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Department:
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SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 19: POISONINGS
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 the dental and poisonings chapter.

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED
19.2 Snakebites	Polyvalent antivenom	Amended (indications, premedication guidance, dosing)
19.2.1 Cytotoxic and neurotoxic snakebite	Polyvalent antivenom	Directions and indications for use amended
19.2.2 Boomslang snakebite	Adrenaline (epinephrine), SC	Not added
	Boomslang monovalent antivenom	Directions for use amended
19.2.3 Snake venom in the eye	Polyvalent antivenom	Caution added
19.3 Scorpion envenomation	Opiates	Indication amended and caution retained
- Severe muscle pain and cramps	Calcium gluconate, IV	Directions for use amended
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- Decontamination	Gastric lavage	Directions for use amended
	Activated charcoal, oral	Indication, contra-indications and directions for use amended
	Polyethylene glycol (PEG) balanced electrolyte solution, NGT	Added for whole bowel irrigation
- Seizures	Benzodiazepines	Retained with cross reference to section 14.4.1: Status epilepticus; indication amended
	Phenytoin	Caution added to avoid in relevant poisonings
19.5.1 Paracetamol poisoning	Nomogram	Text describing nomogram updated
	Toxic dose of paracetamol	Amended
	N-acetylcysteine, IV	Dosing regimen amended
	N-acetylcysteine, oral	Retained and dosing regimen added
19.5.2 Salicylate poisoning	Sodium bicarbonate, IV	Directions for use amended
	Referral criterion	Added
19.5.3 Opioid poisoning	Naloxone, IV	Retained
19.6.1 Tricyclic antidepressant poisoning	Sodium bicarbonate, IV	Directions for use amended
	Magnesium sulfate, IV	Deleted
19.7 Iron poisoning	Whole bowel irrigation	Indication restricted to severe iron toxicity
	Desferrioxamine (deferoxamine)	Directions for use amended
	Exchange transfusion	Not recommended
19.8 Theophylline poisoning	Metoclopramide, oral/IV	Added
	Ondansetron, oral/IV	Added as an alternative option to metoclopramide (therapeutic interchange database)
	Activated charcoal, oral	Dosing amended
	Diazepam, IV	Removed with cross reference to section 14.4.1: Status epilepticus
	Benzodiazepines	Retained with cross reference to section 14.4.1: Status epilepticus; indication amended
	Hypokalaemia management	Guidance provided
19.9.1 Benzodiazepine poisoning	Flumazenil, IV	Not added
19.9.2 Lithium poisoning	Polyethylene glycol (PEG)	Added for whole bowel irrigation
	Potassium chloride, IV	Deleted with a cross referral to section: 7.2 Major electrolyte abnormalities
	Haemodialysis	Early haemodialysis recommended for severe toxicity
19.10 Isoniazid poisoning	Pyridoxine, oral	Route of administration expanded and indication clarified
	Pyridoxine, parenteral	Not added
- Seizures	Lorazepam, IV/IM	Added
	Diazepam, IV	Added
	Clonazepam, IV	Added
	Midazolam, IM/IV	Added

	Midazolam buccal, (using the parenteral formulation)	Added
	Phenytoin	Caution added to avoid use
19.11 Calcium channel blocker and beta blocker poisoning	Management of beta blocker and CCB toxicity	Guidance combined in a single STG management follows similar therapeutic principles
	Glucagon	Not added
- for hypotension	Sodium chloride, 0.9%, IV	Retained
	Ringer Lactate, IV	Not added
	Balsol, IV	Not added
- hypotension not effectively controlled	Calcium gluconate, IV	Retained, dosing amended
	Calcium chloride, IV	Alternative option to calcium gluconate
19.14.1 Cocaine poisoning	Polyethylene glycol (PEG)	Added for whole bowel irrigation
- Delirium with severe agitation	Lorazepam, IM	Deleted with cross reference to section 20.8: Delirium with perceptual disturbances
	Midazolam, IM	
	Clonazepam, IM	
	Diazepam, IV	
	Haloperidol, IM	
	Promethazine, IM	
	Chlorpromazine, IM	
- Arrhythmias	Lidocaine	Caution deleted (i.e. "Lidocaine may precipitate seizures").
	Beta-blockers	Contra-indication retained
19.14.2 Poisoning with amphetamine derivatives	Labetalol, IV	Not added
19.17.2 Ethylene glycol poisoning	Ethanol	Retained as antidote, indications added and directions for use amended
	Haemodialysis	Retained for severe poisoning/ profound acidosis
	Fomeprizole	Not added
- Metabolic acidosis	Sodium bicarbonate, IV	Directions for use amended
19.17.3 Methanol poisoning	Anion gap calculation	Aligned to section: 19.17.2 Ethylene glycol poisoning
	Ethanol	Retained as antidote
	Haemodialysis	Retained for severe poisoning/ profound acidosis
	Folinic acid, IV	Not added
19.18.1 Amitraz poisoning	Activated charcoal	Added, once patient is stabilised
19.18.2 Organophosphate poisoning	Protective equipment for staff	Recommendation added
	Activated charcoal	Added, once patient is stabilised
	Atropine, IV	Treatment protocol amended
	Obidoxime	Not added
- severe agitation	Diazepam, IV	Added
19.18.3 Paraquat poisoning	Dithionate urine test	HTA for diagnostics recommended
19.19 Anticoagulant (warfarin and rodenticide superwarfarin) poisoning		
- warfarin poisoning	Protein C concentrate	Not added
	Vitamin K, parenteral	Retained
- Elevated INR with significant bleeding	FFP/ lyophilised plasma	Placed first in treatment protocol
	Vitamin K	Placed second in treatment protocol
- Rodenticide/Super warfarins	Vitamin K	INR cut-off for administration retained as < 4
19.2.1 Heavy metal poisoning	Common heavy metal poisonings	General overview provided of presentation
19.22 Poisoning with substances that cause methaemoglobinaemia	N-acetylcysteine, IV	Deleted
	Ascorbic acid, IV	Deleted
Medicine review	Protamine	Not added

19.2 SNAKEBITES

STG delineated to provide guidance on i) cytotoxic and neurotoxic snakebite; ii) haemotoxic/boomslang snakebite; iii) snake venom in the eye.

Following table was editorially updated:

Venom type	Cytotoxic	Neurotoxic	Mixed cytotoxic and neurotoxic	Haemotoxic
Snake species	Puff adder, Gaboon adder, spitting cobras(Mozambique, black-necked, zebra), stiletto snake, night adders, horned adders	Black and green mamba, non-spitting cobras (Cape, forest, snouted)	Rinkhals, Berg adder, Peringuey's adder, desert mountain adder, garter snakes, shield-nose snake, coral snake	Boomslang, vine snakes.
Clinical features of envenomation	Pain, swelling, blisters, necrosis, regional lymphadenopathy, hypotension, coagulopathy, compartment syndrome	Pins and needles, metallic taste, visual disturbances, ptosis, drowsiness, sweating, drooling, dysphagia, progressive weakness, respiratory paralysis	Combined cytotoxic and neurotoxic features	Spontaneous bleeding (can present late >24 hours after bite), headaches, dizziness, fainting
Antivenom (when indicated)	Polyvalent antivenom for Puff adder, Gaboon adder and spitting cobras only	Polyvalent antivenom for all species	Polyvalent antivenom for rinkhals only	Boomslang monovalent antivenom for boomslang bites only.

Polyvalent antivenom: *amended (indications, premedication guidance, dosing)*
Indications: Deeltion of '*confirmed mamba bites…, even before the onset of symptoms and signs'* from the text of the STG as this was not standard practice (as antivenom given to a patient with a dry bite was considered to be harmful).

