SOUTH AFRICAN PRIMARY HEALTHCARE ESSENTIAL MEDICINES LIST
PHC CHAPTER 21: EMERGENCIES AND INJURIES
NEMLC RECOMMEDATIONS FOR MEDICINE AMENDMENTS (2020-4 REVIEW CYCLE)

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG) and supporting medicine reviews and costing analyses.
Note that the associated EML chapter has been subjected to subsequent clinical editing. These editorial amendments may not be reflected in the report below.

A: AMENDMENTS

SECTION	MEDICINE/ MANAGEMENT	ADDED/DELETED/AMENDED/NOT ADDED/ RETAINED
21.1.1 Cardiac arrest, adults	Cardiac arrest algorithm for suspected communicable diseases	Added
- Ventricular tachycardia	Amiodarone, IV	Not added
-Cardiopulmonary resuscitation	Guidance on fluid administration	Amended
- Additional guidance – termination of resuscitation (TOR)	Duration of asystole	Amended
21.1.2 Cardiopulmonary arrest, children	Cardiac arrest algorithm	Amended
	Paediatric resuscitation tape weight measurements	Added
	Age-based weight estimates	Added
	Guidance to continue resuscitation	Amended
21.1.5 Management of suspected choking/foreign body aspiration in children	Choking algorithm and related guidance	Amended
21.2 Medical Emergencies		
21.2.1 Paediatric Emergencies	Referral for children with cerebral palsy	Not Added
21.2.1.1 Rapid triage of children presenting with acute conditions in clinics and CHCS	Triage process of all sick children	Amended
21.2.4 Delirium *-Physical restraint*	Guidance on physical restraint	Added
21.2.4 Delirium *-Medicine treatment*	Guidance amended	Amended
21.2.4 Delirium *-Acute management*	Aligned to Section 16.1.2 and 16.1.3	Aligned
	Diazepam – dose frequency	Clarified
	Benzodiazepines – cautions amended	Amended
	Haloperidol, IM	Retained
	Olanzapine, oro-dispersible	Added
	Olanzapine, IM	Added
21.2.4 Delirium *- Alcoholics/ Malnourished (adults)*	Thiamine, parenteral	Dose & route of administration amended
21.2.6 Hypoglycaemia and hypoglycaemic coma	Thiamine, parenteral	Aligned
21.2.8 Pulmonary oedema, acute *- If patient very anxious or restless*	Morphine, IV	Deleted & caution added to the STG
21.2.9 Shock	Fluid replacement in children – sodium chloride 0.9%:	Dose amended
	Fluid replacement in children – ringers lactate	Added
21.2.10 Anaphylaxis	Guidance on anaphylaxis associated with vaccinations	Added
	Management – salbutamol nebulized	Dose clarified
	Management – ipratropium bromide nebulized	Dose clarified
21.3 Trauma and Injuries	Referral for patients with brain and spinal cord injuries	Not added
21.3.1.1 Animal bites *- Suspected rabid bite*	Wound irrigation	Amended
	Rabies vaccine	Directions for use amended
	Human rabies immunoglobulin	Directions for use amended
	Equine rabies immunoglobulin	Added

	Amoxicillin/clavulanic acid in children – 8hrly regimen	Retained
21.3.1.2 Human Bites	Amoxicillin/clavulanic acid in children – 8hrly regimen	Retained
21.3.1.3 Insect stings, scorpion stings and spider bites	Description	Editorial amendment
	Chlorphenamine oral	Indication amended
	Chlorphenamine oral	Caution deleted
	Paracetamol dosing guidance	Amended
	Contact information	Added
21.3.1.4 Snakebites **-** *Venom in the eyes*	Local anaesthetic, ophthalmic drop	Added as a therapeutic class
	Tetracaine 0.1%, ophthalmic drops	Retained as an example of class in the STG
	Oxybuprocaine 4%, ophthalmic drops	Added to the TI database as an example of class
- Snake antivenom	Antivenom	Criteria for administration amended
	Contact information	Amended
21.3.2 Burns **-** *Septic burns*	Paracetamol dosing guidance	Amended
	Povidone iodine, topical	Retained
	Silver sulfadiazine, topical	Not added
	Mupirocin, topical	Not added
	Nano-crystalline dressings	Not added
	Melaleuca alternifolia, topical	Not added
	Referral – rehabilitation services	Added
21.3.3 Exposure to poisonous substances		
- *Tricyclic poisoning*	Sodium bicarbonate, parenteral	Not added
- *Organophosphate and carbamate poisoning*	Atropinisation	Indication amended
	Atropine, IV	Directions for use not amended
- Opioid overdose	Naloxone, IV	Directions for use amended
- Paracetamol poisoning	N-acetylcysteine, oral	Dose not amended
- *Toxic alcohol (ethylene glycol and methanol) poisoning*	Ethanol loading dose	Not added – cross reference to AH Chp 19.17.2 included
21.3.6.1 Post exposure prophylaxis, occupational **-** *PEP for healthcare workers following hepatitis B exposure*	Hepatitis B Immunoglobulin	Amended
- Delay in obtaining HBsAb results	Time period of delay	Amended
21.3.6.2 Post exposure prophylaxis, occupational	General measures	Editorial amendment
	Adverse effects of PEP	Guidance amended
21.3.6.2 Post exposure prophylaxis, rape and sexual assault	HIV PEP – guidance for children	Amended
	HIV PrEP	Added as a cross reference to the PHC STGs and EML (PrEP section)
- Emergency contraception after pregnancy is excluded	Copper IUCD	Added (as first line option)
	Levonorgestrel, oral	Retained (as 2nd line option)
- *Obese women*	Levonorgestrel, oral	Dose not amended
- *STI prophylaxis for pregnant women*	Ceftriaxone, IM	Retained
	Azithromycin, oral	Retained
	Metronidazole, oral	Retained
	Cefixime, oral	Not added
	Erythromycin, oral	Not added
	Spectinomycin, parenteral	Not added
21.3.7 Soft Tissue Injuries	Paracetamol dosing guidance	Amended
	Referral of patients with haemophilia	Not added
21.3.8 Sprains and strains	Paracetamol dosing guidance	Amended
	Referral – rehabilitation services	Added

C. SUBSEQUENT UPDATES TO THE 2020-4 EDITION

Version no.	Section	Amendments
1.1	21.3.1.1 ANIMAL BITES	**Rabies vaccine and rabies immunoglobulin (RIG)** Guidance clarified on authorised prescribers.

21.1.1 CARDIAC ARREST, ADULTS

COVID-19 considerations

Cardiac arrest algorithm for suspected communicable diseases: *added*

Resuscitation Council of South Africa's "Advanced cardiac arrest algorithm - suspected respiratory communicable disease",[1,2] adapted with permission was included in this section – see Figure 21.2: Advanced cardiac arrest algorithm - suspected respiratory communicable disease below. The following adaptations have been made to the Resuscitation Council of South Africa's "Advanced cardiac arrest algorithm:

Added	Refer to Adult and Paediatric Hospital Level STG's and EML for guidance on use of anti-arrhythmic

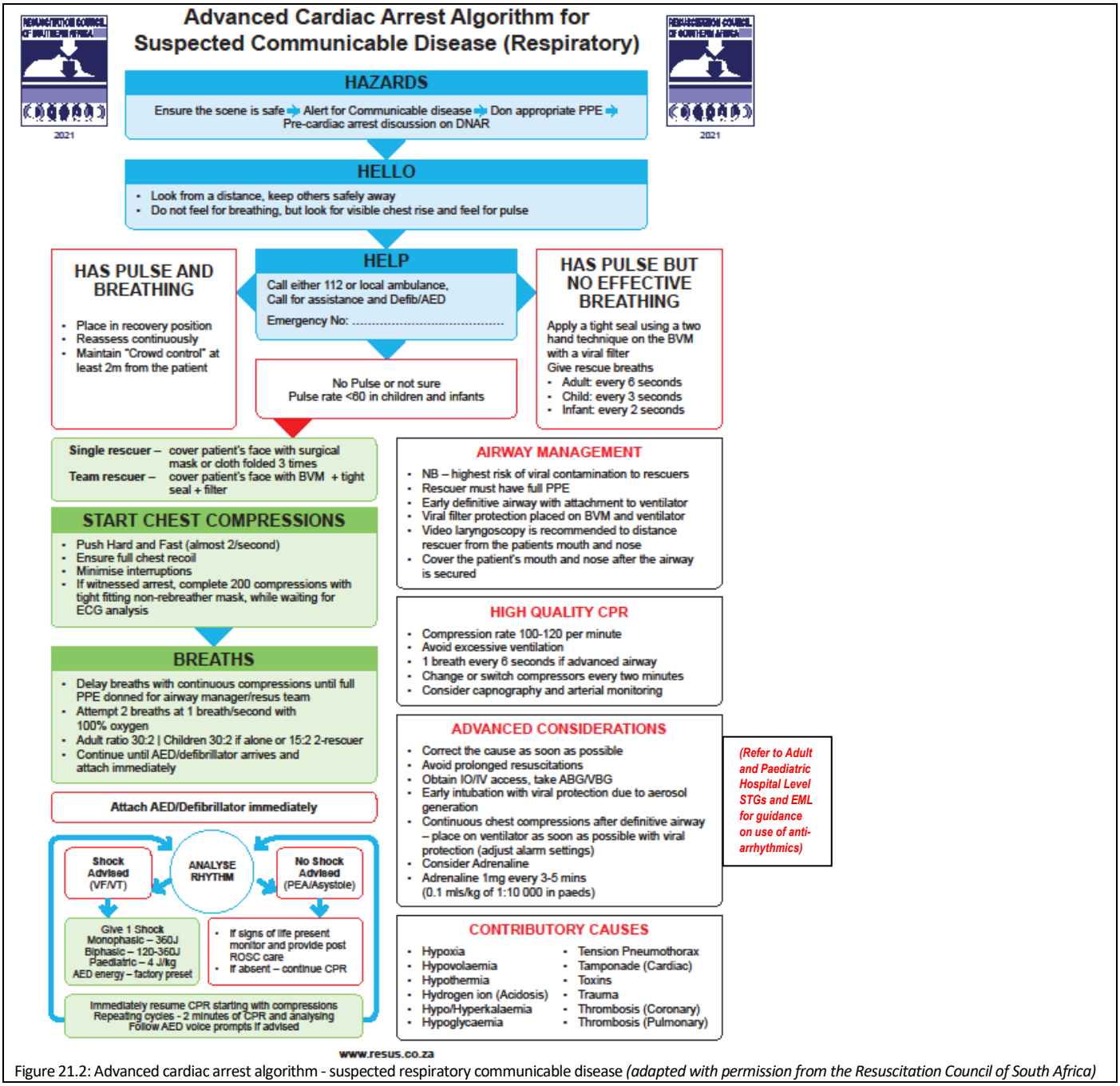


Figure 21.2: Advanced cardiac arrest algorithm - suspected respiratory communicable disease *(adapted with permission from the Resuscitation Council of South Africa)*

[1] Resuscitation Council of South Africa. Advanced Cardiac Arrest Algorithm for Suspected Communicable Disease (Respiratory), 2021. https://resus.co.za/

[2] Brown A, Schwarcz L, Counts CR, Barnard LM, Yang BY, Emert JM, et al. Risk for Acquiring Coronavirus Disease Illness among Emergency Medical Service Personnel Exposed to Aerosol-Generating Procedures. Emerg Infect Dis. 2021 Sep; 27(9): 2340-2348. https://pubmed.ncbi.nlm.nih.gov/34197282/

The following text was also included in the STG, aligned with guidelines:[3]

- » The infection risk that CPR poses to providers due to aerosolization of coronavirus particles is not negligible.
- » This potential risk should be weighed against the probability of achieving spontaneous return of circulation to inform the decision to initiate or stop CPR.
- » For in hospital cardiac arrest in patients with suspected COVID-19, CPR has been shown to not be beneficial unless an immediate reversible cause is suspected, e.g., dislodgement of ET tube, etc. and is therefore not recommended.
- » For out of hospital cardiac arrest in patients with suspected COVID-19, it is recommended to not start conventional CPR in unwitnessed cardiac arrest as it will likely not be beneficial.
- » Appropriate PPE should be worn by all staff before initiating CPR: FFP3 mask, visor, gloves and gown.

Guidance regarding PPE was based on a retrospective cohort study[4] that showed that overall, the incidence of rRT-PCR positive tests among EMS personnel following PPE protocols (wearing a mask, eye protection, gloves, and a gown) was low: 0.57 per 10,000 person-days (30 positive tests in 525,154 person-days).

Level of Evidence: Low certainty evidence

Amiodarone, IV: *not added*

The previous NEMLC recommendation not to include bolus amiodarone for management of ventricular fibrillations or pulseless ventricular tachycardia not responsive to defibrillation, in the PHC STGs and EML was upheld. Previously, NEMLC recommended that amiodarone IV/IO should be administered at secondary level facilities. Furthermore, previous review of amiodarone in the Adult Hospital STGs and EML, 2019 edition found that the role of antiarrhythmics in adult cardiopulmonary resuscitation was uncertain:

NEMLC report for the Adult Hospital Level Emergencies and injuries chapter (2017-9 review cycle):

However, recent meta-analyses suggest that there is uncertainty about the efficacy of antiarrhythmics in cardiac arrest to improve rates of return of spontaneous circulation, survival to hospital discharge or neurological outcomes when compared to placebo. Conflicting outcomes for survival to hospital admission was reported for use of antiarrhythmics in advanced life support: McLeod et al, 2017[5] showed that amiodarone (RR 1.18; 95% CI: 1.08 to 1.30) was associated with a statistically significant increase in survival to hospital admission, whilst Chowdury et al, 2017[6] showed that amiodarone had no significant effect on survival to admission (OR=1.33; 95% CI 0.91 to 1.97; I_2 = 92%; p=0.14).

Cardiopulmonary resuscitation (CPR)

Guidance on fluid recommendations: *amended*

The following text was deleted from the STG as not pragmatic for primary healthcare level of care:

Initiate fluids, IV/IO access

Sodium chloride 0.9%, IV, 1000 mL.

- ~~Consider giving a fluid bolus of 1 litre during CPR if an increase in preload may benefit the patient, e.g. hypovolaemia shock, distributive shock, haemorrhagic shock.~~
- ~~Avoid fluid boluses during CPR if an increase in the preload could be detrimental to the patient e.g. massive pulmonary embolism or cardiac tamponade.~~

Additional guidance – termination of resuscitation (TOR)

Duration of asystole: *amended*

A more objective statement was considered for inclusion in the PHC STG, *"Asystole of >20 minutes is considered unsurvivable".* However, there is a paucity of evidence that informs this decision, and most recommendations are based on consensus.[7]

The 2020 AHA guidelines note that in a recent meta-analysis of seven published studies (n=33,795 patients), only 0.13% (95% CI 0.03 to 0.58%) of patients who fulfilled the Basic Life Support (BLS) termination criteria survived to

[3] Atkins DL, Sasson C, Hsu A, Aziz K, Becker LB, Berg RA, et al.; 2022 Interim Guidance to Health Care Providers for Basic and Advanced Cardiac Life Support in Adults, Children, and Neonates With Suspected or Confirmed COVID-19: From the Emergency Cardiovascular Care Committee and Get With The Guidelines-Resuscitation Adult and Pediatric Task Forces of the American Heart Association in Collaboration With the American Academy of Pediatrics, American Association for Respiratory Care, the Society of Critical Care Anesthesiologists, and American Society of Anesthesiologists. Circ Cardiovasc Qual Outcomes. 2022 Apr;15(4):e008900. https://pubmed.ncbi.nlm.nih.gov/35072519/

[4] Brown A, Schwarcz L, Counts CR, Barnard LM, Yang BY, Emert JM, et al. Risk for Acquiring Coronavirus Disease Illness among Emergency Medical Service Personnel Exposed to Aerosol-Generating Procedures. Emerg Infect Dis. 2021 Sep;27(9):2340-2348. https://pubmed.ncbi.nlm.nih.gov/34197282/

[5] McLeod SL, Brignardello-Petersen R, Worster A, You J, Iansavichene A, Guyatt G, Cheskes S. Comparative effectiveness of antiarrhythmics for out-of-hospital cardiac arrest: A systematic review and network meta-analysis. Resuscitation. 2017 Dec;121:90-97. https://www.ncbi.nlm.nih.gov/pubmed/29037886

[6] Chowdhury A, Fernandes B, Melhuish TM, White LD. Antiarrhythmics in Cardiac Arrest: A Systematic Review and Meta-Analysis. Heart Lung Circ. 2018 Mar;27(3):280-290. https://www.ncbi.nlm.nih.gov/pubmed/28988724

[7] 2020 American Heart Association. 2020 American Heart Association Guidelines for CPR and ECC https://cpr.heart.org/en/resuscitation-science/cpr-and-ecc-guidelines

hospital discharge[8]. The BLS TOR rule recommends terminating resuscitation if all the following three criteria are met: the cardiac arrest was not witnessed by EMS personnel, no return of spontaneous circulation (ROSC) before transport, and no shock delivered before transport.
The 2020 AHA guidelines also note in a meta-analysis of two published studies (n=10,178), only 0.01% (95% CI, 0.00-0.07%) of patients who fulfilled the ALS termination criteria survived to hospital discharge. The ALS TOR rule recommends terminating resuscitation if all the following four criteria are fulfilled: the cardiac arrest was not witnessed, there was no bystander CPR, there was an absence of ROSC before transport, and an absence of defibrillation before transport.
Both the BLS and ALS TOR (termination of resuscitation) rules have been shown to have good predictive value.[9]
Level of Evidence: Low certainty evidence

NEMLC MEETING OF 23 JUNE 2022:
NEMLC accepted the proposed recommendation ("*Asystole of >20 minutes is considered unsurvivable"*). However, the STG text was amended further as below

Amended from:

~~Consider stopping resuscitation attempts and pronouncing death if:~~
- ~~Further resuscitation is clearly clinically inappropriate, e.g. incurable underlying disease, or~~
- ~~The decision to stop CPR attempts depends on the specifics of the individual patient and should be based on clinical judgement~~
- ~~Consider continuing CPR attempts until enough information is available to inform the decision to stop~~
- ~~This decision should take into consideration the potential risk that CPR poses to the rescuer, considering the prevalence of COVID-19.~~
- ~~Asystole of >20 minutes is considered unsurvivable.~~

~~Consider carrying on for longer especially when:~~
- ~~hypothermia and drowning~~
- ~~poisoning or medicine overdose~~
- ~~neurotoxic envenomation (e.g.black and green mamba or Cape cobra snakebite) – see Section 21.3.1.4: Snakebites~~

Amended To:

Termination of resuscitation:
- The decision to stop CPR attempts depends on the specifics of the individual patient and should be based on clinical judgement.
- Consider stopping resuscitation attempts and pronouncing death if there is incurable underlying disease, or if asystole > 20 minutes or in the absence of the factors for prolonging resuscitation as listed below.

