyperkalaemia in chronic kidney disease (eGFR < 60 mL/minute). Check the serum potassium before starting these medicines, and monitor serum potassium on therapy. ACE-inhibitors and ARBs are contra-indicated in pregnancy.
Allopurinol	Contra-indicated in patients with eGFR <30 mL/minute. Do not stop uric acid lowering drugs during an
Amitriptyline + citalopram	Concomitant use of amitriptyline and citalopram may increase the risk of serotonin syndrome or neuroleptic malignant syndrome. Furthermore, there is a potential risk for QT- prolongation.

Anti-epileptic medicines	Phenytoin, phenobarbitone, and carbamazepine are potent enzyme inducing agents and should be used with caution with other medicines metabolised by the liver, especially warfarin, antiretrovirals, progestin subdermal implants, and oral contraceptives.
Benzodiazepines	Benzodiazepines can cause respiratory depression. Monitor patients closely as benzodiazepines can exacerbate an abnormal mental state or mask important neurological signs of deterioration. Prolonged treatment with benzodiazepines often leads to tolerance and withdrawal symptoms if the medicine is discontinued abruptly. Combination therapy with more than one benzodiazepine is not indicated.
ß–blockers	ß–blockers should not be used in cocaine poisoning. ß–blockers may cause bronchospasm in asthmatics.
Ciprofloxacin	Irrational use of quinolones contributes to the emergence of XDR-TB and potential masking of active TB.
Clindamycin	Clindamycin has good coverage against Gram positive organisms and anaerobes, so the addition of metronidazole is unnecessary.
Folic acid + vitamin B12	Anaemia megaloblastic: Give vitamin B12 and folic acid together until the test results are available as giving folic acid alone in patients with a B12 deficiency may precipitate a permanent neurological deficit.
Haloperidol	Dosing may vary according to clinical circumstances, e.g. lower doses in the elderly or where HIV infection or HIV-related dementia is known or suspected. In frail and elderly patients, reduce the dose by half.
Lithium	Therapeutic drug monitoring is essential when using lithium. Clinical toxicity may occur even within the therapeutic range. Concomitant use of many medicines e.g. ACE-inhibitors, NSAIDs and diuretics may increase the risk of lithium toxicity.
Loperamide	Contraindicated in dysentery, acute non-inflammatory diarrhoea, antibiotic-associated diarrhoea and amoebic dyssentery; as it may result in toxic megacolon.
Low molecular weight heparin (LMWH)	In morbid obesity dosing of LMWH should be individualised, in discussion with a specialist. In renal failure (eGFR < 30 mL/minute), the recommended dose of LMWH is 1 mg/kg/day. Pregnant women with mechanical prosthetic valves should not receive LMWH unless antifactor Xa levels can be monitored reliably weekly. Therapeutic range is pre-dosing level 0.6 units/mL and a 4-hour peak level of 1–1.2 units/mL.
Metformin	Metformin should be dose adjusted in renal impairment (eGFR: 30-60 mL/minute).
Metronidazole	The addition of metronidazole to amoxicillin/clavulanic acid is unnecessary as amoxicillin/clavulanic acid has adequate anaerobic cover.

Misoprostol (for TOP)	Misoprostol can cause uterine rupture in women with previous Caesarean sections and those of high parity. In these women use 200 mcg of misoprostol or alternative methods such as extra-amniotic saline infusion without misoprostol. The dose of misoprostol, PV, decreases with increasing gestational age because of the risk of uterine rupture.
NSAIDs	Concomitant use of more than one NSAID has no additional clinical benefit and only increases toxicity. Chronic use of all NSAIDs is associated with varying degrees of gastrointestinal, renal, and cardiovascular risks. Long-term use of NSAIDs should weigh potential benefits against these risks.
Oral diabetic agents	Oral diabetic agents should not be used in type 1 diabetes and used with caution in liver and renal impairment.
Insulin in the treatment of DKA	Potassium will fall on insulin treatment and patients with DKA have potassium depletion even if initial potassium is normal or high. It is therefore essential to monitor and replace potassium.
Antivenom	Never administer antivenom without being fully prepared to manage acute anaphylaxis.
Sodium chloride	Rapid correction of sodium, in hyponatraemia, may lead to central pontine myelinolysis, which is often irreversible. Sodium should be frequently monitored and increases should be <9 mmol/L per day.
Spironolactone	Monitoring of sodium, potassium and renal function is essential in patients taking spironolactone. Avoid if eGFR < 30 mL/minute.
SSRIs	Adolescents with depression may have an increased risk of suicidal ideation when initiated on SSRIs.
Streptokinase	Do not use heparin if streptokinase is given.
Sulphonylureas	Hypoglycaemia caused by a sulphonylurea can be prolonged. The patient should be hospitalised with an intravenous glucose infusion, and observed for at least 12 hours after glucose infusion has stopped.
Tricyclic antidepressants	Avoid in patients with cardiac disease and a high risk of overdose.
Testosterone	Screen hypogonadal men for prostate cancer before beginning testosterone replacement.
Unfractionated heparin	Evidence indicates that PTT monitoring is not necessary with weight based dosing of unfractionated heparin. However, in patients with morbid obesity and renal failure (eGFR < 30 mL/minute) unfractionated heparin should be used with PTT monitoring to maintain the PTT at 1.5 to 2.5 times the control. Blood for measurement of PTT should be taken 4 hours after SC dose.
Verapamil	Never give verapamil or adenosine IV to patients with a wide QRS tachycardia as this may precipitate ventricular fibrillation. In atrial flutter, do not use verapamil as it will not convert flutter to sinus rhythm and may cause serious hypotension.
Warfarin	Warfarin use requires regular INR monitoring and dose adjustment according to measured INR. See appendix II.