Dosing of polyvalent antivenom specifically for '*cytotoxic snakebite of head and neck'* was deleted, as this is not standard practice.
Level of Evidence: III Standard practice

19.2.1 CYTOTOXIC AND NEUROTOXIC SNAKEBITE

Polyvalent antivenom: *directions and indications for use amended*

Directions: Aligned with Guidelines[1] [2] that suggest administration of antivenom as long as there are signs of ongoing envenomation.
Level of Evidence: III Guidelines

Indications amended for cytotoxic, neurotoxic bites and where snake is unidentified.
Text amendment guided by expert opinion[3] [4] to:

- Signs of neurotoxicity.
- Positively identified puff adder, Gaboon adder, Mozambique spitting cobra or rinkhals bites AND evidence of progressive severe cytotoxicity.
- Unidentified snakebites and evidence of progressive severe cytotoxicity envenomation i.e.:
  - swelling of whole hand or foot within 1 hour
  - swelling to the knee or elbow in less than 6 hours
  - swelling of the whole limb in less than 12 hours
  - swelling progression > 2.5cm per hour
  - a threatened airway due to swelling
  - evidence of complication e.g. compartment syndrome

Mozambique spitting cobra bite: Aligned with WHO Guidelines[5] to administer a dose of 100 mL of polyvalent antivenom.
Level of Evidence: III Guidelines

[1] World Health Organistaion. Guidelines for the Prevention and Clinical Management of Snakebite in Africa, 2010. http://www.afro.who.int/
[2] Blaylock RS. The identification and syndromic management of snakebite in South Africa. SA Fam Pract 2005;47(9): 48-53). https://journals.co.za/content/mp_safp/47/9/EJC79826
[3] Wood D, Sartorius B, Hift R. Snakebite in NE South Africa: clinical characteristics and risks for severity. S Afr Fam Prac 2016; 58(2):62-67. https://www.tandfonline.com/doi/full/10.1080/20786190.2015.1120934
[4] Wood, Sartorius, Hift. Classifying snakebite in South Africa: validating a scoring system. S Afr Med J 2017;107(1):46-51. https://www.ncbi.nlm.nih.gov/pubmed/28112091
[5] World Health Organistaion. Guidelines for the Prevention and Clinical Management of Snakebite in Africa, 2010. http://www.afro.who.int/

19.2.2 BOOMSLANG SNAKEBITE

Adrenaline (epinephrine), SC: *not added*

Pre-administration with adrenaline (epinephrine) for polyvalent antivenom reduces the risk of severe adverse effects, as the polyvalent antivenom in South Africa is impure. However, the boomslang monovalent antivenom is less antigenic, and premedication with adrenaline is not routinely administered. The package insert recommends adrenaline in patients with significant allergic disease or a history of hypersensitivity to horse serum.

Level of Evidence: III Package insert[6]

Boomslang monovalent anivenom: *directions for use amended*

Aligned with WHO Guidelines.

Level of Evidence: Guidelines[7]

19.2.3 SNAKE VENOM IN THE EYE

Polyvalent antivenom: *caution added*

Caution added that antivenom should not be instilled in the eye or be administered systemically.

Level of Evidence: III Expert opinion[8]

19.3 SCORPION ENVENOMATION

Opiates: *indication amended and caution retained*

Opiates may be required for severe pain control, but increases the risk of respiratory depression, and therefore, caution box was amended as follows:

Opiates ~~are not effective and~~ increase the risk of respiratory depression and if required, should only be used with caution in severe uncontrolled pain.

Level of Evidence: III Guidelines

Severe muscle pain and cramps

Calcium gluconate, IV: *directions for use amended*

The following guidance was added as a note:

- Calcium gluconate 10%, bolus IV infusion, 10 mL over 10 minutes.
  - Repeat if needed, only once

Note: Effect may only last for 20–30 minutes and there is a limited amount that can be given.

Level of Evidence: III Guidelines[9]

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Decontamination

Evidence for drug decontamination *(gastric lavage, activated charcoal, whole bowel irrigation)* is limited and of very low methodological quality. The Toxicology Societies and Centres recommended that "Single dose activated charcoal should not be given routinely; it may be of benefit when given early (within 1 hour, possibly 2 hours), in cases where potentially large amount ingested, of a substance that is absorbed by charcoal."

[6] South African vaccine producers (Pty) Ltd. SAIMR boomslang (tree snake) snake bite antiserum, registered package insert, July 2005.

[7] World Health Organistaion. Guidelines for the Prevention and Clinical Management of Snakebite in Africa, 2010. http://www.afro.who.int/

[8] Müller GJ, Modler H, Wium CA, Veale DJH, Marks CJ. Snake bite in southern Africa: diagnosis and management. CME Oct 2012; 30(10):362-82. http://www.cmej.org.za/index.php/cmej/article/view/2546/2581

[9] SAMF, 2016

Gastric lavage

Gastric Lavage: *directions for use amended*

Gastric lavage is rarely indicated[10]:

Gut decontamination
Gastric lavage is seldom indicated and may cause more harm than benefit. If deemed beneficial, it should only be performed by experienced staff and within 60 minutes of ingestion. Gastric lavage can be considered for cases with: » potentially life-threatening ingestions AND » a protected airway i.e. fully awake and cooperative or intubated with a depressed level of consciousness. Gastric lavage is contra-indicated after ingestion of corrosive substances and volatile hydrocarbons such as paraffin. Technique: Place patient in left lateral head down position Insert orogastric tube if possible, with largest bore and rounded tip. Insert 200ml warmed water or normal saline, and aspirate. Continue until recovered solution is clear of particulate matter.

Level of Evidence: III Position statement

Activated charcoal

Activated charcoal, oral: *indication, contra-indications and directions for use amended*

Refer to medicine review for activated charcoal in poisonings (March 2019):

Activated charcoal for Poisonings_Adul

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

Recommendation: Based on this review, the Adult Hospital Level Committee recommends that single dose activated charcoal (SDAC) should not be given routinely, but recommended for administration within one to two hours of ingestion of a potentially toxic amount of a poison known to be adsorbed by charcoal, in patients with an intact airway (i.e. awake and co-operative patients or with a protected airway). For substances that delay gastric emptying or modified-release preparations, there may be a longer time interval in which to administer SDAC if required.

Rationale: Single dose activated charcoal may be of benefit when given early (within 1 hour), where potentially toxic amounts of poison has been ingested. However, there is insufficient data to support or exclude use after one hour of ingestion, but considered pragmatic to recommend use within 1-2 hours of ingestion of toxin. Despite the uncertainty of the clinically meaningful benefit of activated charcoal in poisonings, volunteer studies of healthy individuals showed reduced absorption of ingested poisons when single dose activated charcoal was administered within an hour. Risk-benefit assessment and recommendation aligned with standard practice, recommending use only in patients with an intact or protected airway.

Level of Evidence: III Pharmacokinetic studies, Case reports, Expert opinion

Of note is that the European Toxicology society's (EAPCCT) position statement is currently under review; to prolong the time period for administration of single dose activated charcoal (still to be published, but presented at the recent Annual Congress).

Indications and contraindications updated in STG as follows:

Poisons where charcoal is ineffective and should not be given	Charcoal may be useful if these poisons are taken in toxic dose
» ethanol, methanol, ethylene glycol » brake fluid » petroleum products (e.g. petrol or paraffin) » iron salts » lead, mercury, arsenic » lithium » strong acids or alkalis » other corrosive agents (e.g. household detergents)	» carbamazepine, barbiturates, phenytoin » dapsone, quinine » theophylline » salicylates » mushroom poisoning (Amanita phalloides) » slow release preparations » digoxin » beta-blockers » NSAIDs

[10] Benson BE, Hoppu K, Troutman WG, Bedry R, Erdman A, Höjer J, Mégarbane B, Thanacoody R, Caravati EM; American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. Position paper update: gastric lavage for gastrointestinal decontamination. Clin Toxicol (Phila). 2013 Mar;51(3):140-6. https://www.ncbi.nlm.nih.gov/pubmed/23418938

Directions for use amended as follows for pragmatic purposes:

- Charcoal, activated, oral, 50 g (equivalent to 36 level medicine measures) diluted in ~~300~~ 100 mL water.
  - When mixing, add a small amount of water to charcoal in a container.
  - Cap and shake container to make a slurry and then dilute further.