Consider carrying on for longer especially with:
- hypothermia and drowning
- poisoning or medicine overdose
- neurotoxic envenomation (e.g.black and green mamba or Cape cobra snakebite) – see Section 21.3.1.4: Snakebites

This decision should take into consideration the potential risk that CPR poses to the rescuer e.g. infectious diseases.

21.1.2 CARDIAC ARREST, CHILDREN

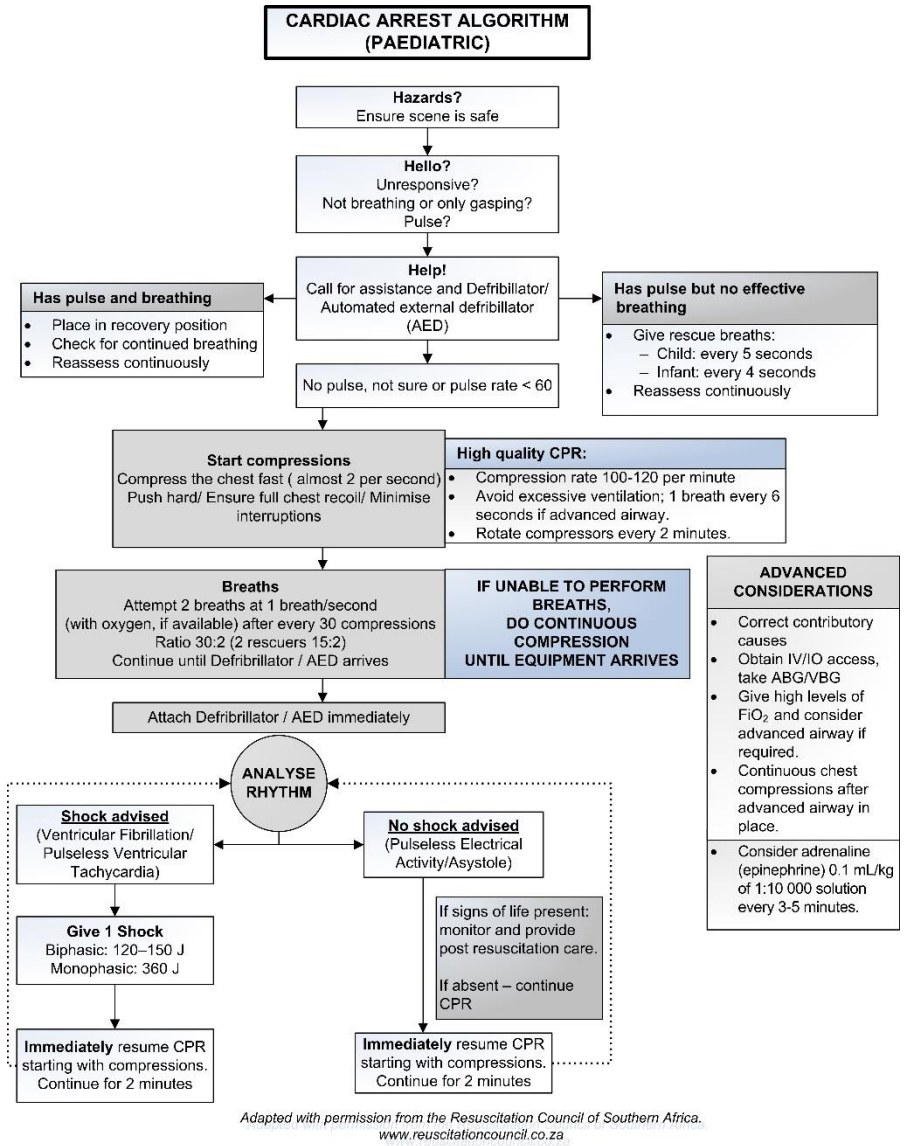
Immediate emergency medicine treatment
Cardiac arrest algorithm: Amended

The cardiac arrest algorithm has been updated in alignment with the most recent advanced cardiovascular life support (ACLS) and basic life support (BLS) guidance, which includes rescue breaths every 2 seconds for infants and every 3 seconds for children. According to the American Heart Association 2020 Guidelines for CPR (AHA 2020)[10], *"When performing CPR in infants and children with an advanced airway, it may be reasonable to target a respiratory rate range of 1 breath every 2 to 3 seconds (20-30/min), accounting for age and clinical condition. Rates exceeding these recommendations may compromise hemodynamics."*

[8] Ebell MH, Vellinga A, Masterson S, Yun P. Meta-analysis of the accuracy of termination of resuscitation rules for out-of-hospital cardiac arrest. Emerg Med J. 2019 Aug;36(8):479-484. https://pubmed.ncbi.nlm.nih.gov/31142552/
[9] Lin YY, Lai YY, Chang HC, Lu CH, Chiu PW, Kuo YS, Huang SP, et al. Predictive performances of ALS and BLS termination of resuscitation rules in out-of-hospital cardiac arrest for different resuscitation protocols. BMC Emerg Med. 2022 Mar 27;22(1):53. https://pubmed.ncbi.nlm.nih.gov/35346055/
[10] 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Last accessed online Mar 2024: https://professional.heart.org/en/science-news/2020-aha-guidelines-for-cpr-and-ecc

Following, engagement with the Resus Council of South Africa (RCSA) regarding the recommended number of rescue breaths for children and infants, we received confirmation that the RSCA has subsequently amended its algorithm to align with the AHA guidance i.e. rescue breaths every 2 seconds for infants and every 3 seconds for children[11].

Amended from:



Adapted with permission from the Resuscitation Council of Southern Africa.
www.reuscitationcouncil.co.za

[11] Email Correspondence on file. 10 May 2024

Amended to:

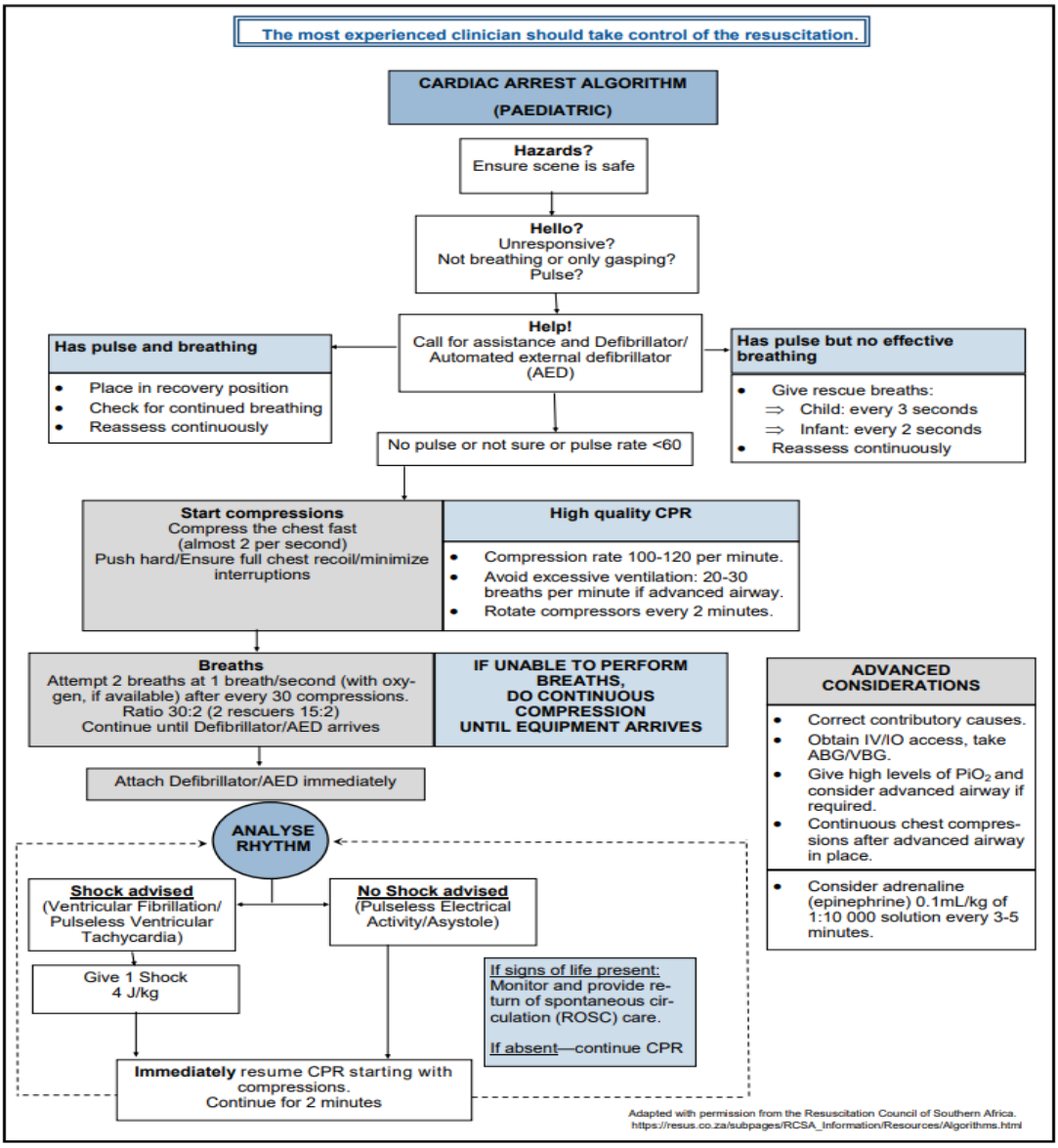


Figure 21.3 Advanced cardiac arrest algorithm for children

Paediatric resuscitation tape weight measurements: *Added*

Age-based weight estimates: *Added*

Child weight estimation using paediatric resuscitation tape, taking into consideration body composition and habitus,[12] has been included in the STG. Tape measurements are considered to be more accurate than age-based formulas and the PAWPER tape is the most accurate tape measure in the South African setting[13]; and it is validated in our setting[14]. If tape measures are not available (including the Broselow tape[15]), then age-based weight estimates may be used – the following formula is used in the Advanced Paediatric Life Support protocol: weight(kg) = (age (yrs) +4) X2, calculation.[16]

Level of Evidence: Low certainty

[12] Wells M, Goldstein LN, Bentley A. The accuracy of emergency weight estimation systems in children-a systematic review and meta-analysis. Int J Emerg Med. 2017 Sep 21;10(1):29. https://pubmed.ncbi.nlm.nih.gov/28936627/

[13] Manyoni MJ, Goldstein LN, Wells M. A comparison of four weight estimation systems for paediatric resuscitation. S Afr J Surg. 2019 Jun;57(2):40-46. https://pubmed.ncbi.nlm.nih.gov/31342683/

[14] Wells M. A validation of the PAWPER XL-MAC tape for total body weight estimation in preschool children from low- and middle-income countries. PLoS One. 2019 Jan 7;14(1):e0210332. https://pubmed.ncbi.nlm.nih.gov/30615693/

[15] Wells M, Goldstein LN, Bentley A, Basnett S, Monteith I. The accuracy of the Broselow tape as a weight estimation tool and a drug-dosing guide - A systematic review and meta-analysis. Resuscitation. 2017 Dec;121:9-33. https://pubmed.ncbi.nlm.nih.gov/28958796/

[16] Advanced Life Support Group (ALSG). Advanced Paediatric Life Support: A Practical Approach to Emergencies, 6th Edition. Chichester (West Sussex, UK): BMJ Books; 2016.

Guidance to continue with resuscitation, *amended*

The following STG text was amended for correctness and consistency

Consider carrying on for longer especially with

- » hypothermia and drowning
- » ~~suspected~~ poisoning or medicine overdose ~~or carbon monoxide poisoning~~
- » neurotoxic envenomation (e.g.black and green mamba or Cape cobra snakebite) – see Section 21.3.1.4: Snakebites

This decision should take into consideration the potential risk that CPR poses to the rescuer e.g. infectious diseases.

21.1.5 MANAGEMENT OF SUSPECTED CHOKING/FOREIGN BODY ASPIRATION IN CHILDREN

Choking algorithm & related guidance: *Amended*

The algorithm for the management of choking in children has been updated to the latest algorithm (2021) from the Resus Council of South Africa[17]. Amendments are as tabulated below and include:

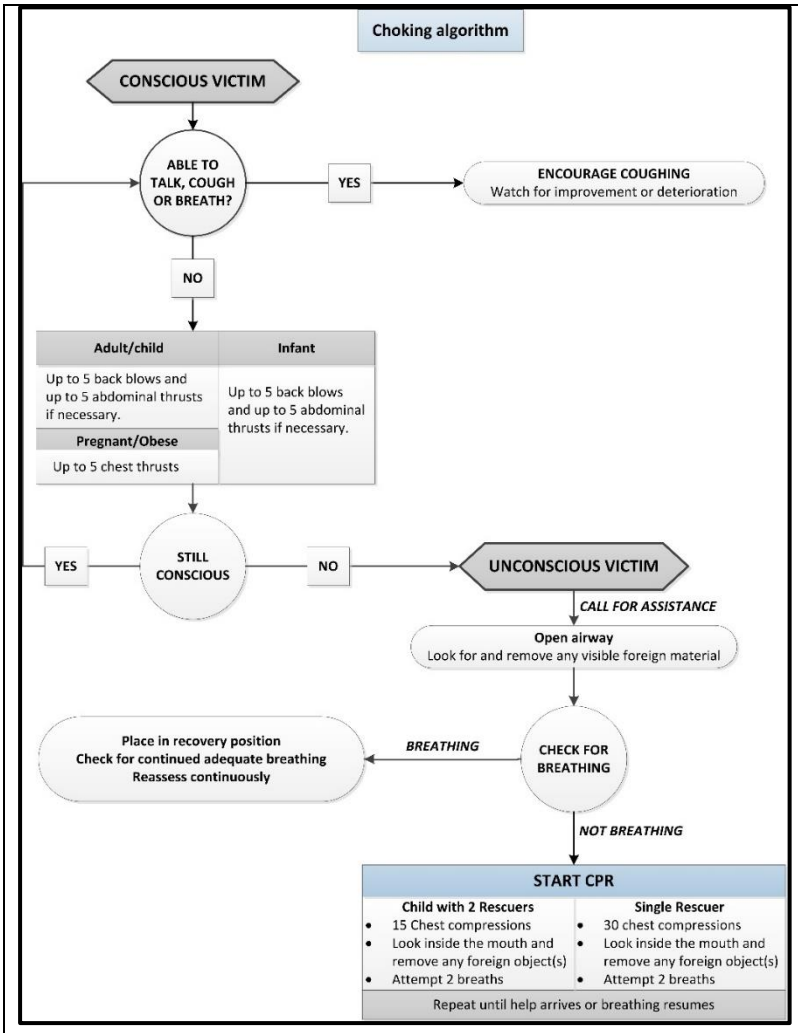
- Adults & children - amended from *'5 back blows & up to 5 abdominal thrusts if necessary'* to *'up to 5 abdominal thrusts and if ineffective up to 5 back slaps.'*
- Infants - amended from *'Up to 5 back blows and up to 5 abdominal thrusts'* to *'Up to 5 back slaps. And up to 5 chest thrusts if necessary.'*

Amended from:

If the child is **able to talk and breathe**	Encourage the child to cough repeatedly while arranging transfer to hospital urgently with supervision.
If the child is **conscious but with no effective cough or breathing**	Give 5 back blows, followed by 5 chest/ abdominal thrusts, followed by re-assessment of breathing. and then repeated as a cycle until recovery or child becomes unconscious. See differences below for infants and children.
If the child is **unconscious with no effective breathing**	Call for assistance. Open airway and check for any visible foreign body and remove. Start CPR: compressions and breaths (30:2) (check airway for foreign body each time before giving breaths).