PENICILLIN DESENSITISATION

This has been included for information only.

Perform only in an ICU setting or in a setting where recognition and management of anaphylaxis can be assured.

Discontinue all ß-adrenergic antagonists. Have an IV line, ECG monitor and spirometer in place. Once desensitised, treatment must not lapse as risk of subsequent allergy increases.

A history of Stevens-Johnson's syndrome, exfoliative dermatitis, erythroderma are absolute contra-indications to desensitisation (use only as an approach to IgE sensitivity).

Oral route is preferred. 1/3 of patients develop a transient reaction during desensitisation or treatment, which is usually mild.

Oral penicillin desensitisation protocol

A: Prepare stock solution of oral phenoxymethylpenicillin 250mg/ 5mL and dilutions for steps 1-7 and 8-10 B: Administer increasing doses of penicillin strictly at 15 minutes intervals		
Step	**Medicine mg/mL**	**Amount to administer (mL)**
To make 0.5 mg/mL solution: Add 0.5 mL of stock phenoxymethylpenicillin solution to 49.5 mL water (total volume 50mL)		
1	0.5 mg/mL solution (1000 units/mL)	0.1 mL orally
2		0.2 mL orally
3		0.4 mL orally
4		0.8 mL orally
5		1.6 mL orally
6		3.2 mL orally
7		6.4 mL orally
To make 5 mg/mL solution: Dilute 1 mL of stock phenoxymethylpenicillin solution with 9 mL water (total volume 10mL)		
8	5 mg/mL solution (10000 units/mL)	1.2 mL orally
9		2.4 mL orally
10		4.8 mL orally
Stock phenoxymethylpenicillin 250 mg/5 mL = 50 mg/mL		
11	50 mg/mL (80000 units/mL)	1.0 mL orally
12		2.0 mL orally
13		4.0 mL orally
14		8.0 mL orally

After step 14, observe for 30 minutes, then administer desired dose of intravenous penicillin.

Intravenous penicillin desensitisation protocol

A. Prepare stock solution for intravenous administration of benzathine penicillin G of 100mg/ml and dilutions for steps 1-5, 6-8, and 9-12. Label dilutions carefully.

Use 600mg vial =1MU

a. reconstitute dry powder with 6mls water for injection to make stock of 100mg/ml (steps 13-16)
b. Take 1ml of 100mg/ml stock and reconstitute with 9ml to make a 10mg/ml solution (steps 9-12)
c. Take 1ml of 10mg/ml benzathine penicillin G and reconstitute with 9mLs water to make a 1mg/ml solution (steps 6-8)
d. Take 1ml of 1mg/ml benzathine penicillin G and reconstitute with 9mLs water to make a 0.1mg/ml solution (steps 1-5)

B. Administer increasing doses of penicillin **strictly at 15 minutes intervals**

Step	Medicine (mg/ml)	Volume to administer (ml)	Route Cumulative dose (mg)
Use 0.1 mg/mL solution			
1	0.1	0.1	0.01
2	0.1	0.2	0.03
3	0.1	0.4	0.07
4	0.1	0.8	0.15
5	0.1	1.6	0.31
Use 1mg/ml solution			
6	1	0.32	0.63
7	1	0.64	1.27
8	1	1.2	2.47
Use 10mg/ml solution			
9	10	0.24	4.87
10	10	0.48	10
11	10	1	20
12	10	2	40
Use 100mg/ml stock solution			
13	100	0.4	80
14	100	0.8	160
15	100	1.6	320
16	100	3.2	640

Cumulative dose of 640mg (1MU) given on completion of step 16. Observe the patient for 30 minutes and then administer the full therapeutic dose intravenously.

COTRIMOXAZOLE DESENSITISATION

Attempt desensitisation in patients with a history of cotrimoxazole intolerance, unless this was life-threatening, e.g.: Stevens-Johnson syndrome. (See section 4.6: Erythema Multiforme, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis). Unless the rash is severe or associated with systemic symptoms, continue treatment with careful observation for deterioration.

Desensitisation should be attempted using cotrimoxazole suspension 240 mg/5mL. Dilute the suspension appropriately and consult with your pharmacist if necessary.

Note: Do not administer antihistamines or steroids with this regimen.

Time (hours)	**Cotrimoxazole dose (mL of**
0	0.0005
1	0.005
2	0.05
3	0.5
4	5
5	Two single strength tablets (each tablet