Whole bowel irrigation (WBI)

Polyethylene glycol (PEG) balanced electrolyte solution, NGT: *added*

Added for management of whole bowel irrigation, as recommended per the American Academy of Clinical Toxicology & European Association of Poison Centres and Clinical Toxicologists' position statement[11] and aligned with NEMLC-approved Paediatric Hospital Level STGs and EML, 2017[12].

Rationale: Standard of care

Level of Evidence: III Position statement, Guidelines

The following text included in STG, aligned with position statement[13]:

Whole bowel irrigation can be done for potentially toxic ingestions of substances that are:
- » not absorbed by activated charcoal (e.g. iron and lithium)
- » sustained-release and enteric-coated products
- » or for removal of illicit drugs in body packers.

Patients must have a protected airway i.e. fully awake and cooperative or intubated with a depressed level of consciousness.

For seizures

Benzodiazepines: *retained with cross reference to section 14.4.1: Status epilepticus*

Phenytoin: *caution added to avoid in relevant poisonings*

Where management for seizures required (i.e: Sections 19.6.1: Tricyclic antidepressant poisoning; 19.8 Theophylline poisoning; 19.9.2: Lithium poisoning; 19.10: Isoniazid poisoning; 19.14.1: Cocaine poisoning; 19.14.2: Amphetamine derivatives poisoning; 19.18.1: Amitraz poisoning; 19.20: Carbon monoxide poisoning), benzodiazepines recommended with a cross-referral to section 14.4.1: Status epilepticus.

Furthermore, note added to avoid phenytoin in this clinical settings due to potential cardiotoxicity.

Level of Evidence: III Guidelines[14]

19.5.1 PARACETAMOL POISONING

The nomogram was updated in the 2015 Adult Hospital Level STGs and EML, 2015[15]; however, the text was not aligned. Therefore, the text of the STG was editorially amended as follows:

Indications for continuing NAC infusion:
- ~~»~~ serum paracetamol level above the treatment line on the nomogram ~~(Note the lower treatment line for high risk patients)~~
- » serum paracetamol level under the treatment line and abnormal ALT
- » more than 24 hours post-ingestion, measurable paracetamol level and/or ALT abnormal

Toxic dose of paracetamol

Amended to align with international practice (American and Australian Guidelines[16]) from:

~~*"Toxic dose defined as* ***>150 mg/kg*** *or* ***7.5 g*** *(whichever is less)".*~~

To:

"Toxic dose defined as ***>200 mg/kg*** *or* ***10 g*** *(whichever is less)".*

N-acetylcysteine, IV: *dosing regimen amended*

[11] Thanacoody R, Caravati EM, Troutman B, Höjer J, Benson B, Hoppu K, Erdman A, Bedry R, Mégarbane B. Position paper update: whole bowel irrigation for gastrointestinal decontamination of overdose patients. Clin Toxicol (Phila). 2015 Jan;53(1):5-12. https://www.ncbi.nlm.nih.gov/pubmed/25511637

[12] Paediatric Hospital Level STGs and EML, 2017

[13] Thanacoody R, Caravati EM, Troutman B, Höjer J, Benson B, Hoppu K, Erdman A, Bedry R, Mégarbane B. Position paper update: whole bowel irrigation for gastrointestinal decontamination of overdose patients. Clin Toxicol (Phila). 2015 Jan;53(1):5-12. https://www.ncbi.nlm.nih.gov/pubmed/25511637

[14] SAMF, 2016

[15] Adult Hospital Level STGs and EML, 2015

[16] Chiew AL, Fountain JS, Graudins A, Isbister GK, Reith D, Buckley NA. Summary statement: new guidelines for the management of paracetamol poisoning in Australia and New Zealand. Med J Aust. 2015 Sep 7;203(5):215-8. Erratum in: Med J Aust. 2015 Oct 19;203(8):320. Med J Aust. 2016 Aug 15;205(4):167. https://www.ncbi.nlm.nih.gov/pubmed/26852051

Dosing regimen amended and simplified from a 3-dose 21-hour regimen to a 2-dose 20-hour regimen, that has shown to be associated with less adverse reactions (especially reduced anaphylactoid reactions with low risk exposures), less dosing errors, less bags for nurses to manage, but similar efficacy. Consideration was made of the 12 hour 2-bag dosing regimen from the SNAP study [17] (12 hour regimen had less vomiting, anaphylactoid reactions and treatment interruption, but not powered to detect non-inferiority to standard 21 hour regimen), but the evidence is premature and there are concerns with the methodological quality.

The dosing regimen was updated to:

- N-acetylcysteine, IV:
  - Initial infusion: 200 mg/kg in 500 mL 5%dextrose over 4 hours
  - Second infusion: 100 mg/kg in 1000 mL 5% dextrose over 16 hours.
  - Any further N-acetylcysteine is given according to the third infusion regimen.

Level of Evidence: III Observational study[18]

N-acetylcysteine, oral: *retained and dosing regimen added*

Where parenteral formulation is unavailable, oral NAC recommended as a safe alternative where IV administration is not an option. Previous recommendation of oral NAC if IV formulation is unavailable has been expanded to include a dosing regimen, as follows:

If N-acetylcysteine, IV is unavailable:

- N-acetylcysteine, oral, 140 mg/kg, followed by 70 mg/kg 4 hourly for seventeen doses**.**

Note: Avoid giving activated charcoal if giving N-acetylcysteine orally as it will reduce the systemic absorption and thus negate the effect of oral N-acetylcysteine.

Level of Evidence: III Observational studies[19] [20] [21]

Recommendation: Guidance for oral NAC to be updated in the PHC STGs and EML.

19.5.2 SALICYLATE POISONING

Sodium bicarbonate, IV: *directions for use amended*

Acidotic patient in this clinical setting requires urgent referral, and guidance provided to arrange transfer even at the stage of administration of sodium bicarbonate to a dialysis centre.

Text was amended as follows for definitive action:

Medicine treatment

Treat acidosis and enhance renal excretion (intravenous sodium bicarbonate and urinary alkalinisation, blood pH 7.45-7.5 and urine pH 7.5–8.5) in consultation with specialist advice and arrange for transfer.

Referral

Where acidosis does not respond rapidly to sodium bicarbonate, ~~consider~~ refer for haemodialysis. ~~Survival has been shown to be substantially greater with hemodialysis versus no hemodialysis in patients with peak salicylate levels **>50 mg/dL.**~~

Referral criterion: *added*

Haemodialysis

A recent case-control study (n=56) showed that survival was substantially greater with hemodialysis (56%) versus no hemodialysis (0%) in patients with peak salicylate levels >50 mg/dL. Thus, for patients intubated for salicylate poisoning with a level >50 mg/dL hemodialysis is recommended.

Level of Evidence: II Case control study[22]

[17] Adult Hospital Level STGs and EML, review cycle of 2012

[18] Wong A and Graudins A. Simplification of the standard three-bag intravenous acetylcysteine regimen for paracetamol poisoning results in a lower incidence of adverse drug reactions. Clin Toxicol (Phila) 2016;54(2):115-199.

[19] Yarema MC, Johnson DW, Berlin RJ, Sivilotti ML, Nettel-Aguirre A, Brant RF, Spyker DA, Bailey B, Chalut D, Lee JS, Plint AC, Purssell RA, Rutledge T, Seviour CA, Stiell IG, Thompson M, Tyberg J, Dart RC, Rumack BH. Comparison of the 20-hour intravenous and 72-hour oral acetylcysteine protocols for the treatment of acute acetaminophen poisoning. Ann Emerg Med. 2009 Oct;54(4):606-14. https://www.ncbi.nlm.nih.gov/pubmed/19556028

[20] Williamson K, Wahl MS, Mycyk MB. Direct comparison of 20-hour IV, 36-hour oral, and 72-hour oral acetylcysteine for treatment of acute acetaminophen poisoning. Am J Ther. 2013 Jan;20(1):37-40. https://www.ncbi.nlm.nih.gov/pubmed/23299230

[21] Rumack and Bateman. Acetaminophen and acetylcysteine dose and duration: past, present and future. Clin Toxicol (Phila) 2012;50(2):91-98. https://www.ncbi.nlm.nih.gov/pubmed/22320209

[22] McCabe DJ, Lu JJ. The association of hemodialysis and survival in intubatedsalicylate-poisoned patients. Am J Emerg Med. 2017 Apr 10. pii:S0735-6757(17)30280-2.