(Infant: < 1 year of age; Child: > 1 year of age until puberty).

[17] Resus Council of S.Africa. Choking algorithm 2021 https://resus.co.za/Documents/Algorithms/RESUS%20CHOKING%20ALGORITHM.pdf



Amended to:

If the child is **able to talk and breathe**	Encourage the child to cough repeatedly while arranging transfer to hospital urgently with supervision.
If the child is **conscious but with no effective cough or breathing**	Give up to 5 abdominal thrusts and if ineffective up to 5 back slaps, followed by re-assessment of breathing. Repeat as a cycle until recovery or child becomes unconscious. See technique below and figure 21.4 for differences between infants and children.
If the child is **unconscious with no effective breathing**	Call for assistance. Open airway and check for any visible foreign body and remove. Start CPR: compressions and breaths (30:2) (check airway for foreign body each time before giving breaths).

(Infant: < 1 year of age; Child: > 1 year of age until puberty).

Table 21.3: Managing suspected choking/foreign body aspiration in children

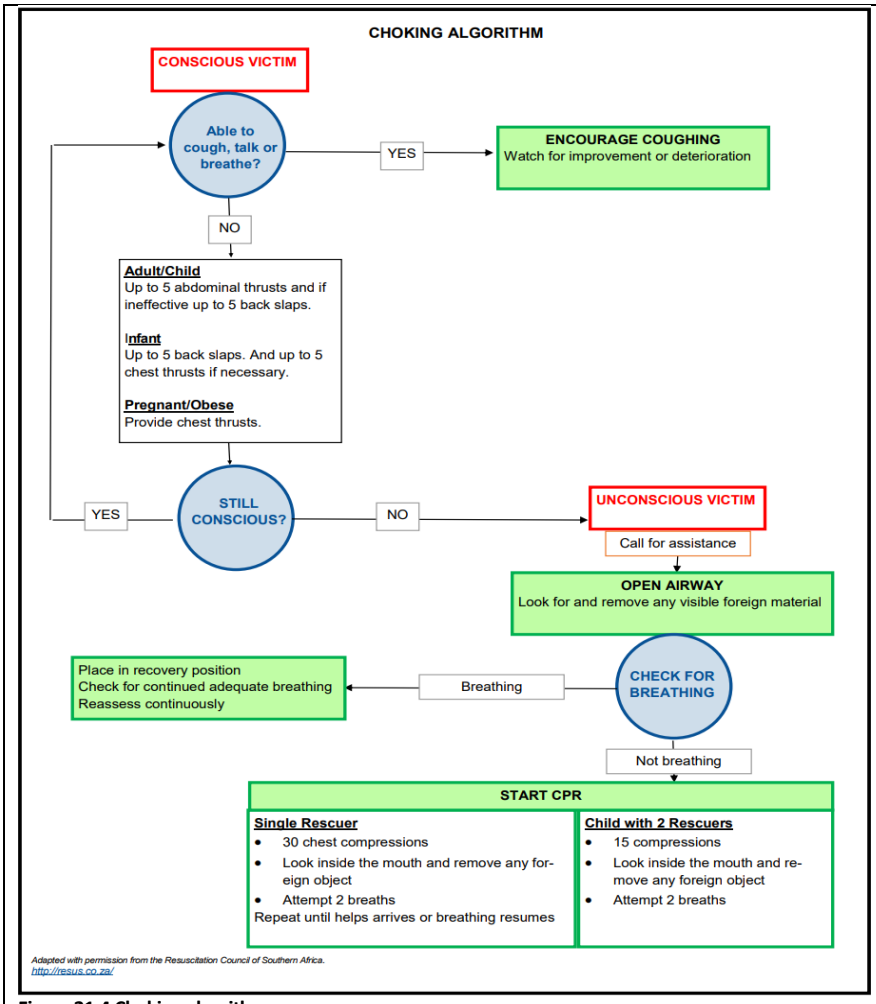


Figure 21.4 Choking algorithm

21.2. MEDICAL EMERGENCIES

21.2.1 PAEDITARIC EMERGENCIES

Referral for children with cerebral palsy: *Not added*

External comment received from RuRehab to refer children with cerebral palsy for neurodevelopmental assessment and rehabilitation was not supported in this section but has more appropriately been included under Section 15.7 Cerebral palsy.

21.2.1.1 RAPID TRIAGE OF CHILDREN PRESENTING WITH ACUTE CONDITIONS IN CLINICS AND CHCS

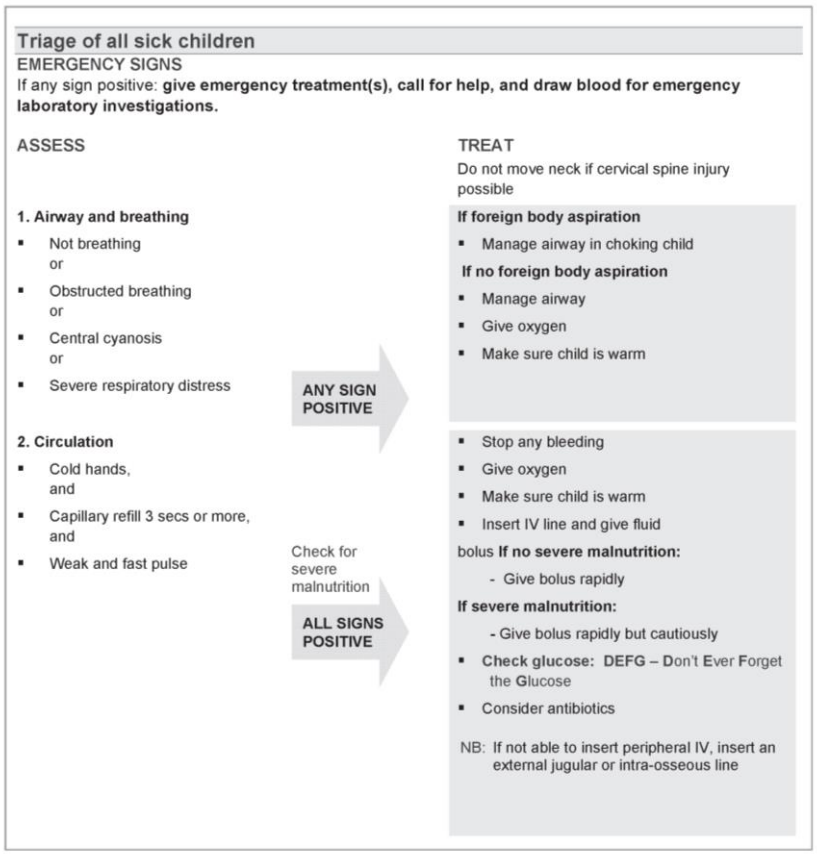
Triage process of all sick children**:** *Amended*

Guidance on the triage of sick children was updated to include cross references to other relevant sections of the EML for further information on management of sick children and duplicated text was removed. Guidance was also aligned to the Integrated Management of Childhood Illness (IMCI) guidelines 2022[18].

[18] National Department of Health. Integrated management of childhood illness. 2022 https://knowledgehub.health.gov.za/elibrary/integrated-management-childhood-illness-2022

Amended from:

Triage is the process of rapidly examining all sick children when they first arrive at clinics in order to place them in one of three categories (Emergency, Priority, Non-urgent):



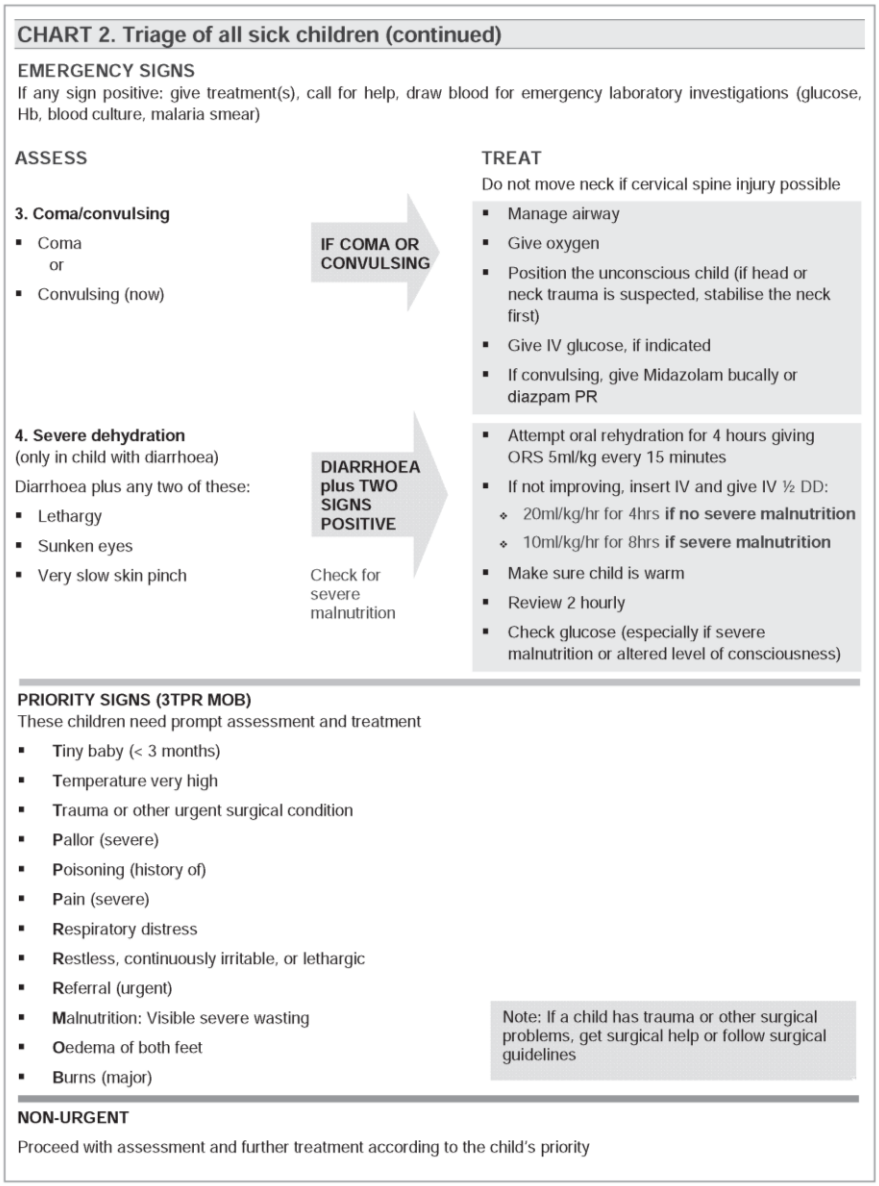


Figure 21.5: Triage of sick children
Adapted from Pocketbook of Hospital Care for Children. Management of Common Childhood Illnesses. National Department of Health, South Africa, 2016. www.health.gov.za/

If any emergency sign is present, give emergency treatment(s), call for help, and draw blood for emergency laboratory investigations as clinically indicated.

(A&B) Airway and Breathing

Not breathing
or
Obstructed breathing
or
Central cyanosis
or
Severe respiratory distress

(C) Circulation

Cold hands
and
Capillary refill ≥3 seconds
and
Weak and fast pulse

(C) Coma/convulsing

Coma
or
Convulsing (now)

(D) Severe dehydration (e.g. in child with diarrhoea)

Diarrhoea

plus

Any two of:

- Lethargy
- Sunken eyes
- Very slow skin pinch

PRIORITY

Priority signs

These children need prompt assessment and treatment
Tiny baby (< 3 months of age)
High Temperature
Trauma or other urgent surgical condition
Pallor (severe)
Poisoning (history of)
Pain (severe)
Respiratory distress
Restless, continuously irritable, or lethargic
Referred for urgent attention
Malnutrition: visible severe wasting
Oedema of both feet
Burns (major)

NON-URGENT (queue)

No emergency or priority signs.
Proceed with assessment and further treatment according to the child's priority.

The Emergency Triage Assessment and Treatment (ETAT) tool, presented above, should be a minimum standard of triage in community health centres.

(Alternative tool P-SATS is available, see the Paediatric Hospital level STGs and EML).

Amended to:

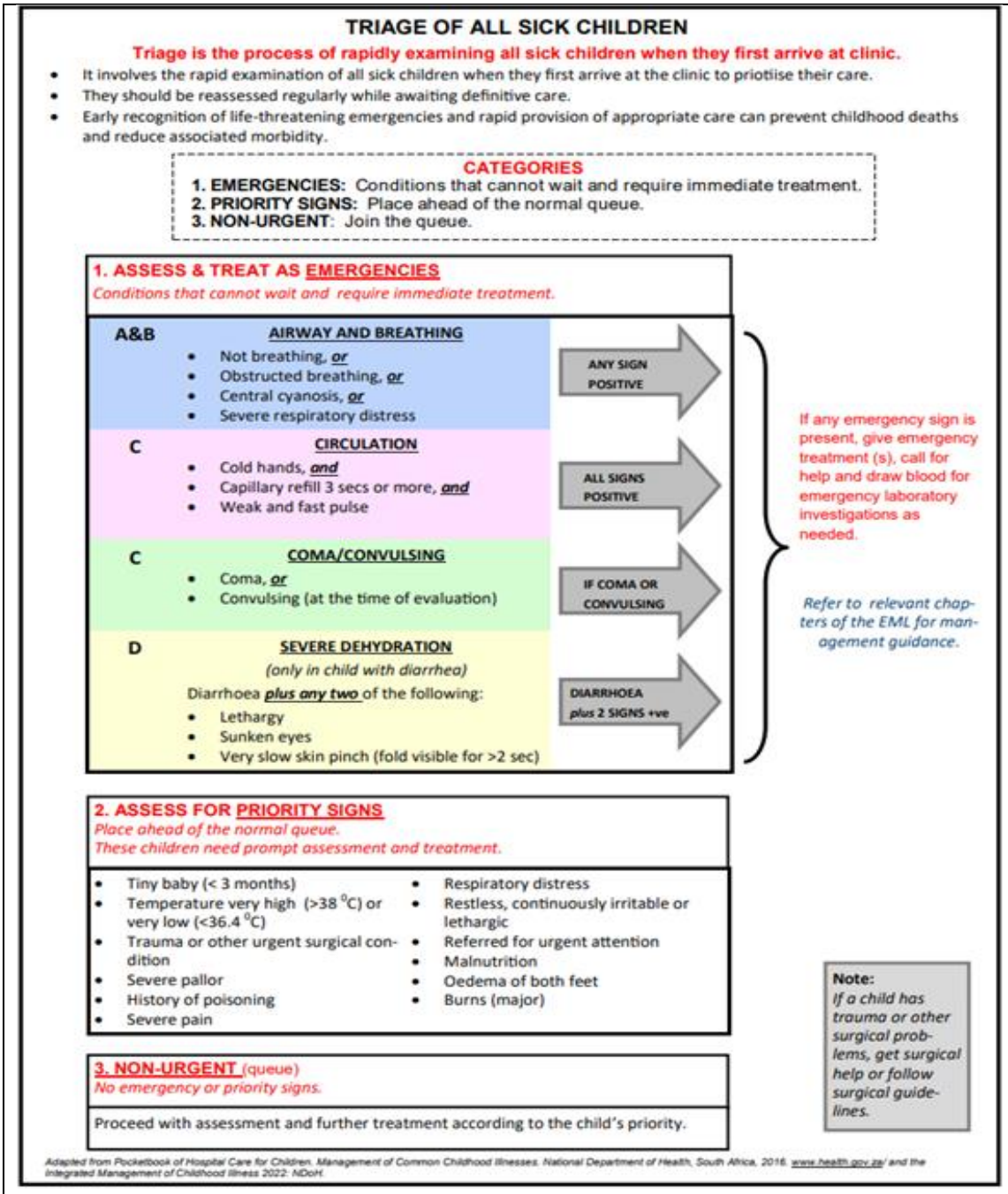


Figure 21.5: Triage of sick children

The Emergency Triage Assessment and Treatment (ETAT) triage process, presented above, should be a minimum standard of triage in community health centres.

For management guidance, refer to relevant sections of the EML as listed below:
For foreign body aspiration see Section 21.1.5
For acute asthma see Section 17.1.1
For acute bronchiolitis see Section 17.1.3
For croup see Section 17.2.1
For shock see Section 21.2.11
For hypoglycaemia and hypoglycaemic coma see Section 21.2.6
For acute diarrhoea see Section 2.9.1

21.2.4 DELIRIUM

Guidance on Physical Restraint: *added*

The guidance as tabulated below was added to the STG

CAUTION – Physical Restraint

- » Worsens the outcomes of delirious patients: this is a last resort when all else has failed and is a short-term measure until chemical restraint and other measures have been achieved.
- » Manual restraint: respectful, controlled, applied by personnel of the same sex as the patient.
- » Mechanical restraint: only if absolutely necessary to protect the patient and others for as short a time as possible. Document the type, sites and duration of any restraints used. 15-minute monitoring of vital signs, the mental state, restraint sites, and reasons for use.