Following text was added to the STG:

Where acidosis does not respond rapidly to sodium bicarbonate, consider haemodialysis. Survival has been shown to be substantially greater with hemodialysis versus no hemodialysis in patients with peak salicylate levels >50 mg/dL.

19.5.3 OPIOID POISONING

Naloxone, IV: *retained*

An external comment was received cautioning of administering naloxone to opioid-dependant patients, as over administration may precipitate a withdrawal syndrome. The Adult Expert Review Committee (ERC) considered the risk-benefit of naloxone administration, and the option of survival versus withdrawal syndrome was preferred.

Recommendation: Naloxone to be retained, but dosed incrementally with continuous monitoring until the patient is fully awake to minimise side-effects.

Rationale: Editorial amendment of the text of the STG for clarity purposes.

Level of Evidence: III Expert opinion

The text of the STG was amended as follows:

- Naloxone, IV, 0.4 mg immediately, in patients with respiratory depression.
  - Effectiveness is limited by short half-life of ± 1 hour and repeated incremental doses may be needed at 2 to 3 minute intervals.
  - If there is no response after 10 mg of naloxone is administered, the diagnosis of opioid-induced or partial opioid-induced toxicity should be questioned.
  - Consider intramuscular or subcutaneous administration, if the intravenous route is not available.
  - **Note:** Continuous monitoring of patient where naloxone was administered is important until patient is fully awake and no longer naloxone dependant.

Note: Management of opiate withdrawal is included in chapter 15: Mental Health Conditions and Substance Misuse, section 15.10: Opiate withdrawal, e.g.: heroin. This chapter is still under review and is expected to be tabled at NEMLC for ratification for external peer review early 2019.

19.6.1 TRICYCLIC ANTIDEPRESSANT POISONING

Sodium bicarbonate, IV: *directions for use amended*

The following was amended aligned with standard clinical practice[23]:

- Sodium bicarbonate, IV 1–2 mEq/kg as an 8.4% solution, as bolus doses to achieve a pH of 7.45–7.55. (Specialist consultation).
  - Monitor acid-base status, serum potassium and sodium
  - If sodium bicarbonate is unavailable or fluid restrictions limit intake, consider hyperventilation of intubated patients.

Level of Evidence: III Standard of care

Magnesium sulphate, IV: *deleted*

Torsades de pointes reported to be uncommon, as tricyclic poisoning presents with wide complex VT.

Cross reference was made to section 3.3 Cardiac dysrhythmias, and text was editorially amended as follows:

In severe cases, ~~provide~~ inotropic support and anti-arrhythmics (see section 3.3: Cardiac dysrhythmias) may be required in addition to serum alkalinisation. ~~and monitor response.~~ Hypotension is due to myocardial dysfunction and alpha-adrenergic vasodilation; be careful not to fluid overload the patient.

Level of Evidence: III Expert opinion

19.7 IRON POISONING

Whole bowel irrigation: *indication restricted to severe iron toxicity*

Due to insufficient evidence and potential risks, whole bowel irrigation (WBI) only indicated where there is severe iron toxicity (> 60 mg/kg) anticipated or where modified-release preparations have been ingested and are still visible on x-

[23] Bruccoleri RE, Burns MM. A Literature Review of the Use of Sodium Bicarbonate for the Treatment of QRS Widening. J Med Toxicol. 2016 Mar;12(1):121-9. https://www.ncbi.nlm.nih.gov/pubmed/26159649

ray. WBI not recommended where the dose of iron is unknown as the risks outweigh the benefit in the asymptomatic patient. Reliable biomarker for iron overdose is acidosis.

Desferrioxamine (deferoxamine): *directions for use amended*
Aligned with Guidelines[24] [25] [26] and text updated to:

Desferrioxamine (deferoxamine) may be used for the following indications (in consultation with the Poisons Information Helpline):
» Severe symptoms (altered mental status, hemodynamic instability, metabolic acidosis).
» Serum iron concentration > 90 micromol/L .
» Peak serum iron concentration > 60 micromol/L, AND persistent gastrointestinal symptoms.
- Desferrioxamine (deferoxamine), IV infusion, 15 mg/kg/hour to a total of 80mg/kg, i.e. given over about 6 hours. Beware of hypotension.
  - **Note:** Prolonged use > 24 hours of high doses is associated with acute lung injury and should be avoided. However, in severe poisonings, additional doses may be required.

Exchange transfusion: *not recommended*
There have been case reports that demonstrate that exchange transfusion or continuous veno-venous hemofiltration may assist in decreasing serum iron and improving clinical status in patients with massive overdose and life-threatening toxicity. However, these modalities carry a significant risk of complications, and should be regarded as novel and unreliable therapies of last resort in iron poisoning[27].

19.8 THEOPHYLLINE POISONING

Metoclopramide, oral/IV: *added*
Ondansetron, oral/IV: *added as an alternative option to metoclopramide*
As vomiting is common, similar guidance that is recommended in the alimentary chapter has been provided (listed in the STG). However, in the event that there is a stock-out of metoclopramide – ondansetron oral/IV added as an alternative option (to be listed in the therapeutic interchange database).
Level of Evidence: III Expert opinion

Activated charcoal, oral: *dosing amended*
Aligned with Guidelines to advise multiple doses of activated charcoal to enhance elimination.
Level of Evidence: III Guidelines[28]

Diazepam, IV: *removed with a cross-referral to section 14.4.1: Status epilepticus*
Benzodiazepines: *retained with cross reference to section 14.4.1: Status epilepticus; indication amended*
External comment was received that *"diazepam does not work"* – in the context of severe hypokalaemia, which is a simple proxy for severe theophylline toxicity and patient is likely to fit. Theophylline seizures often prolonged and resistant to therapy. So presume the suggestion is that when they have reached the stage of seizures, simple diazepam "not enough", and commentator recommended that all patients would require haemodialysis. However, acute dialysis is not a pragmatic option for all theophylline poisonings in the South African public health care setting. Recommended management of seizures includes benzodiazepines; whilst severe toxicity with refractory seizures, severe hypokalaemia and theophylline level > 555 umol/L (100 mg/L) should be referred for dialysis. The STG cross-refers to section: 14.4.1 Status epilepticus.
Level of Evidence: III Guidelines[29], Expert opinion

STG was editorially amended as follows for correctness:

[24] Hoffman RS, Howlands MA, Lewin Na, Nelson LS, Goldfrank LR. Goldfrank's Toxicologic Emergencies. 10th ed. China: McGraw-Hill Education; 2015.
[25] Bateman DN, Jefferson RD, Thomas S, Thompson JP, Vale JA. Oxford Desk Reference: Toxicology. Oxford: Oxford University Press: 2014. P166-167.
[26] SAMF, 2016
[27] Goldfrank Toxicologic Emergencies 10th edition (2015). One case report showing good outcome.
[28] Ghannoum M, Wiegand TJ, Liu KD, Calello DP, Godin M, Lavergne V, Gosselin S, Nolin TD, Hoffman RS; EXTRIP workgroup. Extracorporeal treatment for theophylline poisoning: systematic review and recommendations from the EXTRIP workgroup. Clin Toxicol (Phila). 2015 May;53(4):215-29. https://www.ncbi.nlm.nih.gov/pubmed/25715736
[29] Ghannoum M, Wiegand TJ, Liu KD, Calello DP, Godin M, Lavergne V, Gosselin S, Nolin TD, Hoffman RS; EXTRIP workgroup. Extracorporeal treatment for theophylline poisoning: systematic review and recommendations from the EXTRIP workgroup. Clin Toxicol (Phila). 2015 May;53(4):215-29. https://www.ncbi.nlm.nih.gov/pubmed/25715736

For ~~sedation or~~ seizures: R56.8 + (T48.6/X44.99/X64.99/Y14.99)
- Benzodiazepines. See section: 14.4.1 Status epilepticus.

Note: Phenytoin should be avoided (due to potential cardiotoxicity).

Hypokalaemia management: *guidance provided*

- Hypokalaemia is a proxy for severity of theophylline poisoning. Hypokalaemia results in dysrhythmias and refractory seizures that requires urgent haemodialysis.
- Hypokalaemia also requires cautious management with potassium chloride, as in theophylline poisoning, hypokalaemia is a reflection of potassium shifts and not whole body depletion.
- Evidence of ECG changes is indicative of late stages of theophylline poisoning that may result in death.

The following text was amended considering the factors above and aligned with Guidelines[30]:

Correct hypokalaemia cautiously:
- Potassium chloride, IV, maximal dose 40 mmol/L and maximal rate of 20 mmol/hour.

Level of Evidence: III Guidelines, Expert opinion

19.9.1 BENZODIAZEPINE POISONING

Flumazenil, IV: *not added*

In the previous 2015 review cycle, flumazenil was not recommended for inclusion to the Adult Hospital Level EML (2015 review cycle), refer to extract from NEMLC report of 15 October 2015 below:

NEMLC meeting of 15 October 2015:
Flumazenil, IV: *not added*
Flumazenil is contraindicated in patients with known or suspected TCA poisoning, as it is associated with an increased risk of fatal benzodiazepine-withdrawal seizures.
Recommendation: A warning be added to the text of the STG about the contra-indication of flumazenil in tricyclic antidepressant poisoning due to due to ADRs of associated fatal seizures.
Level of Evidence: III Case reports[31]

With the subsequent publication of a meta-analysis that showed that the use of flumazenil administered for suspected benzodiazepine poisoning in emergency department was associated with a significantly increased risk of serious adverse effects compared to placebo (12/498 versus 2/492; RR 3.81; 95% CI: 1.28 to 11.39; p = 0.02), STG text was retained as follows as flumazenil should not be used routinely.

Note: The use of flumazenil is not recommended in any patient with possible benzodiazepine poisoning as it increases the risk of convulsions and dysrhythmias.

Level of Evidence: II Meta-analysis of RCTs of low to moderate quality[32]

19.9.2 LITHIUM POISONING

Polyethylene glycol (PEG) balanced electrolyte solution, NGT: *added for WBI*

WBI with polyethylene glycol aligned with NEMLC-approved Paediatric Hospital Level STGs and EML[33] and position paper update[34].

Level of Evidence: III Guidelines

[30] Ghannoum M, Wiegand TJ, Liu KD, Calello DP, Godin M, Lavergne V, Gosselin S, Nolin TD, Hoffman RS; EXTRIP workgroup. Extracorporeal treatment for theophylline poisoning: systematic review and recommendations from the EXTRIP workgroup. Clin Toxicol (Phila). 2015 May;53(4):215-29. https://www.ncbi.nlm.nih.gov/pubmed/25715736

[31] Haverkos GP, DiSalvo RP, Imhoff TE. Fatal seizures after flumazenil administration in a patient with mixed overdose. Ann Pharmacother. 1994 Dec;28(12):1347-9. PubMed PMID: 7696723.

- Seger DL. Flumazenil--treatment or toxin. J Toxicol Clin Toxicol. 2004;42(2):209-16. http://www.ncbi.nlm.nih.gov/pubmed/15214628

[32] Penninga EI, Graudal N, Ladekarl MB, Jürgens G. Adverse Events Associated with Flumazenil Treatment for the Management of Suspected Benzodiazepine Intoxication - A Systematic Review with Meta-Analyses of Randomised Trials. Basic ClinPharmacolToxicol. 2016 Jan;118(1):37-44.http://www.ncbi.nlm.nih.gov/pubmed/26096314

[33] Paediatric Hospital Level STGs and EML, 2017

[34] Thanacoody R, Caravati EM, Troutman B, Hojer J, Benson B, Hoppu K et al. Position paper update: whole bowel irrigation for gastrointestinal decontamination of overdose patients. Clin Toxicol (Phila) 2015;53:5-12. https://www.ncbi.nlm.nih.gov/pubmed/25511637

Potassium chloride, IV: *deleted with a cross referral to section: 7.2 Major electrolyte abnormalities*
Lithium toxicity is associated with electrolyte imbalances including hypokalemia and hypercalcemia; noting that hyponatraemia can exacerbate lithium toxicity.

Referral
Recommendation included for early referral for haemodialysis in severe lithium poisoning and in patients with renal impairment, aligned with Guidelines.
Level of Evidence: III Guidelines[35]

19.10 ISONIAZID POISONING

Pyridoxine, oral: *route of administration expanded and indication clarified*
Pyridoxine, parenteral: *not added*

Oral pyridoxine
Route of administration of oral pyridoxine expanded to include via naso-gastric tube.

Parenteral pyridoxine
Parenteral pyridoxine is not readily available. Dosing is based on case reports given gram for gram replacement[36]. There are anticipated problems with giving vitamin B co parenteral agents (as suggested by commentator above) – Available vitamin B 1 ml ampoule contains pyridoxine 5mg, nicotinamide 100mg, B1 10mg, B2 2mg etc. To administer 5g pyridoxine equates to 10x10ml vials that costs R140.10[37]. Side –effects would be experienced with other high doses of co-administered vitamin Bs – e.g. 10 g nicotinamide will be administered which will result in flushing. Administering parenteral vitamin B co not considered pragmatic. There are case reports where oral pyridoxine was administered in severe isoniazid poisoning.
Recommendation: Parenteral vitamin B co not be recommended for isoniazid poisoning.
Rationale: Impractical to administer large amounts of vitamin B complex IV and there is a possibility of side-effects with cost implications. Case reports available in the published literature of oral pyridoxine administered in severe isoniazid poisoning
Level of Evidence: III Case reports[38]

Seizures
Guidance reinforces that pyridoxine actively treats seizures. Prompt initiation of pyridoxine therapy is recommended.

Benzodiazepines, as an interim measure to control seizures:
Lorazepam, IV/IM: *added*
Diazepam, IV: *added*
Clonazepam, IV: *added*
Midazolam, IM/IV: *added*
Midazolam buccal: *added using the parenteral formulation*
Aligned with Guidelines[39] and recommendations in section 14.4.1: Status epilepticus.
Level of Evidence: III Guidelines

[35] Decker BS, Goldfarb DS, Dargan PI, Friesen M, Gosselin S, Hoffman RS, Lavergne V, Nolin TD, Ghannoum M; EXTRIP Workgroup. Extracorporeal Treatment for Lithium Poisoning: Systematic Review and Recommendations from the EXTRIP Workgroup. Clin J Am Soc Nephrol. 2015 May 7;10(5):875-87. https://www.ncbi.nlm.nih.gov/pubmed/25583292
[36] Wason S, Lacouture P, Lovejoy F. Single high-dose pyridoxine treatment for isoniazid overdose. JAMA 1981;246(10):1102-1104.
[37] Contract circular RT297-2019
[38] Dilrukshi M, Ratnayake C, Gnanathasan C. Oral pyridoxine can substitute for intravenous pyridoxine in managing patients with severe poisoning with isoniazid and rifampicin fixed dose combination tablets: a case report. BMC Res Notes 2017;10:370. https://www.ncbi.nlm.nih.gov/pubmed/28789699
[39] Hoffman RS, Howlands MA, Lewin Na, Nelson LS, Goldfrank LR. Goldfrank's Toxicologic Emergencies. 10th ed. China: McGraw-Hill Education; 2015.