Medicine treatment: *guidance amended*

Guidance on management of delirium amended as tabulated below

MEDICINE TREATMENT

- » ~~Treat the underlying medical condition.~~
- » Manage the underlying medical or surgical condition.
- » The aim is to contain the person while awaiting transfer to hospital and to enable initial care of the underlying condition.
- » Keep antipsychotic or benzodiazepine use to a minimum.
- » Use small doses regularly rather than large doses less frequently.
- » Adjust doses according to clinical circumstances, e.g., lower doses in the elderly, debilitated.

Acute management, *aligned*

Guidance for the acute management of delirium has been aligned with a cross reference to Section 16.1.2 and 16.1.3 of the STG as tabulated below

For ~~the management of~~ severe aggression and disruptive behaviour, see Section 16.1.2 ~~15.1~~: Aggressive, disruptive behaviour in adults or Section 16.1.3 Aggressive, disruptive behaviour in children and adolescents.

Diazepam – dose frequency: *Clarified*

The frequency for administering a second dose of diazepam IV has been specified as tabulated below:

AMENDED FROM

- Diazepam, slow IV, 10 mg no faster than 5 mg/minute for immediate sedative or hypnotic action.
  If no response, give a 2nd dose.

AMENDED TO:

- Diazepam, slow IV, 10 mg no faster than 5 mg/minute for immediate sedative or hypnotic action.
  - If no response, give a 2nd dose after 30 to 60 minutes.

Benzodiazepines, *amended*

The cautions for the use of benzodiazepines have been amended to accommodate for the addition of olanzapine and oral haloperidol to the STG as tabulated below

CAUTION - Benzodiazepines

- » Benzodiazepines, especially diazepam IV, can cause respiratory depression.
- » Monitor vital signs closely during and after administration. In the frail and elderly patient or where respiratory depression is a concern, reduce the dose by half.
- » The safest route of administration is oral followed by IM with the IV route having the highest risk of respiratory depression and arrest. Use the safest route wherever possible.
- » In patients with respiratory insufficiency: use oral haloperidol or olanzapine oro-dispersible tablets, IM, or oral instead of IM or IV benzodiazepines. ~~Use haloperidol instead of benzodiazepines in patients with respiratory insufficiency.~~
- » Do NOT use IM olanzapine with IM/IV benzodiazepines.
- » In the short-term, benzodiazepines can aggravate delirium.
- » Allow at least 15–30 minutes for the medication to take effect. Repeated IM doses of benzodiazepines may result in toxicity owing to accumulation.

Haloperidol, IM: *retained*
Olanzapine, oro-dispersible: *added*
Olanzapine, IM: *added*

Refer to the medicine review on the Knowledge Hub or included below for more information.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	
Recommendation: The PHC/ Adult Hospital Level Committee suggests using olanzapine (orodispersible and parenteral formulations) as an option to manage delirium where non-pharmacological management is not sufficient and if haloperidol, intramuscular formulation is unavailable *Rationale:* Available low-quality evidence shows that olanzapine is comparable to haloperidol. **Level of Evidence: Low to very low certainty evidence** **Review indicator:** Evidence of harm, efficacy					
NEMLC RECOMMENDATION (20 OCTOBER 2022 MEETING): NEMLC recommended the use of olanzapine oro-dispersible tablet or IM injection for delirium with agitated and acutely disturbed behaviour. Once the patient is able to swallow, to continue with oral haloperidol or olanzapine, until behaviour is contained.					
Monitoring and evaluation considerations					
Research priorities					

Oro-dispersible olanzapine dissolves on the tongue and is absorbed via the oral mucosa and therefore may be administered in those who cannot/will not swallow which may be beneficial in agitated patients.

The STG has been amended as tabulated below:

Amended from:

If the most likely cause of delirium is a medical disorder and if very restless:

- Haloperidol, IM, 5 mg, immediately.
  In elderly: 2.5 mg, immediately.
  If no response give a second dose.

Amended to:

If the most likely cause of delirium is a medical disorder and if very restless or agitated:

- Haloperidol, oral, 0.75–1.5 mg, repeated in 30–60 minutes, if required

OR

If unable to swallow or oral medication declined:

- Haloperidol, IM, 0.5–1mg.

OR

If haloperidol, IM is not available:

- Olanzapine, oral dispersible tablet or IM, 2.5–5 mg.
  - Use lowest dose with caution in the elderly
  - May be repeated in 30–60 minutes, if required
  - Monitor vital signs and beware of oversedation, neuroleptic malignant syndrome, and acute dystonia.

Alcoholics/ Malnourished (adults)

Thiamine, parenteral: *dose & route of administration amended*

Refer to the evidence summary on Knowledge Hub for more information.

- *Thiamine dose:* There is limited evidence - a Cochrane review[19] reviewed one RCT (n=169)[20] in which participants with a history of chronic alcohol use were assigned to one of five doses of IM thiamine (5, 20, 50, 100 and 200 mg once daily), with outcomes measured after 2 days of treatment. On day 3 of treatment, participants were assessed by a psychologist on the delayed alternation test. This RCT demonstrated a significant difference favouring a dose of 200mg a day compared to 5mg/day in the number of trials taken to reach criteria on a delayed alternation test (MD -17.90, 95% CI -35.4 to -0.40, P = 0.04). Guideline recommendations on the dose of thiamine for the management of patients with suspected or diagnosed Wernicke's encephalopathy varies, with case series reports suggesting that doses of 500mg or more IV, were safe and efficacious. While the Cochrane reviewers concluded that no good evidence could be derived from available RCTs to help physicians choose the right dose, frequency, route or duration of thiamine treatment for preventing or treating WKS due to alcohol abuse, most guidelines recommend higher doses of thiamine i.e. 100mg and more.
- *Route of administration:* It was noted that the SAMF[21], 2016 as well as the British National Formulary[22] cautions about anaphylactic reactions associated with IV administration of thiamine; the latter citing MHRA/CHM advice, 2007:

  IMPORTANT SAFETY INFORMATION MHRA/CHM ADVICE (SEPTEMBER 2007):
  Although potentially serious allergic adverse reactions may rarely occur during, or shortly after, parenteral administration, the CHM has recommended that:
  - This should not preclude the use of parenteral thiamine in patients where this route of administration is required, particularly in patients at risk of Wernicke-Korsakoff syndrome where treatment with thiamine is essential;
  - Intravenous administration should be by infusion over 30 minutes;
  - Facilities for treating anaphylaxis (including resuscitation facilities) should be available when parenteral thiamine is administered.
- *Pragmatic implications:* Thiamine is only available as 100 mg/mL vials and a large volume e.g. 5 mL by IM injection may be poorly tolerated by patients and possibly considered to be impractical.

Recommendations:

- Dose be amended to a maximum of 200 mg IM in both the Adult Hospital and PHC STGs and EML for prevention of Wernicke's encephalopathy.

NEMLC MEETING OF 23 JUNE 2022:
NEMLC accepted the proposal to amend the dose of thiamine from "100mg" to "200mg", aligned with available RCT evidence, for the prevention of Wernicke's encephalopathy. NEMLC also deliberated on the route of administration and recommended that for the prevention of Wernicke's encephalopathy, that thiamine should be administered intramuscularly and not by the intravenous route.

21.2.6 HYPOGLYCAEMIA AND HYPOGLYCAEMIC COMA

Thiamine, IV/IM: *aligned*

Aligned with section 21.2.4: Delirium – see above.

21.2.8 PULMONARY OEDEMA, ACUTE

If patient very anxious or restless

Morphine, IV: *deleted & caution added to the STG*

[19] Day E, Bentham PW, Callaghan R, Kuruvilla T, George S. Thiamine for prevention and treatment of Wernicke-Korsakoff Syndrome in people who abuse alcohol. Cochrane Database Syst Rev. 2013 Jul 1;2013(7):CD004033. https://pubmed.ncbi.nlm.nih.gov/23818100/

[20] Ambrose ML, Bowden SC, Whelan G. Thiamin treatment and working memory function of alcohol-dependent people: preliminary findings. Alcohol Clin Exp Res. 2001 Jan;25(1):112-6. https://pubmed.ncbi.nlm.nih.gov/11198705/

[21] South African Medicines Formulary 14th Ed.

[22] British National Formulary, 2020

Refer to the medicine review on the Knowledge Hub or below or alternatively, the publication by Hendrikse et al.[23] for further detail.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		x			
Recommendation: The PHC/Adult Hospital Level Committee suggests not to use morphine for the treatment of acute pulmonary distress. *Rationale:* Available evidence shows that morphine may increase in-hospital and all-cause mortality and may result in a large increase in invasive mechanical ventilation compared to not using morphine. No available data could be found on whether morphine increases non-fatal adverse events, ICU or hospital length of stay. **Level of Evidence:** Low certainty of evidence **Review indicator:** New high-quality evidence of a clinically relevant benefit					
NEMLC RECCOMENDATION – 23 JUNE 2022: **NEMLC MEETING OF 23 JUNE 2022:** NEMLC accepted the proposal to remove morphine for the treatment of acute pulmonary distress. However, recommended that a caution be included in the STG, accordingly: **CAUTION** Do not use morphine for pulmonary oedema, as there is observational data providing a signal of harm. Furthermore, once the respective chapter is finalised, it was recommended that a circular be drafted and disseminated regarding the harms associated with use of morphine for distress in pulmonary oedema.					
Monitoring and evaluation considerations					
Research priorities					

21.2.9 SHOCK

Fluid replacement in children – sodium chloride 0.9%: *Dose amended*
Fluid replacement in children – ringers lactate: A*dded*

The dose of sodium chloride 0.9% as an IV bolus dose for the management of shock in children was amended from 20mL/kg as a rapid bolus to 10mL/kg over 20 minutes. This has been aligned to the Integrated Management of Childhood Illness (IMCI) guidelines 2022[24].

Furthermore, ringers lactate has been added as an alternative fluid replacement solution to sodium chloride 0.9% in alignment with the Paediatric EML.

21.2.10 ANAPHYLAXIS

General measures

Guidance on anaphylaxis associated with vaccinations: *added*
Guidance was included in the STG on non-pharmacological management of anaphylaxis associated with vaccinations, aligned with WHO guidance[25], as follows:

Anaphylaxis associated with vaccinations:
» Always keep a fully equipped emergency tray at the immunisation point.
» It is advisable to observe clients for 15 minutes after a vaccination. If a client is known with severe allergies, an observation period of 30 minutes is advised.

[23] Hendrikse C, Ngah V, Kallon II, Thom G, Leong TD, Cohen K, McCaul M. Signal of harm in morphine use in adults with acute pulmonary oedema: A rapid systematic review. S Afr Med J. 2023 Aug 3;113(8):39-43. doi: 10.7196/SAMJ.2023.v113i8.348. PMID: 37882120.
[24] National Department of Health. Integrated management of childhood illness. 2022. https://knowledgehub.health.gov.za/elibrary/integrated-management-childhood-illness-2022
[25] Immunization stress-related response. A manual for program managers and health professionals to prevent, identify and respond to stress related responses following immunization. Geneva: World Health Organization; 2019. https://apps.who.int/iris/handle/10665/330277

» Clients who develop symptoms should be assessed for possible vaccination associated anaphylaxis by considering the following:
  - If signs and symptoms are generalised – involving more than 2 body systems, manage as anaphylaxis.
  - If signs and symptoms are serious or life-threatening, even if only one body system is involved (including hypotension, respiratory distress significant swelling of lips or tongue), treat as anaphylaxis.
  - If isolated rash in an otherwise well client, monitor for 30 minutes.
» Collapse following vaccination might be due to anaphylaxis or other causes such as a vasovagal episode:
  - Call for help and put patient on his/her back and raise legs.
  - Check if responsive – if unresponsive, commence CPR (See section 21.1)
  - A vasovagal episode is usually associated with a transient loss of consciousness (< 1 minute), relieved by raising the legs when supine, transient low BP and low HR.
  - Collapsing after vaccination usually occurs 5-10 minutes post-vaccination, but can occur up to an hour afterwards.
  - Treat as anaphylaxis if loss of consciousness is not brief and not relieved by raising the legs, if any of the signs or symptoms of anaphylaxis occur.

	ANAPHYLAXIS	ACUTE STRESS RESPONSE	
		GENERAL	VASOVAGAL REACTION WITH SYNCOPE
Onset	Usually 5 min after immunization but may be delayed up to 60 min	Sudden, occurs before, during or shortly after (< 5 min) immunization	Sudden, occurs before, during or shortly after (< 5 min) immunization. May present after 5 min if the individual stands suddenly.
System			
Skin	Generalized urticaria (hives) or generalized erythema, angioedema, localized or generalized, generalized pruritus with or without skin rash, generalized prickle sensation, localized injection site urticaria, red and itchy eyes	Pale, sweaty, cold, clammy	Pale, sweaty, cold, clammy
Respiratory	Persistent cough, noisy breathing and airway constriction: wheeze, stridor. If very severe, respiratory arrest.	Hyperventilation (rapid, deep breathing)	Normal to deep breaths
Cardiovascular	↑ heart rate, ↓ blood pressure, circulatory arrest	↑heart rate, normal or ↑systolic blood pressure	↓ heart rate with or without transient ↓in blood pressure
Gastrointestinal	Nausea, vomiting, abdominal cramps	Nausea	Nausea, vomiting
Neurological and other symptoms	Uneasiness, restlessness, agitation, loss of consciousness, little response when supine or lying flat	Fearfulness, light-headedness dizziness, numbness, weakness, tingling around the lips, spasms in hands, feet	Transient loss of consciousness, good response once supine or lying flat, with or without tonic–clonic seizure

Table 21.5: Differences between anaphylaxis, general acute stress response and vasovagal reaction with syncope
Source: Immunization stress-related response. A manual for program managers and health professionals to prevent, identify and respond to stress related responses following immunization. Geneva: World Health Organization; 2019.
https://apps.who.int/iris/handle/10665/330277

Management – salbutamol nebulized: *Dose clarified*
Management – ipratropium bromide nebulized in adults and children: *Doses clarified*

The doses of nebulized salbutamol and ipratropium bromide for the management of wheeze have been aligned to updated guidance in the PHC Chp 17 Respiratory chapter Section 17.1.1 Acute asthma. Updates are as tabulated below:

Amended from:

If wheeze:

- Salbutamol 0.5%, solution, nebulised, with high flow oxygen.
  .5–1 mL (2.5–5 mg) salbutamol 0.5% solution, in 4 mL of sodium chloride 0.9%.

AND

- Ipratropium bromide, solution, added to salbutamol solution.
  Children: 0.5–1 mL (0.125–0.25 mg)
  Adults: 2 mL (0.5 mg)

Amended to:

If wheeze:

- Salbutamol 0.5%, (5mg/mL) solution, nebulised, with high flow oxygen.
  - Children: 0.5–1 mL (2.5–5 mg) salbutamol 0.5% solution,
  - Adults: 1 mL (5 mg) salbutamol 0.5% solution,

AND

- Ipratropium bromide, solution, added to salbutamol solution.
  - Children: Ipratropium bromide 0.25mg/2ml; nebuliser solution: 2mL (0.25 mg) nebulised with salbutamol and made up to a total volume of 4mL with sodium chloride 0.9%.
  - Adults: Ipratropium bromide 0.5mg/2ml; nebuliser solution, 2 mL (0.5 mg) nebulised with salbutamol and made up to a total volume of 4mL with sodium chloride 0.9%.

21.3.TRAUMA AND INJURIES

Referral for patients with brain and spinal cord injury: *Not added*

External comment received from RuRehab to refer patients with brain and spinal cord injuries for rehabilitation was not supported as this referral guidance has been more appropriately included under, Section 15.8 Spinal Cord injuries.

21.3.1.1 ANIMAL BITES

Suspected rabid bite

Background: At the NEMLC meeting of the 6 December 2018, NEMLC accepted the following proposed changes made by the previous Adult Hospital Level Committee for the PHC Rabies STG:

NEMLC MEETING OF 6 DECEMBER 2018:

A: POST EXPOSURE MANAGEMENT

AMENDMENT	EVIDENCE AND RATIONALE
2.1 Wound Management	
• Wound irrigation time changed from "5 to 10 minutes" to "15 minutes".	Thorough wound washing reduces the viral inoculum at the wound site[26]. **Level of Evidence: III Guidelines**
2.2.1 Response to different severity of exposure	
• Category risk assessment removed, and management based on severity of exposures, as per algorithm, below	Numbering of categories removed so that risk assessment is simpler and more pragmatic, encouraging acceptability by healthcare workers (and thus implementation more likely). **Level of Evidence: III Expert opinion**

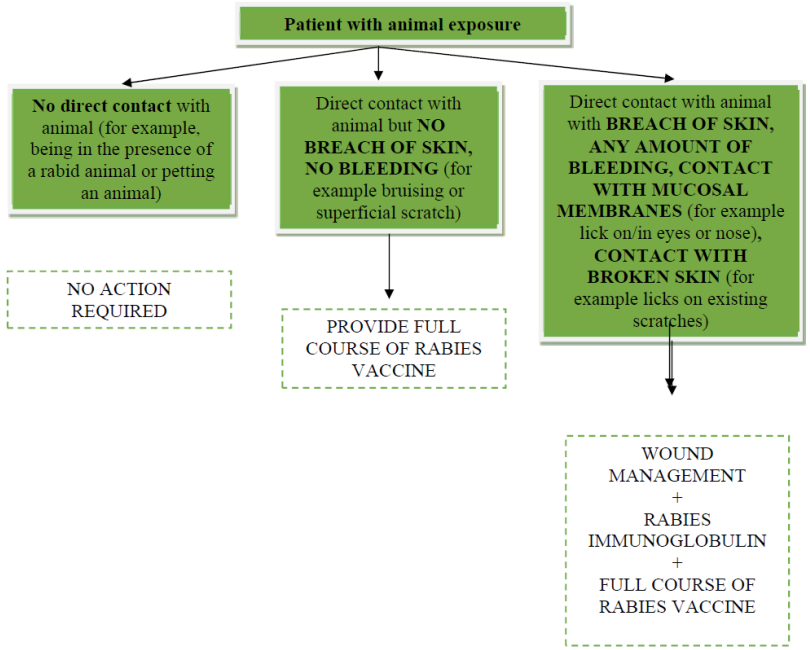


Figure 1: Algorithm for rabies PEP for patients with **no history of previous rabies PrEP or PEP.**

2.2.2 Regimen for rabies vaccine administration

[26] Kaplan MM et al. Studies on the local treatment of wounds for the prevention of rabies. Bull World Health Organ.1962;26:765–775.

• Doses in rabies vaccine regimen: ○ Immunocompetent: *not amended* - No change in dosing regimen ○ Immunocompromised*: amended* - Dosing regimen amended from a 5- to 4-dose regimen (with individual case management of severely immunocompromised e.g.: symptomatic HIV – to determine if additional dose is required if inadequate seroconversion after vaccination.).	Aligned with WHO Rabies Guidelines April 2018 update[27] that recommends the 4-dose Essen IM regimen to all HIV-infected and other potentially immunocompromised persons who are clinically stable (e.g: HIV-infected on ART with undetectable viral load). Studies[28] [29] [30] [31]have shown an immunogenic response by day 14 (subjects had neutralizing antibody concentrations ≥ 0.5 IU/ml) in the immunocompromised. WHO Guidelines states that clinically well HIV patients on ART reacts to administration of vaccines, similarly to the immunocompetent observed.[32] **Level of Evidence: III Immunogenicity studies, Guidelines**
• Directions for IM administration*: not amended* Deltoid muscle in adults, anterolateral thigh in small children (aged < 2 years)	n/a
• *Products available on the SA market:*	Currently only one product is available on the market. Alternate SAHPRA-registered product is unavailable due to GMP concerns at the API manufacturer.
2.2.3 Regimen for rabies immunoglobulin (RIG) administration	
• Directions for administration: *amended* Maximum infiltration of RIG in and around the wound with limited benefit from additional IM administration of any remaining RIG at a site distant to the wound.	Systematic review of in vitro and in vivo studies showed that maximum infiltration of the RIG dose (calculated by body weight) into and around the wound is effective; and there is possibly limited benefit of IM administration of the remaining RIG at a site distant to the wound.[33] It is suggested that the remaining RIG could be given to other patients (especially if RIG is in short supply).[34] [35] Data reported from rabies-endemic settings showed > 99% survival rate in the absence of RIG; but with effective wound management and immediate and completeness of course.[36] **Level of Evidence: III Immunogenicity studies, Observational studies**
• Time of RIG administration*: not amended* — Recommendation not to administer RIG in previously immunised patients or after day 7 following first rabies vaccine dose, retained. — WHO Guidelines recommend that if there are supply challenges with RIG, allocation should be prioritised[37] (high priority cases include: bat exposure; high risk exposure – multiple bites with breach of skin and mucosa exposure; severe immunodeficiency; animal is a confirmed or probable rabid case).	Aligned with April 2018 WHO Guideline recommendations. **Level of Evidence: III Guidelines**
• Equine rabies immunoglobulin: *added* Alternative to HRIG, when there are supply challenges with HRIG, dosed at 40 IU/kg. Anaphylaxis, though rare, can occur and treating healthcare worker should be prepared to manage this ADR (Skin testing before eRIG administration is not recommended as unreliable in predicting adverse effects.	Aligned with April 2018 WHO Guideline recommendations. **Level of Evidence: III Guidelines[38]**
2.3.1 Immunocompromised individuals	

[27] World Health Organisation. Rabies vaccines: WHO position paper – April 2018. Weekly epidemiological record: No 16, 2018, 93, 201–220. http://www.who.int/wer

[28] Sirikwin S, Likanonsakul S, Waradejwinyoo S, Pattamadilok S, Kumperasart S, Chaovavanich A, Manatsathit S, Malerczyk C, Wasi C. Antibody response to an eight-site intradermal rabies vaccination in patients infected with Human Immunodeficiency Virus. Vaccine. 2009 Jul 9;27(32):4350-4. doi: 10.1016/j.vaccine.2009.03.027.

[29] Thisyakorn U, Pancharoen C, Wilde H. Immunologic and virologic evaluation of HIV-1-infected children after rabies vaccination. Vaccine. 2001 Jan 8;19(11-12):1534-7.

[30] Sampath G, Parikh S, Sangram P, Briggs DJ. Rabies post-exposure prophylaxis in malnourished children exposed to suspect rabid animals. Vaccine. 2005 Jan 19;23(9):1102-5.

[31] Rahimi P, Vahabpour R, Aghasadeghi MR, Sadat SM, Howaizi N, Mostafavi E, Eslamifar A, Fallahian V. Neutralizing Antibody Response after Intramuscular Purified Vero Cell Rabies Vaccination (PVRV) in Iranian Patients with Specific Medical Conditions. PLoS One. 2015 Oct 6;10(10):e0139171. doi: 10.1371/journal.pone.0139171. eCollection 2015. Erratum in: PLoS One. 2015;10(10):e0142244.

[32] Simani OE, Izu A, Violari A, Cotton MF, van Niekerk N, Adrian PV, Madhi SA. Effect of HIV-1 exposure and antiretroviral treatment strategies in HIV-infected children on immunogenicity of vaccines during infancy. AIDS. 2014 Feb 20;28(4):531-41. doi: 10.1097/QAD.0000000000000127.

[33] Madhusudana SN, Ashwin BY, Sudarshan S. Feasibility of reducing rabies immunoglobulin dosage for passive immunization against rabies: results of In vitro and In vivo studies. Hum Vaccin Immunother. 2013 Sep;9(9):1914-7. doi: 10.4161/hv.25431.

[34] Bharti OK et al. Injecting rabies immunoglobulin (RIG) into wounds only: A significant saving of lives and costly RIG. Hum Vaccin Immunother. 2017; 13(4):762–765.

[35] Bharti OK et al. Local infiltration of rabies immunoglobulins without systemic intramuscular administration: An alternative cost-effective approach for passive immunization against rabies. Hum Vaccin Immunother. 2016; 12(3):837–842.

[36] WHO. Rabies Working Group Report, SAGE meeting October 2017. Available at http://www.who.int/immunization/sage/meetings/2017/october/1_Background_paper_WG_RABIES_final.pdf?ua=1, accessed February 2018.

[37] WHO. Evidence to recommendation Table 3: prioritization of RIG. Available at http://www.who.int/immunization/policy/position_papers/rabies_prioritization_rig.pdf

[38] World Health Organisation. Rabies vaccines: WHO position paper – April 2018. Weekly epidemiological record: No 16, 2018, 93, 201–220. http://www.who.int/wer

• PEP dosing regimen: *amended* i. Regimen includes 4-doses of vaccines (days 0,7,14,28) ii. RIG x 1 dose only recommended for the severely immunocompromised (excludes clinically well HIV-infected patients on ART).	See discussion above - 2.2.2 Regimen for rabies vaccine administration.
2.3.2 Pregnant and lactating women	
Safety of rabies vaccine and RIG in pregnancy and breastfeeding noted.	Aligned with April 2018 WHO Guideline recommendations. **Level of Evidence: III Guidelines**[39]
2.3.3 Patients who have received previous PrEP or PEP	
• Rabies vaccine: *dosing not amended* • RIG: *recommendation not to administer RIG retained* — Repeat exposure <3 months after a previous exposure, and had received a complete PEP: only wound treatment is required; vaccine nor RIG is needed. — For repeat exposures occurring >3 months after the last PEP: 2-dose IM rabies vaccine on days 0 and 3 recommended and RIG is not indicated.	Aligned with April 2018 WHO Guideline recommendations. **Level of Evidence: III Guidelines**
2.3.4 Delayed presentation	
• Double dosing of vaccine: *deleted* The following recommendation *"If patient presents after 48 hours, administer double the initial dose on day 0"*, replaced by, *"Rabies PEP should ideally be provided as soon after exposure as possible. When patients, present well after the exposure event, regard the first day of presentation as day 0 for vaccine and RIG administration".*	Aligned with April 2018 WHO Guideline recommendations. **Level of Evidence: III Guidelines**

Recommendation: The Adult Hospital Level Committee recommends that the above-mentioned amendments pertaining to post exposure management be included in the respective STGs.

The STG was updated accordingly – see below (changes only):

Amended from:

2.1 Wound Management

Wash wound thoroughly with soap under running water for 5–10 minutes.

2.2.1 Response to different severity of exposure

Category	Type of exposure	Management
1	» Touching/feeding of animal. » Licking of intact skin.	» No treatment if history is reliable. » If history not reliable, treat as category 2.
2	» Nibbling of uncovered skin. » Superficial scratch without bleeding.	» Wound management. » Administer full course vaccine. Only stop if animal tested negative for rabies or is still healthy after 10 days' observation. » Don't give immunoglobulin, except in immunocompromised patients.
3	» Bites/scratches that penetrate the skin and with any visible blood. » Licking of broken skin or mucous membranes e.g. eyes and mouth. » Bat bites: – Any close contact with a bat: single or multiple bites or scratches and bruising (even with minor bites or unapparent skin penetration). – Direct physical contact with bat saliva or neural tissue; contact of mucous membranes with bat saliva, droppings or urine.	» Wound management. » Administer full course vaccine. » Only stop if animal tested negative for rabies or is still healthy after 10 days' observation. » Administer rabies immunoglobulin. » Administer tetanus vaccine. » Prescribe antibiotics.

2.2.2 Regimen for rabies vaccine administration

Rabies vaccination

Only indicated for category 2 and 3 exposure. Available from the nearest district hospital.

Children

- Rabies vaccine, 1 amp, IM anterolateral thigh.
  - Day 0 – single dose
  - Day 3 – single dose

Amended to:

2.1 Wound Management

Wash wound thoroughly with soap under running water for 15 minutes.

2.2.1 Response to different severity of exposure

PATIENT WITH ANIMAL EXPOSURE			
Severity of exposure	**No direct contact** with animal (for example, being in the presence of a rabid animal or petting an animal)	Direct contact with animal but **no breach of skin, no bleeding** (for example bruising or superficial scratch)	Direct contact with animal with **breach of skin, any amount of bleeding, contact with mucosal membranes** (for example lick on/in eyes or nose), **contact with broken skin** (for example licks on existing scratches), **any contact with a bat.**
Management based on severity of the exposure	Washing of exposed skin surfaces	Wound management ***AND*** Full course of rabies vaccine (Rabies immunoglobulin, only if severely immuno-compromised)	Wound management ***AND*** Rabies immunoglobulin ***AND*** Full course of rabies vaccine

2.2.2 Regimen for rabies vaccine administration

Rabies vaccination

Only indicated for direct animal contact.

Patients who have previously been fully immunised or who received PEP more than 3 months ago need only two doses: on Day 0 and Day 3.

Patients who have received previous PEP or PrEP within the previous 3 months do not require vaccination against rabies. Only wound treatment is required.

[39] World Health Organisation. Rabies vaccines: WHO position paper – April 2018. Weekly epidemiological record: No 16, 2018, 93, 201–220. http://www.who.int/wer

Day 7 – single dose Day 14 – single dose Day 28 – single dose(only if immunocompromised). <u>Adults</u> • Rabies vaccine, 1 amp, IM deltoid. Day 0 – single dose Day 3 – single dose Day 7 – single dose Day 14 – single dose Day 28 – single dose(only if immunocompromised).	Available from the nearest district hospital. <u>Children</u> • Rabies vaccine, 1 amp, IM anterolateral thigh. Day 0 – single dose Day 3 – single dose Day 7 – single dose Between day 14-28 – single dose <u>Adults</u> • Rabies vaccine, 1 amp, IM deltoid. Day 0 – single dose Day 3 – single dose Day 7 – single dose Between day 14-28 – single dose
2.2.3 Regimen for rabies immunoglobulin (RIG) administration	
Rabies immunoglobulin: Only indicated for: – Category 3, immunocompetent patients. – Category 2 and 3 immunocompromised patients. – All bat exposures. Available from the nearest district hospital. If not immediately available, source and give as soon as possible. • Rabies immunoglobulin 20 IU/kg. Infiltrate as much as possible in and around the wound and inject the rest IM (not buttock, unless the wound is on the buttock). Follow with a complete course of vaccine.	**Rabies immunoglobulin (RIG):** ○ Only indicated for: – Direct animal contact with breach of skin/ bleeding/ mucosal contact,, immunocompetent patients – Any direct animal contact, immunocompromised patients – All bat exposures ○ Patients who have received PEP or PrEP do not require RIG. Only wound treatment is required. ○ Available from the nearest district hospital. ○ If not immediately available, source and give as soon as possible. ○ When 7 days have lapsed since the initial rabies vaccination, RIG is no longer indicated as the vaccine induced immune response will be effective at that time. ○ Infiltrate as much as possible in and around the wound. ○ It is **no longer** recommended to inject the remainder of the calculated RIG dose at a site distant to the wound. ○ In the case of smaller wounds/areas where it is not possible to infiltrate the entire calculated dose, infiltrate as much as is anatomically feasible in and around the wound site/s without causing compartment syndrome. ○ In case of large and multiple wounds, RIG can be diluted with sodium chloride 0.9% solution if necessary to ensure infiltration of all wounds. ○ Follow with a complete course of vaccine. • Human-derived rabies immunoglobulin (HRIG), IM 20 IU/kg. Infiltrate as much as possible in and around the wound. **OR** • Equine-derived rabies Immunoglobulin (ERIG), IM 40 IU/kg. ○ Only administer ERIG in facilities where anaphylaxis or adverse reactions can be managed (Refer to Section 21.2.10). **Table 21.7:** Summary of regimen for HRIG and ERIG <table><tr><th>Product name</th><th>Max. dose</th><th>Description</th><th>Site of administration</th><th>Schedule</th></tr><tr><td colspan="3">HRIG</td><td rowspan="4">Infiltrate up to the maximum calculated dose in and around the wound site/s. For smaller wounds where it is not possible to infiltrate all of the calculated dose, infiltrate as much as is anatomically feasible in and around the wound site/s.</td><td rowspan="4">On day 0 (when patient presents for first time)/ as soon as possible after exposure to be effective to neutralise virus. When RIG is not available it should be sourced as a matter of urgency. When 7 days have lapsed since initial rabies vaccination, RIG is no longer indicated.</td></tr><tr><td>Rabigam®</td><td>20 IU/kg</td><td>150 IU/mL (Supplied in 2 mL vial)</td></tr><tr><td>KamRAB®</td><td>20 IU/kg</td><td>150 IU/mL (Supplied in 2, 5 and 10 mL vials).</td></tr><tr><td colspan="3">ERIG</td></tr><tr><td>Equirab®</td><td>40 IU/kg</td><td>200 IU/mL (Supplied in 5 mL vial).</td><td></td><td></td></tr></table>*Source: NICD updated human rabies prophylaxis guideline. www.nicd.ac.za*
2.3.1 Immunocompromised individuals	
n/a	Individuals with documented immunodeficiency, such as symptomatic HIV infection, patients with cancer on chemotherapy/radiotherapy, and patients on long-term corticosteroids dosed at 20mg/day for ≥2 weeks, should be evaluated on a case-by-case basis and receive a complete course of PEP including RIG and 4 doses of rabies vaccine in all exposures with direct animal contact. Note: HIV-infected individuals receiving ART who are clinically monitored and well managed are not considered immunocompromised. Such patients have been shown to respond normally to rabies vaccines.
2.3.3 Patients who have received previous PrEP or PEP	
n/a	Patients who have received PEP or PrEP do not require RIG. Only wound treatment is required.

Rabies vaccine and rabies immunoglobulin (RIG) – authorised prescribers: *Guidance clarified*

STG guidance has been updated to clarify that rabies immunoglobulin (RIG) is limited to prescribing by doctors only i.e. categorised as 'doctor prescribed.' Rabies vaccine has been categorised as 'doctor initiated' and any follow up doses as per STG guidance, may be prescribed by all authorised prescribers. Updates to version 1.1 of the STG are as tabulated below:

AMENDED FROM (Ed 2020-4 v1.0):

Rabies immunoglobulin (RIG):

Only indicated for:

- Direct animal contact with breach of skin/ bleeding/ mucosal contact, immunocompetent patients
- Any direct animal contact, immunocompromised patients
- All bat exposures

Patients who have received PEP or PrEP do not require RIG. Only wound treatment is required.