Phenytoin: *caution added to avoid*

Seizures in INH poisoning can be controlled by repairing the critical deficiency in the inhibitory neurotransmitter gamma amino butyric acid (GABA) with GABA agonists such as pyridoxine and benzodiazepines. However, as phenytoin does not have GABA agonist activity unlikely to be of benefit in isoniazid poisoning.

Level of Evidence: III Guidelines[40]

Pharmacovigilance: Isoniazid poisoning is not a notifiable condition. NEMLC had concerns that with the implementation of the large public health programme such as isoniazid (INH) prophylaxis, some of the harms may be missed if intentional overdoses are not reported. However, information for intentional INH overdoses would probably best be sourced through surveys in emergency settings.

NEMLC recommended that the NDoH Programmatic Pharmacovigilance investigate isoniazid and iron over-doses in 2 sentinel sites over a period of one year.

19.11 CALCIUM CHANNEL BLOCKER AND BETA BLOCKER POISONING

Management of beta blocker and CCB toxicity: *guidance combined in a single STG management follows similar therapeutic principles*

Aligned with Guidelines[41], though calcium gluconate, IV is specific to calcium channel blocker toxicity.

The following narrative was added to the text of the STG:

> The treatment of suspected cardiogenic shock in calcium channel blocker and beta blocker poisoning follows similar therapeutic principles. The mainstay of treatment is high-dose insulin euglycaemia therapy and catecholamine infusions to improve inotropy and chronotropy.

Level of Evidence: III Guidelines

Glucagon: *not added for beta-blocker and calcium channel blocker overdose*

Resuscitation Council of South Africa algorithm recommends glucagon for beta-blocker and calcium channel blocker overdose. The Adult ERC reviewed the evidence for this recommendation - refer to the medicine review, glucagon for beta blocker and calcium channel poisonings (October 2018):

Glucagon for
Beta-blocker & CaCl

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

Recommendation: Based on this review, the Adult Hospital Level Committee thst glucagon not be recommended for the treatment of beta-blocker or calcium channel blocker overdose.

Rationale: The evidence is insufficient (available data includes animal data and case series) for the Adult Hospital Level Committee to make a recommendation for the use of protamine for the treatment of beta-blocker or calcium channel blocke roverdose.

Level of Evidence: III Expert opinion

Note: Evidence of efficacy not compelling, and the Adult Hospital Level Committee was of the opinion that time spent on a full medicine review was not feasible. Furthermore, guidance is already provided for a vasopressor e.g. adrenaline infusion for persistent hypotension or dobutamine for bradycardia in this clinical setting. Cross reference to section 3.3: Cardiac dysrhythmias was added.

[40] Hoffman RS, Howlands MA, Lewin Na, Nelson LS, Goldfrank LR. Goldfrank's Toxicologic Emergencies. 10th ed. China: McGraw-Hill Education; 2015.
[41] Graudins A, Lee HM, Druda D. Calcium channel antagonist and beta-blocker overdose: antidotes and adjunct therapies. Br J Clin Pharmacol. 2016 Mar;81(3):453-61. https://www.ncbi.nlm.nih.gov/pubmed/26344579

Medicine treatment

The was added, aligned with Guidelines:

- » Caution is advised for all decontamination procedures as they increase vagal tone and may exacerbate bradycardia.
- » Activated charcoal may be considered before the onset of symptoms.
- » WBI can be considered for ingestion of modified-release preparations.

Level of Evidence: III Guidelines[42]

For hypotension

Sodium chloride, 0.9%, IV: *retained*
Ringer Lactate, IV: *not added*
Balsol, IV: *not added*
Refer to the NEMLC report for chapter 20: Emergencies and injuries for details on the updated evidence review for Ringer Lactate.

If hypotension not effectively controlled add:

Calcium gluconate, IV: *retained and dosing amended*
Calcium chloride, IV: *alternative to calcium gluconate where there are supply challenges and added to Therapeutic interchange database*
Aligned with the SAMF, 2016, the dosing of calcium gluconate, IV was amended as follows noting that calcium gluconate has been preferred historically to minimize peripheral vein irritation. However, calcium chloride may be considered where there are supply issues with calcium gluconate (Dose: calcium chloride 10 %, IV, 10–20 mL every 10–20 minutes).

- Calcium gluconate 10%, IV, ~~10~~ 30–60 mL given over 15–30 minutes, with ECG monitoring.
  - This may be repeated a maximum of 4 times.

Level of Evidence: III Guidelines[43] [44]

19.14.1 COCAINE POISONING

Whole bowel irrigation (WBI)

Polyethylene glycol (PEG) balanced electrolyte solution, NGT: *added for WBI*
WBI with polyethylene glycol aligned with NEMLC-approved Paediatric Hospital Level STGs and EML[45] and position paper update[46].
Level of Evidence: III Guidelines

Delirium with severe agitation

Lorazepam, IM: *deleted with cross reference to section 20.8: Delirium with perceptual disturbances*
Midazolam, IM: *deleted with cross reference to section 20.8: Delirium with perceptual disturbances*
Clonazepam, IM: *deleted with cross reference to section 20.8: Delirium with perceptual disturbances*
Diazepam, IV: *deleted with cross reference to section 20.8: Delirium with perceptual disturbances*
Haloperidol, IM: *deleted with cross reference to section 20.8: Delirium with perceptual disturbances*
Promethazine, IM: *deleted with cross reference to section 20.8: Delirium with perceptual disturbances*
Chlorpromazine, IM: *deleted with cross reference to section 20.8: Delirium with perceptual disturbances*

Arrhythmias

Lidocaine: *caution deleted (i.e. "Lidocaine may precipitate seizures").*
Beta-blockers: *contra-indication retained*

[42] St-Onge M, Anseeuw K, Cantrell FL, Gilchrist IC, Hantson P, Bailey B, Lavergne V, Gosselin S, Kerns W 2nd, Laliberté M, Lavonas EJ, Juurlink DN, Muscedere J, Yang CC, Sinuff T, Rieder M, Mégarbane B. Experts Consensus Recommendations for the Management of Calcium Channel Blocker Poisoning in Adults. Crit Care Med. 2017 Mar;45(3):e306-e315. https://www.ncbi.nlm.nih.gov/pubmed/27749343
[43] SAMF, 2016
[44] Graudins A, Lee HM, Druda D. Calcium channel antagonist and beta-blocker overdose: antidotes and adjunct therapies. Br J Clin Pharmacol. 2016 Mar;81(3):453-61. https://www.ncbi.nlm.nih.gov/pubmed/26344579
[45] Paediatric Hospital Level STGs and EML, 2017
[46] Thanacoody R, Caravati EM, Troutman B, Hojer J, Benson B, Hoppu K et al. Position paper update: whole bowel irrigation for gastrointestinal decontamination of overdose patients. Clin Toxicol (Phila) 2015;53:5-12. https://www.ncbi.nlm.nih.gov/pubmed/25511637

Evidence could not be sourced that there is a greater risk of seizures in myocardial infarctions due to cocaine poisonings, associated with lidocaine. Furthermore, beta-blockers are contra-indicated in management of myocardial infarctions.
Level of Evidence: III Expert opinion

19.14.2 POISONING WITH AMPHETAMINE DERIVATIVES

Labetaolol, IV: *not added*
Historically, labetalol IV was reviewed for severe hypertension in this setting.
Rationale: *"Concern that labetalol may not have sufficient alpha- blocking activity that may be of value. There are no RCTs for the treatment of hypertensive emergencies in this setting. Options for the management of hypertensive emergencies in the cardiovascular chapter include nitrates and ACE inhibitors. In the absence of robust data it is recommended that hypertensive emergencies be managed according to the section: Hypertension, Severe"*[47].