Available from the nearest district hospital.

If not immediately available, source and give as soon as possible.

When 7 days have lapsed since the initial rabies vaccination, RIG is no longer indicated as the vaccine induced immune response will be effective at that time.

Infiltrate as much as possible in and around the wound.

It is **no longer** recommended to inject the remainder of the calculated RIG dose at a site distant to the wound.

In the case of smaller wounds/areas where it is not possible to infiltrate the entire calculated dose, infiltrate as much as is anatomically feasible in and around the wound site/s without causing compartment syndrome.

In case of large and multiple wounds, RIG can be diluted with sodium chloride 0.9% solution if necessary to ensure infiltration of all wounds.

Follow with a complete course of vaccine.

- Human-derived rabies immunoglobulin (HRIG), IM 20 IU/kg. Infiltrate as much as possible in and around the wound.

OR

- Equine-derived rabies Immunoglobulin (ERIG), IM 40 IU/kg. Infiltrate as much as possible in and around the wound.
  Administer ERIG only in facilities where anaphylaxis or adverse reactions can be managed. (Refer to Section 21.2.10).

Product name	Max. dose	Description	Site of administration	Schedule
HRIG			Infiltrate up to the maximum calculated dose in and around the wound site/s. For smaller wounds where it is not possible to infiltrate all of the calculated dose, infiltrate as much as is anatomically feasible in and around the wound site/s.	On day 0 (when patient presents for first time)/ as soon as possible after exposure to be effective to neutralise virus. When RIG is not available it should be sourced as a matter of urgency. When 7 days have lapsed since initial rabies vaccination, RIG is no longer indicated.
Rabigam®	20 IU/kg	150 IU/mL (Supplied in 2 mL vial)		
KamRAB®	20 IU/kg	150 IU/mL (Supplied in 2, 5 and 10 mL vials).		
ERIG				
Equirab®	40 IU/kg	200 IU/mL (Supplied in 5 mL vial).		

Table 21.7: Summary of regimen for HRIG and ERIG
Source: NICD updated human rabies prophylaxis guideline.
www.nicd.ac.za

Rabies vaccination:

Only indicated for direct animal contact.

Patients who have previously been fully immunised or who received PEP more than 3 months ago need only two doses: on Day 0 and Day 3.

Patients who have received previous PEP or PrEP within the previous 3 months do not require vaccination against rabies. Only wound treatment is required.

Available from the nearest district hospital.

AMENDED TO (Ed 2020-4 v1.1)

Rabies immunoglobulin (RIG) – doctor prescribed:

Only indicated for:

- Direct animal contact with breach of skin/ bleeding/ mucosal contact, immunocompetent patients
- Any direct animal contact, immunocompromised patients
- All bat exposures

Patients who have received PEP or PrEP do not require RIG. Only wound treatment is required.

Available from the nearest district hospital.

If not immediately available, source and give as soon as possible.

When 7 days have lapsed since the initial rabies vaccination, RIG is no longer indicated as the vaccine induced immune response will be effective at that time.

Infiltrate as much as possible in and around the wound.

It is **no longer** recommended to inject the remainder of the calculated RIG dose at a site distant to the wound.

In the case of smaller wounds/areas where it is not possible to infiltrate the entire calculated dose, infiltrate as much as is anatomically feasible in and around the wound site/s without causing compartment syndrome.

In case of large and multiple wounds, RIG can be diluted with sodium chloride 0.9% solution if necessary to ensure infiltration of all wounds.

Follow with a complete course of vaccine.

- Human-derived rabies immunoglobulin (HRIG), IM 20 IU/kg (doctor prescribed). Infiltrate as much as possible in and around the wound.

OR

- Equine-derived rabies Immunoglobulin (ERIG), IM 40 IU/kg (doctor prescribed). Infiltrate as much as possible in and around the wound.
  Administer ERIG only in facilities where anaphylaxis or adverse reactions can be managed. (Refer to Section 21.2.10).

Product name	Max. dose	Description	Site of administration	Schedule
HRIG			Infiltrate up to the maximum calculated dose in and around the wound site/s. For smaller wounds where it is not possible to infiltrate all of the calculated dose, infiltrate as much as is anatomically feasible in and around the wound site/s.	On day 0 (when patient presents for first time)/ as soon as possible after exposure to be effective to neutralise virus. When RIG is not available it should be sourced as a matter of urgency. When 7 days have lapsed since initial rabies vaccination, RIG is no longer indicated.
Rabigam®	20 IU/kg	150 IU/mL (Supplied in 2 mL vial)		
KamRAB®	20 IU/kg	150 IU/mL (Supplied in 2, 5 and 10 mL vials).		
ERIG				
Equirab®	40 IU/kg	200 IU/mL (Supplied in 5 mL vial).		

Table 21.7: Summary of regimen for HRIG and ERIG
Source: NICD updated human rabies prophylaxis guideline.
www.nicd.ac.za

Rabies vaccination – doctor initiated:

Only indicated for direct animal contact.

Patients who have previously been fully immunised or who received PEP more than 3 months ago need only two doses: on Day 0 and Day 3.

Patients who have received previous PEP or PrEP within the previous 3 months do not require vaccination against rabies. Only wound treatment is required.

Children – Rabies vaccine, 1 amp, IM anterolateral thigh. Day 0 – single dose Day 3 – single dose Day 7 – single dose Between day 14-28 – single dose Adults – Rabies vaccine, 1 amp, IM deltoid. Day 0 – single dose Day 3 – single dose Day 7 – single dose Between day 14-28 – single dose **CAUTION** Do not administer rabies vaccine into buttocks (gluteus maximus).	Available from the nearest district hospital. Children – Rabies vaccine, 1 amp, IM anterolateral thigh (doctor initiated). Day 0 – single dose Day 3 – single dose Day 7 – single dose Between day 14-28 – single dose Adults – Rabies vaccine, 1 amp, IM deltoid (doctor initiated). Day 0 – single dose Day 3 – single dose Day 7 – single dose Between day 14-28 – single dose **CAUTION** Do not administer rabies vaccine into buttocks (gluteus maximus).

Antibiotic treatment in children - Amoxicillin/clavulanic acid: *Retained*
Dosing guidance on the use of amoxicillin/clavulanate as an 8 hourly regimen has been retained. The 14:1 amoxicillin/calvulanate BD suspension that is currently on tender is not registered for use for animal or human bites. The dose of clavulanate may not be sufficient to provide adequate anaerobe cover that is usually required for bites. The guidance will be reviewed once a more suitable BD suspension formulation is available on tender.

21.3.1.2 HUMAN BITES

Antibiotic treatment in children - Amoxicillin/clavulanic acid: *Retained*
See Section 21.3.1.1 animal bites above.

21.3.1.3 INSECT STINGS, SCORPION STINGS AND SPIDER BITES

Description: *editorial amendment*
Chlorphenamine, oral: *indication amended*
Chlorpheniramine, oral: *caution amended*
Paracetamol – dosing guidance: *amended*
The dose guidance for the use of paracetamol has been aligned to the PHC and AH Pain chapters.

Spiders and scorpions
An editorial amendment to the STG was proposed and supported as follows: 'Most are non-venomous or mildly venomous, but some may be extremely venomous resulting in neurotoxicity and constitute a medical emergency.'

The STG text was editorially amended accordingly for clarity purposes with specific guidance that oral antihistamines should only be used if there is severe itching. The caution against use in children less than 2 years of age was deleted to align with SAMF recommendations[40] and the updated PHC Chp 5 Skin (refer to NEMLC report 2020-23 Section 5.2). Updated STG text for medicine treatment follows on below:

Emergency treatment:
Treat anaphylaxis (bee/wasp stings). See Section 21.2.10: Anaphylaxis.
Local symptoms:
- Calamine lotion, apply when needed.

If severe itch:
Children
- Chlorphenamine, oral, 0.1 mg/kg/dose 6–8 hourly. See dosing table, pg 23.3.

~~**CAUTION**~~
~~Do not give an antihistamine to children < 2 years of age~~.

Adults

[40] South African Medicines Formulary 14th Ed.

- Chlorphenamine, oral, 4 mg, 6–8 hourly.

AND

If there is a wide local response to insect bite with inflamed lesion, see Section 5.10.4: Papular urticaria.

Pain:

Children

- Paracetamol, oral, 10–15 mg/kg/dose 6 hourly when required. See dosing table, pg 23.8.

Adults

- Paracetamol, oral, 500mg -1 g 4–6 hourly when required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

Very painful scorpion stings:

- Lidocaine 2%, 2 mL injected around the bite as a local anaesthetic.
  - Local application of ice, if tolerated.

Cytotoxic lesions:

Avoid giving prophylactic antibiotics for bites and stings.

If secondary skin infection (site red, swollen, hot, tender, pus may be present), manage as cellulitis. See Section 5.4.3: Cellulitis.

Spider bites and scorpion stings:

Tetanus prophylaxis (Z23.5)

If not immunised within the last 5 years:

- Tetanus toxoid vaccine (TT), IM, 0.5 mL.

Contact information: *Added*

Contact information added as for snakebites as tabulated below:

For guidance on the identification and clinical management of snake/spider/scorpion bites, contact:
Poisons Information Helpline: 0861555777

For procurement of snake/spider/scorpion antivenom, contact:
South African Vaccine Producers (SAVP):
Telephone (011) 386 6062/6063/6078 (0ffice hours only) or
Email: Benita.mouton@nhls.ac.za
In the rare event that antivenom needs to be released/procured afterhours:
Tel 071 680 9897

21.3.1.4 SNAKEBITES

Venom in the eyes

Local anaesthetic, ophthalmic drops: *added as a therapeutic class*

Tetracaine 1%, ophthalmic drops: *retained as an example of class in the STG*

Oxybuprocaine 0.4%, ophthalmic drops: *added to the TI database as an example of class*

Aligned with the section 18.8: Surgical and diagnostic products of chapter 8: Eye conditions of the Adult Hospital Level STGs and EML, 2019 edition.

Antivenom

Antivenom: *criteria for administration amended*

The following STG text was accepted for deletion for correctness:

~~All patients with systemic signs and symptoms or severe spreading local tissue damage should receive antivenom.~~

Contact information: *Updated*

Contact information updated as tabulated below:

Amended from:

South African Vaccine Producers (SAVP):
Office hours: (011) 386 6062/6063/6078
After hours: (011) 386 6000 or 071 680 9897

Amended to:

For guidance on the identification and clinical management of snake/spider/scorpion bites, contact:
Poisons Information Helpline: 0861555777

For procurement of snake/spider/scorpion antivenom, contact:
South African Vaccine Producers (SAVP):
Telephone (011) 386 6062/6063/6078 (Office hours only) or
Email: Benita.mouton@nhls.ac.za
In the rare event that antivenom needs to be released/procured afterhours:
Tel 071 680 9897

21.3.2 BURNS

Pain

Paracetamol dosing – adults: *Amended*

The dose guidance for the use of paracetamol in adults has been aligned to the PHC and AH Pain chapters as tabulated below:

Amended from:

Adults

- Paracetamol, oral, 1 g 4–6 hourly when required.
  Maximum dose: 15 mg/kg/dose.

Maximum dose: 4 g in 24 hours

Amended to:

Adults

- Paracetamol, oral, 500mg -1 g 4–6 hourly when required (to a maximum of 4 g in 24 hours).
  Maximum dose: 15 mg/kg/dose.

Septic burns

Povidone iodine, topical: *retained*
Silver sulfadiazine, topical: *not added*
Mupirocin, topical: *not added*
Nano-crystalline dressings: *not added*
Melaleuca alternifolia, topical: *not added*

Refer to scoping review on the Knowledge Hub or included below for further detail.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			

Recommendation: Current standard of care in the STG to be retained – topical povidone iodine for infected burns.
Rationale: No new evidence could be identified for alternative treatment options for septic burns.
Level of Evidence: Low to very low certainty
Review indicator: New evidence sufficient to change the recommendation

NEMLC RECOMMENDATION (MEETING OF 23 JUNE 2022):

NEMLC accepted the review and proposed recommendation, but recommended that the PHC/Adult Hospital Level Committee consider reviewing other dressings for wounds, noting that this topic would be prioritised in the topic prioritisation project plan and may be reviewed in the next review cycle. Furthermore, it was noted that wound dressings are not funded from the Provincial Pharmaceutical budgets.

Monitoring and evaluation considerations

Research priorities

Referral – rehabilitation services: *Added*
In response to the request from RuRehab, the following statement has been added to the list of referral criteria:
"Consider rehabilitation services for reducing the risk of contractures and disfigurement."

21.3.3 EXPOSURE TO POISONOUS SUBSTANCES

Tricyclic poisoning
Sodium bicarbonate, parenteral: *not added*
The proposal to add guidance for tricyclic poisoning to the PHC STGs was not accepted as sodium bicarbonate is not listed on the PHC EML.
Level of Evidence: Expert opinion

Organophosphate and carbamate poisoning – atropinisation: *indication amended*
Atropinisation in this clinical setting should probably only be assessed by monitoring secretions in the chest with improvement of oxygenation. The STG text was amended, accordingly:

Reassess after 3–5 minutes for evidence of atropinisation as indicated by reduced bronchial secretions, ~~dry skin, increasing heart rate and blood pressure, and dilating pupils (note: pupil dilatation may be delayed)~~ improvement of oxygenation and decreased oxygen requirements.

Level of Evidence: Expert opinion

Atropine, IV: *directions for use not amended*
The proposal to include atropine infusion after atropinisation was not accepted for primary level of care. It was considered to be impractical to continuously administer large quantities of 80 x 0.5 mg atropine ampoules at primary level of care. However, it was reported that the emergency fraternity is currently querying the availability of IV atropine with SAHPRA.
Recommendation: Retain bolus dosing of atropine in the PHC STG, until such time that a SAHPRA-registered product is available for IV administration of atropine. However, IV infusion of atropine could be considered for inclusion in the Adult Hospital Level STGs and EML.
Level of Evidence: Expert opinion

Opioid overdose
Naloxone, IV: *directions for use amended*
Dosing of naloxone in children was simplified and aligned with the Paediatric Hospital Level STG and expert opinion. Sivilotti (2016)[41] mentions that naloxone for the reversal of respiratory depression, after adequate management of airway and breathing, should be used early in the resuscitation algorithm.
Level of Evidence: Expert opinion

Amended from:

- Naloxone, IV (preferable) or IM

Age and weight	Initial dose (IV/IM)	**Repeat dose:** Reassess every 2 minutes. If breathing still inadequate, give further naloxone every 2–3 minutes.
Children:		
< 5 years or ≤ 20 kg	– 0.1 mg/kg immediately (maximum 2 mg/dose)	Repeat 0.1mg/kg (maximum 2 mg/dose), up to total dose of 10 mg.
≥ 5 years or > 20 kg	– 0.4–2mg immediately	Repeat 0.1mg/kg (maximum 2mg/dose), up to total dose of 10 mg
Adults:		
Adults	– 0.4–2 mg immediately	Double the dose each time (e.g.: 0.8mg, 2mg, 4 mg), up to total dose of 10 mg.

  - Naloxone has a short duration of action (45 minutes) - continue to monitor closely as further doses of naloxone may be needed while awaiting and during transport.
  - In patients addicted to opioids, naloxone may precipitate an acute withdrawal syndrome after several hours. This must not prevent the use of naloxone.
  - Refer all patients

[41] Sivilotti ML. Flumazenil, naloxone and the 'coma cocktail'. Br J Clin Pharmacol. 2016 Mar;81(3):428-36. https://pubmed.ncbi.nlm.nih.gov/26469689/

Amended to:

- Naloxone, IV (preferable) or IM

	Initial dose (IV/IM)	Repeat dose: Reassess every 2 minutes. If breathing still inadequate, give further naloxone every 2–3 minutes.
Children	– 0.1 mg/kg immediately	Repeat 0.1 mg/kg (maximum 2 mg/dose), up to total dose of 10 mg.
Adults	– 0.4 mg immediately	Double the dose each time (e.g.: 0.8 mg, 2 mg, 4 mg), up to total dose of 10 mg.

- Naloxone has a short duration of action (45 minutes) - continue to monitor closely as further doses of naloxone may be needed while awaiting and during transport.
- In patients addicted to opioids, naloxone may precipitate an acute withdrawal syndrome after several hours. This must not prevent the use of naloxone.
- Refer all patients.

Paracetamol poisoning

N-acetylcysteine, oral: *dose not amended*

Oral dose of N-acetylcysteine was confirmed to be correct - NEMLC-approved in the previous review cycle of the Adult Hospital Level STGs and EML, 2019 – see NEMLC report below:

NEMLC report for the Adult Hospital Level Emergencies and injuries chapter (2017-9 review cycle):

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[42] [43] [44]

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

Toxic alcohol (ethylene glycol and methanol) poisoning

Ethanol: *loading doses not added*

Guidance for alcohol and toxic alcohol poisoning was not considered appropriate for inclusion in the Primary Healthcare STG as management is complex and not pragmatic for primary level of care. However, a cross-referral could be made to the Adult hospital Level STGs and EML.