19.16 INGESTION OF CAUSTIC SUBSTANCES

General measures
Guidance for endoscopic evaluation within 24-48 hours and possible surgical intervention, If persistent vomiting, drooling or any difficulty in swallowing, aligned with standard of care[48].
Level of Evidence: III Expert opinion

19.17.2 ETHYLENE GLYCOL POISONING

Ethanol: *retained as antidote, indications added and directions for use amended*
Haemodialysis: *retained for severe poisoning/ profound acidosis*

Ethanol

- *Antidote:* Ethanol as an antidote in ethylene glycol and methanol poisoning is standard clinical practice[49] [50]. Metabolites formic acid (methanol) and glycolic acid (ethylene glycol) are toxic, not the alcohols themselves, and an antidote is indicated by latent period between ingestion and development of symptoms.
- *Indications:* Indications for ethanol as an antidote in methanol/ethylene glycol poisoning described, aligned with standard of care[51].

History of ingestion, plus any two of the following criteria: » Arterial pH < 7.3 » Serum bicarbonate < 20 mmol/L » Presence of urinary oxalate crystals (ethylene glycol only) or visual disturbances (methanol only)

Level of Evidence: III Standard of care

- *Directions for use:* Simplified calculations for ethanol 95% and 40% included in STG; further diluted to 20% to minimise gastrointestinal effects. Further calculations required on how to give the maintenance amounts/volumes required per hour once diluted. The dose of ethanol needs to be increased if the patient is receiving concomitant haemodialysis, al alcohol is dialyzable.
  Level of Evidence: III Guidelines[52]

Fomeprizole: *not added*
Fomeprizole not currently registered with South African Health Products Regulatory Authority.

[47] Adult Hospital Level STGs and EML, 2012 review cycle.
[48] Millar AJ, Cox SG. Caustic injury of the oesophagus. Pediatr Surg Int. 2015 Feb;31(2):111-21. https://www.ncbi.nlm.nih.gov/pubmed/25432099
[49] Jacobsen D, McMartin K. Antidotes for methanol and ethylene glycol poisoning. Clin Toxciol (Phila) 1997;35(2):127-143.
[50] McMartin K, Jacobsen D, Hovda KE. Antidotes for poisoning by alcohol that form toxic metabolites. Br J Clin Pharmacol 2016;81:505-15. https://www.ncbi.nlm.nih.gov/pubmed/26551875
[51] McMartin K, Jacobsen D, Hovda KE. Antidotes for poisoning by alcohols that form toxic metabolites. Br J Clin Pharmacol. 2016 Mar;81(3):505-15. https://www.ncbi.nlm.nih.gov/pubmed/26551875
[52] McMartin K, Jacobsen D, Hovda KE. Antidotes for poisoning by alcohols that form toxic metabolites. Br J Clin Pharmacol. 2016 Mar;81(3):505-15. https://www.ncbi.nlm.nih.gov/pubmed/26551875

Haemodialysis
South African context of delayed access/presentation to health care facility and as access to acute haemodialysis not readily available at secondary level facilities needs consideration. Thus, early antidote (i.e. ethanol) may prevent metabolite formation and limit severity. In late presenters (with symptoms and signs of CNS depression, metabolic acidosis, visual impairment, renal failure), it would possibly be beneficial to give antidote with early haemodialysis.
Diagnosis: Metabolic acidosis calculated. If high anion metabolic acidosis and visual impairment, consider methanol poisoning; if high anion gap metabolic acidosis with renal failure (look at urine for crystals), consider ethylene glycol poisoning.

Recommendation: Early haemodialysis is the treatment of choice for severe ethanol poisoning with profound acidosis; whilst for other cases antidote (i.e. ethanol) preferred.
Rationale: Access to acute haemodialysis not readily available, thus administration of an antidote (i.e. ethanol) is the alternative standard of care to prevent production of toxic metabolites, despite the difficulties in managing these patients. Early haemodialysis recommended for severe cases with profound acidosis, as most of the glycol/methanol would have been metabolised.
Level of Evidence: III Guidelines

Metabolic acidosis
Sodium bicarbonate, IV: *directions for use amended*
Guidance amended to align with Guidelines[53]:

Note:
~~The rapid infusion of large volumes of sodium bicarbonate in an already oliguric patient may precipitate pulmonary oedema and cardiac dysrhythmias and may cause iatrogenic hypernatraemia.~~
Rapid correction of acidosis may precipitate seizures in a hypocalcaemic patient.
Correct severe or clinically evident hypocalcaemia.
Monitor glucose levels and correct hypoglycaemia, if necessary.

Level of Evidence: III Guidelines

19.17.3 METHANOL POISONING

Anion gap calculation was not amended, as it is aligned with the calculation in section 19.17.2: Ethylene glycol poisoning.

Ethanol: *retained as antidote*
Haemodialysis: *retained for severe poisoning/ profound acidosis*
Aligned with Guidelines - See discussion above under ethylene glycol poisoning.
Level of Evidence: III Guidelines[54]

Folinic acid, IV: *not added*
Limited evidence in humans[55] [56] – one human case report could be found of improved formate production[57].
Level of Evidence: III Case report

19.18.1 AMITRAZ POISONING

Activated charcoal: *added, once patient is stabilised.*

[53] McMartin K, Jacobsen D, Hovda KE. Antidotes for poisoning by alcohols that form toxic metabolites. Br J Clin Pharmacol. 2016 Mar;81(3):505-15. https://www.ncbi.nlm.nih.gov/pubmed/26551875
[54] Roberts DM, Yates C, Megarbane B, Winchester JF, Maclaren R, Gosselin S, Nolin TD, Lavergne V, Hoffman RS, Ghannoum M; EXTRIP Work Group. Recommendations for the role of extracorporeal treatments in the management of acute methanol poisoning: a systematic review and consensus statement. Crit Care Med. 2015 Feb;43(2):461-72. https://www.ncbi.nlm.nih.gov/pubmed/25493973
[55] Jacobsen D, McMartin KE. Antidotes for methanol and ethylene glycol poisoning. J Toxicol Clin Toxicol. 1997;35(2):127-43. https://www.ncbi.nlm.nih.gov/pubmed/9120880
[56] Barceloux DG, Bond GR, Krenzelok EP, Cooper H, Vale JA; American Academy of Clinical Toxicology Ad Hoc Committee on the Treatment Guidelines for Methanol Poisoning. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. J Toxicol Clin Toxicol. 2002;40(4):415-46. https://www.ncbi.nlm.nih.gov/pubmed/12216995
[57] Goldfranks Toxicologic Emergencies, 10th edition

Refer to medicine review: Activated Charcoal, above..

19.18.2 ORGANOPHOSPHATE POISONING

General measures

Protective equipment for staff: *recommendation added*

Recommended by Guidelines based on reports of healthcare workers exposed to body fluids from a patients poisoned with orgonaphosphate.

Text of STG was amended, aligned with position statement based on case reports.

Ensure use of personal protective equipment for staff – gloves, gowns and eye protection. If staff come into contact with body fluids, wash off immediately.
Decontamination procedures for the patient should only be done once the patient is fully resuscitated.
Remove patient's clothes and wash the body with soap and water. Place clothes in closed bags.
Maintain adequate ventilation and circulation.
Ventilatory support in ICU may be required due to excess of nicotinic effects.
Suction secretions frequently.

Level of Evidence: III Guidelines[58], Case reports[59] [60]

Medicine treatment

Activated charcoal: *added, once patient is stabilised.*

Refer to medicine review: Single dose activated charcoal, above.

Atropine, IV: *treatment protocol amended*

Aligned with guidelines to provide clear guidance on dosing and monitoring of response to atropine treatment.

Level of Evidence: III Guidelines[61]

Obidoxime: *not added*

Authors of a Cochrane review[62] conclude that "current evidence is insufficient to indicate whether oximes are harmful or beneficial". Single RCT (of 3 retrieved for review) compared the World Health Organization (WHO) recommended doses of obidoxime vs placebo and showed no clinical benefits and a trend towards harm in all sub-groups, despite clear evidence that these doses reactivated acetylcholinesterase in the blood".

Level of Evidence: II Systematic review of low quality RCTs

For severe agitation

Diazepam: *added*

[58] Little M, Murray L; Poison Information Centres of New South Wales, Western Australia, Queensland, New Zealand, and the Australian Capital Territory. Consensus statement: risk of nosocomial organophosphate poisoning in emergency departments. Emerg Med Australas. 2004 Oct-Dec;16(5-6):456-8. https://www.ncbi.nlm.nih.gov/pubmed/15537409

[59] Centers for Disease Control and Prevention (CDC). Nosocomial poisoning associated with emergency department treatment of organophosphate toxicity--Georgia, 2000. MMWR Morb Mortal Wkly Rep. 2001 Jan 5;49(51-52):1156-8. https://www.ncbi.nlm.nih.gov/pubmed/11198947

[60] Stacey R, Morfey D, Payne S. Secondary contamination in organophosphate poisoning: analysis of an incident. QJM. 2004 Feb;97(2):75-80. https://www.ncbi.nlm.nih.gov/pubmed/14747621

[61] Eddleston M, Buckley NA, Eyer P, Dawson AH. Management of acute organophosphorus pesticide poisoning. Lancet. 2008 Feb 16;371(9612):597-607. https://www.ncbi.nlm.nih.gov/pubmed/17706760

Atropine, IV (protocol): Eddleston M, Dawson A, Karalliedde L, Dissanayake W, Hittarage A, Azher S, Buckley NA. Early management after self-poisoning with an organophosphorus or carbamate pesticide - a treatment protocol for junior doctors. Crit Care. 2004 Dec;8(6):R391-7. https://www.ncbi.nlm.nih.gov/pubmed/15566582

[62] Buckley NA, Eddleston M, Li Y, Bevan M, Robertson J. Oximes for acute organophosphate pesticide poisoning. Cochrane Database Syst Rev. 2011 Feb 16;(2):CD005085. https://www.ncbi.nlm.nih.gov/pubmed/21328273

Recommended for acutely agitated delirium in organophosphate poisoning. Diazepam also recommended therapy for seizures (though uncommon if patient well oxygenated). Protective effect of diazepam only shown in animal studies (reduces neural damage and prevents death) as stated by systematic literature review by Eddelston et al (2008).
Level of Evidence: III Systematic review of all available published literature[63]

19.18.3 PARAQUAT POISONING

The option to add the dithionate urine test as a confirmatory option on urine or gastric aspirate to be taken forward through the HTA process for diagnostics.

19.19 ANTICOAGULANT (WARFARIN AND RODENTICIDE SUPERWARFARIN) POISONING

Subheading was amended to include "*warfarin and rodenticide superwarfarin*".

Warfarin poisoning
Protein C concentrate: *not added*
Vitamin K, parenteral: *retained*
External comment was received to consider protein C rather than vitamin K. However, vitamin K is more readily available at secondary level of care facilities:

Elevated INR with significant bleeding
Fresh frozen plasma/lyophilised plasma: *placed first in treatment protocol*
Vitamin K_1: *placed second in treatment protocol*
Refer to rationale in NEMLC report for chapter 2: Blood and blood forming organs.

The following statement was considered important, and text was reformatted in bold font:

» **If warfarin is indicated it should be re-instituted, once the INR is in the therapeutic range.**

Rodenticide ingestion - Super warfarins
Vitamin K_1: *INR cut-off for administration retained as < 4*
INR cut-off: Paediatric Hospital Level Committee had recommended an arbitrary INR cut-off of 2.5 for rodenticide poisonings. However, the cut-off of 4 is aligned with Guidelines[64], noting that children metabolize warfarin more rapidly than adults[65]
Level of Evidence: III Guidelines

19.21 HEAVY METAL POISONING

General overview provided in STG, sourced from AfriTox 2019 database:

Metal	Signs and symptoms
Copper salts	GIT irritation, hepatotoxicity and haemolysis.
Arsenic	Impairs cellular respiration, resulting in multi-organ dysfunction.
Mercury	Clinical effects depend on the route of exposure and type of mercury (inorganic versus organic).
Lead	Chronic toxicity more common. Affects nervous, gastrointestinal, renal and haematopoietic systems.
Gold	Deposition of immune complexes in kidneys and skin; mucus membrane inflammation
Thallium	Alopecia and painful ascending peripheral neuropathy.

Level of Evidence: III Guidelines[66]

19.22 POISONING WITH SUBSTANCES THAT CAUSE METHAEMOGLOBINAEMIA

N-acetylcysteine, inj: *deleted*

[63] Eddleston M, Buckley NA, Eyer P, Dawson AH. Management of acute organophosphorus pesticide poisoning. Lancet. 2008 Feb 16;371(9612):597-607. https://www.ncbi.nlm.nih.gov/pubmed/17706760
[64] Watt BE, Proudfoot AT, Bradberry SM, Vale JA. Anticoagulant rodenticides. Toxicol Rev. 2005;24(4):259-69. https://www.ncbi.nlm.nih.gov/pubmed/16499407
[65] Bauman ME, Black K, Bauman ML, Kuhle S, Bajzar L, Massicotte MP. Warfarin induced coagulopathy in children: assessment of a conservative approach. Arch Dis Child. 2011 Feb;96(2):164-7. https://www.ncbi.nlm.nih.gov/pubmed/21068076
[66] AfriTox, 2019. www.afritox.co.za

Ascorbic acid, inj: *deleted*

Concerns from Poison Information Centre was received of the lack of sufficiently robust evidence for N-acetylycysteine and high dose ascorbic acid to manage methaemoglobinaemia in poisonings, where methylene blue is unavailable. Furthermore, the adverse effects of high dose ascorbic acid and NAC are not insignificant[67]. As symptomatic methaemoglobinaemia in poisoned patients requires specialist management, referral to a poisons information centre was included in the text of the STG, accordingly. **Level of Evidence: III Expert opinion**

PROTAMINE MEDICINE REVIEW

Protamine: *not added*

Background: The NDoH, Affordable Medicines Directorate is promoting the alignment of tenders with the National EML. However, historically, a number of medicines were included on tender, despite these not having been included on the EML. Protamine injection is such a medicine. Thus, the Adult ERC was requested to review the evidence to determine whether it should be considered for inclusion on the EML.

Review: Refer to the medicine review, protamine for anticoagulant toxicity, July 2018:

Protamine for AnticoagulantToxici

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

Recommendations:

- Based on this evidence review, the Adult Hispital Level Committee was of the opinion that protamine not be reccomended for inadvertent IV heparin overdose at this level of care.
  Rationale: The evidence is insufficient (lack of RCTs, available data includes case reports and case series) for the Adult Hospital Level Committee to make a recommendation for the use of protamine in this clinical setting.
  Level of Evidence: III Expert opinion
- In the context of cardiovascular indications, protamine would be used post-cardiac surgery and valve replacement in adults and paediatrics in a tertiary setting. Pragmatic challenges regarding administration and adverse effects, warrants protamine to be used in an ICU setting. It is recommended that protamine be reviewed at Tertiary and Quaternary level of care post cardiac surgery and valve replacement, for use in ICU (adult and neonatal) and renal dialysis.

Protamine national consumption from Feb 2017 to Oct 2018:

Row Labels	Sum of Quantity Delivered (50mg/5ml inj)
Eastern Cape MT	260
Eastern Cape PE	2090
Free State	2780
Gauteng	6080
Kwa-Zulu-Natal	5380
Limpopo	40
Mpumalanga	4280
North West	230
Northern Cape	250
Western Cape	8270
Grand Total	29660

RSAPharma database

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.*

[67] Senthilkumaran S, Benita F, Ananth C, Thirumalaikolundusubramanian P. Dapsone-induced methemoglobinemia: therapeutic alternatives and medicolegal aspects. Am J Emerg Med 2014;32(8):935