21.3.6.1 POST EXPOSURE PROPHYLAXIS, OCCUPATIONAL

PEP for healthcare workers following hepatitis B exposure

Hepatitis B Immunoglobulin: *amended*

Aligned with the National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020[45] - STG text was updated as follows:

Vaccination status and antibody response status of HCW	Source patient			
	Vaccination status	**HBsAg positive**	**HbsAg negative**	**HBsAg unknown**
	Unvaccinated or vaccination incomplete	• HBIG, IM, 500 units* • Hep B vaccine (3 doses at monthly intervals)	• Initiate Hep B vaccination (month 0, 1 and 6)	• HBIG, IM, 500 units* • Hep B vaccine (3 doses at monthly intervals)
	Vaccinated **AND** known to have HBsAb	No treatment	No treatment	No treatment

[42] 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

[43] 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

[44] 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

[45] National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020. https://www.knowledgehub.org.za/elibrary/national-clinical-guidelines-post-exposure-prophylaxis-pep-occupational-and-non

	>10 units/mL#			
	Vaccinated **AND** HBsAb <10 units/mL or level unknown	• HBIG, IM, 500 units * • If HBIG <10 units/mL, repeat HBIG at 1 month • Repeat Hep B vaccine (3 doses at monthly intervals)	No treatment	• HBIG, IM, 500 units* • If HBIG <10 units/mL, repeat HBIG at 1 month • Repeat Hep B vaccine (3 doses at monthly intervals)

Delay in obtaining HBsAb results

Time period of delay: *amended*

Aligned with the National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020[46]- STG text was updated as follows:

If the delay in obtaining HBsAb results is more than ~~24 hours~~ 7 days initiate treatment as for vaccinated AND HBsAb < 10 units/mL.

21.3.6 POST EXPOSURE PROPHYLAXIS

21.3.6.1 POST EXPOSURE PROPHYLAXIS, OCCUPATIONAL

General measures: *Editorial amendment*

An editorial amendment was made as follows for improved clarity:

Where the source patient is on ARVs or has been on ARVs, initiate prophylaxis and seek expert opinion. An extra blood sample (unclotted, EDTA) of the source patient should be stored in case of need for further ~~viral~~ resistance testing.

Adverse effects of PEP: *Guidance amended*

Guidance on when consultation with a virologist or infectious disease specialist is recommended, has been amended as tabulated below:

Amended from:

Note: Adverse effects of PEP:

» PEP is generally not well tolerated. Adverse effects occur in about half of cases and therapy is discontinued in about a third. Efavirenz is not recommended as it is very poorly tolerated in PEP.

TDF is contra-indicated in renal disease or with concomitant use of nephrotoxic medicines, e.g. aminoglycosides (check baseline creatinine clearance). Where TDF is contraindicated, switch to AZT. If AZT is not tolerated, consult or refer for further management.

» Zidovudine often causes nausea and headache and so should only be given if TDF is contraindicated.

If dolutegravir is not tolerated, give ATV/r as the first choice protease inhibitor as LPV/r frequently causes gastrointestinal side effects. ATV/r may commonly cause jaundice (i.e. unconjugated hyperbilirubinaemia without hepatitis) which is harmless.

When the source patient is known to be on a failing ART regimen, modify the PEP regimen

- If the patient is on AZT or stavudine then TDF should be used.
- If the patient is on TDF then AZT should be used.
- If the patient is on efavirenz or nevirapine then ATV/r or LPV/r should be used.

Patients on a failing second line ART regimen almost always have no resistance to protease inhibitors, so ATV/r or LPV/r should still be effective.
Consultation with a virologist or infectious diseases physician is recommended for advice on which antiretroviral medicines to use for PEP.

Amended to:

Note: Adverse effects of PEP:

» PEP is generally not well tolerated. Adverse effects occur in about half of cases and therapy is discontinued in about a third. Efavirenz is not recommended as it is very poorly tolerated in PEP.

» TDF is contra-indicated in renal disease or with concomitant use of nephrotoxic medicines, e.g. aminoglycosides (check baseline creatinine clearance). Where TDF is contraindicated, switch to AZT. If AZT is not tolerated, consult or refer for further management.

» Zidovudine often causes nausea and headache and so should only be given if TDF is contraindicated.

» If dolutegravir is not tolerated, give ATV/r as the first choice protease inhibitor as LPV/r frequently causes gastrointestinal side effects. ATV/r may commonly cause jaundice (i.e. unconjugated hyperbilirubinaemia without hepatitis) which is harmless.

» If the source patient is known to be on a failing ART regimen, modification of the PEP regimen may be required. Consultation with a virologist or infectious diseases physician is recommended for advice on which antiretroviral medicines to use for PEP

[46] National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020. https://www.knowledgehub.org.za/elibrary/national-clinical-guidelines-post-exposure-prophylaxis-pep-occupational-and-non

» If the patient is on AZT or stavudine then TDF should be used.

» Patients on a failing second line ART regimen almost always have no resistance to protease inhibitors, so ATV/r or LPV/r should still be effective.

21.3.6.2 POST EXPOSURE PROPHYLAXIS, RAPE AND SEXUAL ASSAULT

HIV PEP – guidance for children: *Amended*

Guidance on the use of PEP in children has been amended to include a dolutegravir based regimen in line with the South African HIV Clinicians Society Guidelines for PEP[47] as tabulated below:

Amended from:

Children

- Zidovudine (AZT), oral, 12 hourly for 28 days.
  Paediatric dose: 180–240 mg/m2. See dosing table, pg 23.9.
  Maximum: 300 mg/dose.

AND

- Lamivudine (3TC), oral, 4 mg/kg 12 hourly or 8mg/kg daily for 28 days.
  Maximum: 150 mg/dose if given 12 hourly or 300 mg/dose if given daily. See dosing table, pg 23.6.

AND

- Lopinavir/ritonavir (LPV/r), oral 12 hourly for 28 days.
  Paediatric dose: 300/75mg/m2. See dosing table, pg 23.7.
  Maximum: 400/100 mg/dose.

Dosages may vary by±1 mg/kg/dose, to allow a convenient volume of medication.
Use the adult dosage regimen if children require more than the maximum dose.
Follow-up visits should be at 2 weeks, 6 weeks, and 4 months after the rape.

Adults

Management for HIV prevention is the same as for occupational HIV exposure. See section 21.3.6.1 Post-exposure prophylaxis, occupational.

Amended to:

Children <10 years and < 30kg

- Zidovudine (AZT), oral, 12 hourly for 28 days.
  Paediatric dose: 180–240 mg/m2. See Section 23: Standard Paediatric dosing tables.
  Maximum: 300 mg/dose.

AND

- Lamivudine (3TC), oral, 4 mg/kg 12 hourly or 8mg/kg daily for 28 days.
  Maximum: 150 mg/dose if given 12 hourly or 300 mg/dose if given daily. See Section 23: Standard Paediatric dosing tables.

AND

- Dolutegravir (DTG), oral, for 28 days.
  For dosing guidance, see Section 23: Standard Paediatric dosing tables.

Dosages may vary by±1 mg/kg/dose, to allow a convenient volume of medication.
Use the adult dosage regimen if children require more than the maximum dose.
Follow-up visits should be at 2 weeks, 6 weeks, and 4 months after the rape.

Adults and children ≥ 10 years and ≥ 30 kg

Management for HIV prevention is the same as for occupational HIV exposure. See section 21.3.6.1 Post-exposure prophylaxis, occupational.

HIV PrEP: *added as a cross reference to the PHC STGs and EML*

For patients at ongoing high risk of HIV acquisition, guidance was provided to transition from PEP to PrEP as follows:

HIV PrEP

If patient is at ongoing high risk of HIV acquisition, commence PrEP after PEP has been completed.
Perform HIV test 4-weeks after initiating PrEP.

[47] Horak J, Venter WDF, Wattrus C, Papavarnavas N, Howell P, Sorour G, Wallis C, Gill K, Conradie F, Bekker LG. Southern African HIV Clinicians Society 2023 Guideline for post-exposure prophylaxis: Updated recommendations. South Afr J HIV Med. 2023 Sep 28;24(1):1522. doi: 10.4102/sajhivmed.v24i1.1522. PMID: 37795431; PMCID: PMC10546897.

Emergency contraception
Copper IUCD: *added (as first line option)*
Levonorgestrel, oral: *retained (as 2nd line option)*

Copper IUCD placed as the first line option as this agent has less drug-drug interactions compared to oral levonorgestrel 1.5mg and is the agent of choice for obese women. Copper IUCD can also be used as a long-acting reversible contraceptive.[48] [49]

Emergency contraception for obese women
Levonorgestrel, oral: *dose not amended*
An external comment was received that there is no need to double the dose of levonorgestrel for obese women for emergency contraception. Limited data suggests that obese women have an increased risk of pregnancy after use of levonorgestrel and ulipristal acetate emergency contraception compared to those who are not obese.[50] In a pharmacokinetic study with 10 participants, levonorgestrol Cmax in obese participants was half that achieved in participants with normal BMI, and doubling the levonorgestrol dose in obese participants resulted in a similar Cmax to that seen in those with normal BMI[51]. Faculty of Sexual & Reproductive Healthcare (FSRH) Overweight, Obesity and Contraception Guidelines of April 2019, therefore recommends "double-dose (3 mg) of levonorgestrel emergency contraception, if BMI >26 kg/m2 or weight >70 kg". However, the effectiveness of double-dosing in preventing pregnancy is unknown.[52] In a randomised pharmacodynamic study with 70 obese participants, doubling the levonorgestrol dose did not result in improved inhibition of ovulation: proportion of women with no follicle rupture within 5 days of levonorgestrol administration was similar with standard and double dosing.[53] This suggests that doubling the dose may not be sufficient to improve the efficacy of oral levonorgestrol in obese women, although this study did not directly explore the effect of double dosing on subsequent rates of pregnancy. Therefore, until new evidence emerges the recommendation of double-dosing of levonorgestrel amongst obese/overweight women will be retained, aligned with Guidelines. Available evidence also suggests that the effectiveness of the copper IUCD is not affected by body weight or BMI. The copper IUCD is therefore the preferred method for emergency contraception in the obese.[54]
Level of Evidence: Guidelines

The caution box in the STG was amended as follows:

CAUTION
Emergency contraceptive tablets must be taken as soon as possible, preferably within 72 hours of unprotected intercourse, and not later than 5 days.
Enzyme inducers (including efavirenz and carbamazepine) cause a significant reduction in levonorgestrel concentrations.
Women on these medicines should preferably have copper IUCD inserted **or** alternatively double the dose of levonorgestrel.
Women > 80 kg or BMI ≥ 30 should also preferably have copper IUCD inserted **or** alternatively double the dose of levonorgestrel.

STI prophylaxis for pregnant women
Ceftriaxone, IM: *retained*
Azithromycin, oral: *retained*
Metronidazole, oral: *retained*
Cefixime, oral: *not added*

[48] FSRH Guideline (April 2019) Overweight, Obesity and Contraception. BMJ Sex Reprod Health. 2019 Apr;45(Suppl 2):1-69. https://pubmed.ncbi.nlm.nih.gov/31053605/
[49] Turok DK, Jacobson JC, Dermish AI, Simonsen SE, Gurtcheff S, McFadden M, Murphy PA. Emergency contraception with a copper IUD or oral levonorgestrel: an observational study of 1-year pregnancy rates. Contraception. 2014 Mar;89(3):222-8. https://pubmed.ncbi.nlm.nih.gov/24332433/
[50] Jatlaoui TC and Curtis KM. Safety and effectiveness data for emergency contraceptive pills among women with obesity: a systematic review. Contraception 94 (2016) 605–611. https://www.ncbi.nlm.nih.gov/pubmed/27234874
[51] Edelman AB, Cherala G, Blue SW, Erikson DW, Jensen JT. Impact of obesity on the pharmacokinetics of levonorgestrel-based emergency contraception: single and double dosing. Contraception. 2016 Jul;94(1):52-7. https://pubmed.ncbi.nlm.nih.gov/27000996/
[52] FSRH Guideline (April 2019) Overweight, Obesity and Contraception. BMJ Sex Reprod Health. 2019 Apr;45(Suppl 2):1-69. https://pubmed.ncbi.nlm.nih.gov/31053605/
[53] Edelman, Alison B. MD, MPH; Hennebold, Jon D. PhD; Bond, Kise PSM; Lim, Jeong Y. PhD; Cherala, Ganesh PhD; Archer, David F. MD; Jensen, Jeffrey T. MD, MPH Double Dosing Levonorgestrel-Based Emergency Contraception for Individuals With Obesity, Obstetrics & Gynecology: June 9, 2022 - Volume - Issue - 10.1097/AOG.0000000000004717 doi: 10.1097/AOG.0000000000004717
[54] Turok DK, Jacobson JC, Dermish AI, Simonsen SE, Gurtcheff S, McFadden M, Murphy PA. Emergency contraception with a copper IUD or oral levonorgestrel: an observational study of 1-year pregnancy rates. Contraception. 2014 Mar;89(3):222-8. https://pubmed.ncbi.nlm.nih.gov/24332433/

Erythromycin, oral: *not added*
Spectinomycin, parenteral: *not added*
STI prophylaxis for pregnant women is the same as for non-pregnant women, aligned with the PHC STI chapter, Section 12.1.2: Sexually active women. It is noted that the NDoH PEP Guidelines[55] has outdated recommendations (cefixime, erythromycin and spectinomycin) which will be communicated to the relevant NDoH Program.

21.3.7 SOFT TISSUE INJURIES

Paracetamol dosing – adults: *Amended*
The dose guidance for the use of paracetamol has been aligned to the PHC and AH Pain chapters and as detailed under Section 21.3.2 burn above.

Referral for patients with haemophilia: *Not added*
External comment received from RuRehab to refer persons with haemophilia for rehabilitation was not supported as these patients are usually under the care of specialised haemophilia centres with responsibility for directing further referrals accordingly. EML guidance of the management of haemophilia is included in the AH Chp 2: BBFO.

21.3.8 SPRAINS AND STRAINS

Paracetamol dosing – adults: *Amended*
The dose guidance for the use of paracetamol has been aligned to the PHC and AH Pain chapters and as detailed under Section 21.3.2 burn above.

Referral – rehabilitation services: *Added*
In response to the request from RuRehab, the following statement has been added to the list of referral criteria: *"Consider rehabilitation services for sprains, strains, and overuse injuries to improve joint stability and assist with pain management."*

[55] National Department of Health. National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020. https://www.knowledgehub.org.za/elibrary/national-clinical-guidelines-post-exposure-prophylaxis-pep-occupational-and-non

South African National Essential Medicine List
Primary Healthcare/ Adult Hospital Level of Care Medication Review Process
Component: Emergencies and injuries

MEDICINE REVIEW

1. Executive Summary

Date: 18 August 2022
Medicine (INN): Olanzapine (IM, orodispersible)
Medicine (ATC): N05AH03
Indication (ICD10 code): Delirium F05.0/.1/.8/.9
Patient population: Adults with delirium who are agitated or considered a risk to themselves or others, and non-pharmacological measures are ineffective.
Prevalence of condition:
South African studies
- 12.3% of acute medical inpatients (Du Plooy, 2020)[1]
- 17.6% of acutely admitted people with HIV (Day, 2021)[2]

International studies
- Approximately 20% of general adult inpatients and 80% of mechanically ventilated patients in ICU (Nikooie, 2019)[3]

Level of Care: Primary Healthcare
Prescriber Level: Doctor prescribed
Motivator/reviewer name(s): Lesley Robertson, Shelley McGee, Tamara Kredo, Natasha Gloeck, Mashudu Mthethwa, Trudy Leong
PTC affiliation: Lesley Robertson affiliated to Sedibeng District PTC, Gauteng

Key findings

- We conducted a review of Clinical practice guidelines, health technology assessments, systematic reviews of randomised controlled trials (RCTs), RCTs and where necessary systematic reviews of non-randomised/ observational studies or observational studies. Ongoing trials were also sought.
- Two systematic reviews, three RCTS and three clinical guidelines were identified, including comparisons of interest.
- All three clinical guidelines were of relatively high quality assessed against AGREE II. Only one makes a weak recommendation for olanzapine for the treatment of delirium
- Comparison of olanzapine to placebo, was reported in one clinical trial, which rated poor in terms of quality, as part of a systematic review. The impact of olanzapine on duration of delirium (days) was uncertain (MD=-2.4, 95% CI 3.51,-1.29, n = 103, 1 trial. Change in delirium severity, appeared to favour olanzapine (reduction in the delirium rating scale (DRS) MD = -11.1, 95% CI 15.51 to -7.69, n=103, 1 trial.
- For comparison of olanzapine versus haloperidol, change in delirium severity results were reported in most studies however these were at different time points and using different measures. Overall, there was no difference in delirium severity between olanzapine and haloperidol (generally very low to low certainty of evidence). Duration of delirium (days) did not differ significantly between haloperidol and olanzapine, in 1 trial, included in a systematic review (mean Difference (MD) 0.62 days, 95% CI 0.06 to 1.18).
- No reviews nor trials were identified comparing olanzapine to benzodiazepines in the treatment of delirium.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:

	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
Type of recommendation				X	

Recommendation: The PHC/ Adult Hospital Level Committee suggests using olanzapine (orodispersible and parenteral formulations) as an option to manage delirium where non-pharmacological management is not sufficient and if haloperidol, intramuscular formulation is unavailable
Rationale: Available low-quality evidence shows that olanzapine is comparable to haloperidol.
Level of Evidence: Low to very low certainty evidence

Review indicator: Evidence of harm, efficacy
NEMLC RECOMMENDATION (20 OCTOBER 2022 MEETING): NEMLC recommended the use of olanzapine oro-dispersible tablet or IM injection for delirium with agitated and acutely disturbed behaviour. Once the patient is able to swallow, to continue with oral haloperidol or olanzapine, until behaviour is contained.
Monitoring and evaluation considerations
Research priorities

2. **Name of author(s)/motivator(s)**
   Lesley Robertson, Tamara Kredo, Mashudu Mthethwa, Natasha Gloeck, Shelley McGee, Trudy Leong

3. **Author affiliation and conflict of interest details**
   - Lesley Robertson, Department of Psychiatry, University of the Witwatersrand: no conflicts of interest related to olanzapine
   - Tamara Kredo, Cochrane South Africa, South African Medical Research Council; Division of Clinical Pharmacology, Department of Medicine, and Division of Epidemiology and Biostatistics, department of Global Health, Stellenbosch University: no conflicts of interest related to olanzapine
   - Mashudu Mthethwa, Cochrane South Africa, South African Medical Research Council: no conflicts of interest related to olanzapine
   - Natasha Gloeck, Cochrane South Africa, South African Medical Research Council: no conflicts of interest related to olanzapine
   - Shelley McGee, Ophthalmological Society of South Africa: no conflicts of interest related to olanzapine
   - Trudy Leong, Right-To-Care as Secretariat-support to PHC/ Adult Hospital Level Committee of the National Essential Medicines List, NDoH: no conflicts of interest related to olanzapine

4. **Introduction/ Background**
   The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5)[4] describes delirium as an acute disturbance in attention, awareness (reduced orientation to the environment), and cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception). It develops within hours to days and tends to fluctuate during the day, worsening in the evenings. Delirium may be 'hyperactive', with increased mood lability, agitation, and/or uncooperative behaviour, or 'hypoactive', with poor responsiveness and stupor.

   Delirium is a physiological consequence of another medical condition, substance intoxication or withdrawal, exposure to a toxin, or multiple aetiologies. Treatment of delirium necessitates treatment of the underlying cause. Non-pharmacological measures to reduce confusion include a calm, predictable care environment, effective communication, verbal reorientation, and maintenance of the circadian rhythm. Medicine management of agitation, distress, or uncooperative behaviour may be necessary to facilitate nursing and treatment of the underlying condition. Currently, haloperidol, IM is recommended if non-pharmacological measures are insufficient. Haloperidol IM 5mg/ml and 20mg/2ml were discontinued in South Africa by Pfizer and supply has been erratic.

5. **Purpose/Objective i.e., PICO question**:
   - **Population**
     People ≥18 years treated for delirium (formally diagnosed using a validated tool) or sub-syndromal delirium (presence of some delirium symptoms) in an acute care (e.g., primary health clinic/ community health clinic/ hospital emergency room, medical or surgical ward), intensive care, or palliative care setting. Exclude studies solely focusing on people with substance intoxication or withdrawal or people in psychiatric care settings.
   - **Intervention**
     Olanzapine IM and orodispersible tablets, any dose
   - **Comparators**
     Haloperidol IM +/- promethazine IM, any dose

Benzodiazepines: any dose, given orally or IM
Placebo

- **Outcomes**

  Efficacy
  - Duration of delirium (days)
  - Change in delirium severity, assessed by validated instruments.
  - Change in agitation score
  - Delirium resolution (defined as reduction of delirium rating scale below a target set by the authors or complete resolution of symptoms)
  - Use of physical restraint
  - Other – hospital/ intensive care unit (ICU) length of stay (days), hospital discharge disposition (e.g., rehabilitation, chronic care facility, home), health-related quality of life (as reported by study authors)

  Safety
  - Extrapyramidal side effects (EPS); use of anticholinergic medication
  - Adverse events as defined by the study authors (e.g., prolongation of the QTc interval, sudden cardiac death, cerebral vascular events, seizures, extrapyramidal effects, long-term cognitive impairment (e.g., change in Mini Mental Status Exam or as reported by study authors))
  - Mortality

- **Study types**

  Clinical practice guidelines, health technology assessments, systematic reviews of randomised controlled trials (RCTs), RCTs and, if the latter is unavailable, systematic reviews of non-randomised/ observational studies or observational studies. Ongoing trials were also sought.

Methods:

a. **Data sources**:
   Clinical Practice Guidelines sources searched were the Guidelines International Network (GIN) Library, the National Institute for Health and Care Excellence (NICE) and the British Association of Clinical Pharmacology, as well as relevant clinical practice guidelines from Australia, New Zealand and Canada on their government websites, searched via Google. Systematic reviews and randomised controlled trials were sought in PubMed, the Cochrane Library, and Epistemonikos.

b. **Search strategy –** A search strategy was developed for PubMed and adapted to other databases (Appendix 1). A search for systematic reviews and RCTs was conducted on PubMed, the Cochrane Library, and Epistemonikos on 4 March 2022 (Appendix 1). The search was inclusive of all populations (with acute agitation or delirium) as the two review topics were happening in parallel and this was most efficient approach for searching and screening.

Screening, data extraction and analysis, evidence synthesis: Records were uploaded into the reference management software, COVIDENCE. Titles and abstracts were screened independently and in duplicate (NG, MM, TK, LR). Thereafter, full text screening was done by two reviewers, including tagging the study design (RCT or SR) and the population (delirium or acute agitation) and checked by a third reviewer. Discrepancies were discussed with LR and TK to finalise selection. We took a step-wise approach, screening for systematic reviews first and then for RCTs. Data extraction for included reviews was done by one reviewer and checked by a second reviewer. Eligible clinical guidelines were appraised with the AGREE II tool by two reviewers (MM and NG). Eligible systematic reviews were appraised using the AMSTAR II Checklist, and eligible RCTs were assessed for Risk of Bias using the Cochrane's RoB 2.0 Tool. Data was extracted into Characteristics of Included studies tables (tables 2 and 3). For dichotomous outcomes, we reported risk ratios (RR) with 95% confidence intervals (CI). We reported results from the review or trial where possible. Despite the intervention in these studies being haloperidol, and olanzapine being the comparator, outcomes of results were not reanalysed in RevMan to align with the review

question as denominators for the systematic reviews were not available and we wanted to keep the results standardised. Where available, we reported on the GRADE (level of certainty) of the evidence.

c. Excluded studies: Reasons for excluding full-texts were agreed in duplicate with a third reviewer finalizing any disputes.

Results:

1. Search results

We searched PubMed, Epistemonikos and the Cochrane Library on 4 March 2022. We identified 778 records which were imported for screening, with 147 duplicates removed. Furthermore, three records were identified from experts in the field and three were identified through reference searching. We screened 636 abstracts, of which 541 were irrelevant. 95 full-text studies were assessed for eligibility; 86 studies were excluded. There were nine included studies: two systematic reviews, three RCTs and four ongoing studies.

The Prisma Flow Chart is available in Appendix 2.

2. Description of included clinical guidelines, systematic reviews and RCTs

Table 1 reports a summary of the guidelines, Table 2 reports the main characteristics and outcomes of the included systematic reviews, and Table 3 reports the main characteristics and outcomes of included randomised controlled trials. Appendix 2 describes the excluded studies and Appendix 3 provides a summary of ongoing trials.

2.1. Clinical guidelines:

We identified three guidelines

1. National Institute for Health and Care Excellence (NICE). Delirium: diagnosis, prevention and management[6]
2. Scottish Intercollegiate Guidelines Network (SIGN). Risk reduction and management of delirium[7]
3. Victorian Government Department of Human Services. Clinical practice guidelines for the management of delirium in older people[8]

Following appraisal with AGREE II, all three were assessed as moderate to good quality (see Table 1). The NICE guideline was first issued in July 2010, and updated in March 2019. This guideline offers guidance around modifiable risk factors to identify people at risk of developing acute delirium, diagnosis of delirium in long-term, critical and acute care settings, and pharmacological as well as non-pharmacological interventions for reducing delirium incidence and consequences, and reducing the severity, duration and consequences of delirium in adults (18 years and older) in a hospital or long-term residential care. This guideline had an overall AGREE II score of 83%. Of note is that olanzapine was removed from the updated NICE guideline (2019), as haloperidol now has UK marketing authorisation for delirium treatment (though, discontinued from the South African market).

The SIGN delirium guideline was first published in March 2019. This guideline provides guidance for reducing the risk of delirium, as well as the detection, assessment, treatment and follow up of adults with delirium in all settings (patient homes, long term care, hospitals, and hospices). This guideline had an overall AGREE II score of 67%.

The Victorian Government Department of Human Services' guideline for the management of delirium in older people was published in 2006 and provides recommendations in the assessment and management of older people (65 years and older, or 45 years and older in in Aboriginal and Torres Strait Islander people) in Australia in hospitals, and across healthcare settings, as well as the prevention of delirium in at-risk older people, identifying and defining appropriate health service provision and management options to ensure the best possible health outcomes. This guideline had an overall AGREE II score of 83%.

Recommendations related to this review (olanzapine vs haloperidol) are summarized in Table 1. Domain scores for the AGREE II Appraisals can be found in Appendix 3.

Table 1: Summary of Guidelines and AGREE II scores

Name	Recommendation	AGREE II
National Institute for Health and Care Excellence (NICE). **Delirium: diagnosis, prevention and management**	The NICE group recommends that if a person with delirium is distressed or considered a risk to themselves or others and verbal and non-verbal de-escalation techniques are ineffective or inappropriate, consider giving short-term (usually for 1 week or less) *haloperidol or olanzapine*, starting at the lowest clinically appropriate dose and titrating cautiously according to symptoms (conditional, very low certainty evidence) In the most recent review of this guidance (2019) olanzapine was removed as a treatment option in favour of haloperidol, which had achieved authorisation for the indication of delirium in the United Kingdom.	83%
Scottish Intercollegiate Guidelines Network (SIGN). **Risk reduction and management of delirium**.	The SIGN group states "Because the studies identified are underpowered, larger trials are needed before recommendations can be made on the use of antipsychotics for the treatment of patients in ICU with delirium." (1++ - High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias)	67%
Victorian Government Department of Human Services. **Clinical practice guidelines for the management of delirium in older people.**	The Victorian Government Department of Human services recommends that antipsychotic medication should only be used for the treatment of severe behavioural disturbances and or severe emotional disturbances when there is clear intent for its use (e.g. severe agitation interfering with sleep-wake cycle). When used, "Titrated antipsychotics need to be closely monitored by nursing and medical staff. The dosage and frequency should be titrated carefully against the level of agitation at each review. Titration must commence from a low dose typically commencing with the equivalence of 0.25-0.50mg of haloperidol; olanzapine 2.5 mg orally; or risperidone 0.25 mg orally." (III-2 – a comparative study with concurrent controls (non-randomised experimental trial, cohort study, case-control study, interrupted time-series with a control group))	83%

2.2 Systematic reviews

We identified two systematic reviews for inclusion

1. Finucane 2020. Drug therapy for delirium in terminally ill adults[9]
2. NICE Review within the NICE guideline[6]

Finucane 2020[9], a Cochrane Systematic Review, reviewed evidence of pharmacological therapy for delirium management in terminally ill adults (including terminal agitation, distress or restlessness). The setting was not specified. The NICE review[6] reviewed delirium management in hospitalized participants (age 18 years or older) regardless of whether in a surgical, medical, ICU and emergency ward, mental health settings, and long-term care settings. In both reviews, delirium was defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5 or earlier criteria).

Primary outcomes assessed in Finucane 2020 were 1) delirium symptoms within 24 to 48 hours, 2) agitation score within 24 to 48 hours and 3) the number of adverse events (including extrapyramidal side effects). Secondary outcomes included 1) the use of any rescue medication (such as midazolam), 2) cognitive status and 3) survival.

Primary outcome measures in the NICE review were 1) duration of delirium and 2) number recovered from delirium. The secondary outcomes included 1) severity of delirium, 2) length of stay, 3) incidence of cognitive impairment or dementia, 4) number of patients in hospital discharged to new long-term care placement, 5) mortality, 6) number of patients with persisting delirium, 7) quality of life (patient), 8) quality of life (carer), and

9) adverse effects associated with the intervention (including extrapyramidal side effects). Outcome results are summarised in Table 2.

There was only one included RCT (Lin 2008) in Finucane 2020 that compared haloperidol to olanzapine. The full text for the included RCT was not found despite extensive searching (searching online databases, contacting trial and review authors). Two outcomes of interest were reported in this RCT and are further detailed in Table 2.
Within the NICE review, olanzapine was considered in two comparisons: olanzapine versus no treatment (one RCT, Hu 2006 – 103 participants, full text not available for review) and haloperidol versus olanzapine (Hu 2006 and Skrobik 2004, Skrobik 2004 is summarized below under the RCTs, Table 3). Finucane 2020 had a moderate AMSTAR II rating. The quality was marked down as authors did not explain their selections of study designs included in the review. The NICE review had a high AMSTAR II rating of 4. GRADE evidence ratings are summarized in Table 2.

2.3 RCTs

We identified three randomised controlled trial for inclusion

1. Skrobik 2004. Olanzapine vs haloperidol: treating delirium in a critical care setting[10]
2. Jain 2017. Comparison of efficacy of haloperidol and olanzapine in the treatment of delirium[11]
3. Van der Vorst 2020. Olanzapine versus haloperidol for treatment of delirium in patients with advanced cancer: a phase III randomized clinical trial[12]

The trials were conducted in three countries (Canada (one site), India (one site) and The Netherlands (five sites)). Sample sizes varied from 73 to 100 participants and took place in a medical-surgical ICU (Skrobik 2004[10]), medical emergency wards (Jain 2017[11]) and a medical oncology ward or high-care hospice facility (van der Vorst 2020[12]). All three trials compared haloperidol to olanzapine. In Skrobik 2004, participants were randomised to haloperidol, initiated at 2.5 to 5mg 8 hourly (either orally or via an enteral tube) or olanzapine at 5mg daily. Older patients (60 years and above) received a lower starting dose (haloperidol 0.5 to 1mg, olanzapine 2.5mg). Titration thereafter was based on clinician judgment. In Jain 2017, the mean daily doses of olanzapine and haloperidol were 5.49mg (range 2.5mg) and 2.10mg (range 1 to 5mg) respectively. Doses were determined by the participants' Memorial Delirium Assessment Scale (MDAS) score. In van der Vorst 2020, dosing was age-adjusted and based on clinical practice guidelines. Patients under 75 years old were started on haloperidol 1mg or olanzapine 5mg. This was titrated every 40min for haloperidol and two hours for olanzapine, according to the delirium observation scale (DOS) to a maximum on day 1 of 20mg po or 10mg subcutaneously (sc) for haloperidol, and 20mg po or IM for olanzapine. The doses were halved for patients 75 years and older.

Jain 2017 reported on duration of delirium (days). Skrobik 2004, Jain 2017 and van der Vorst 2020 reported on change in delirium sensitivity – however, the three trials used different instruments of measuring this outcome and so we could not compare in meta-analysis (Skrobik 2004 used change in delirium index scores, Jain 2017 used mean MDAS scores at baseline and at the end of the study period, and van der Vorst used delirium response rate (DRR) as defined by Delirium Rating Scale-R-98 (DRS-R-98) assessment). Van der Vorst 2020 reported on delirium resolution (days). In terms of safety outcomes, Skrobik 2004 and van der Vorst 2020 reported on extrapyramidal side effects. Jain 2017 and van der Vorst 2020 reported on adverse events.

Two of the trials (Skrobik 2004 and Jain 2017) were rated as having a high risk of bias. Skrobik 2004 was rated high due to quasi-randomization of allocation sequence and baseline differences between allocation groups, no information around participant blinding and effects of assignment, no information around a prespecified plan or protocol. Jain 2017 was rated high due to this being a single-blind study, limited information on statistical methods, no information around data available for all participants and missingness, potential bias from researchers not being blinded, and no information around a pre-specified analysis plan. Van der Vorst 2020 was rated as having some concerns of bias due to no information around pre-specified plan or protocol.

3. Description of excluded studies

We excluded 86 full texts – 41 for wrong indication, 16 were awaiting classification, 10 for wrong study design, 7 for wrong intervention, 5 for wrong patient population, 3 for wrong outcomes, 3 for wrong language and 1 registered trial was stopped with recruitment issues. The excluded studies with reasons are listed in Appendix 2.

EFFECTIVENESS OF THE INTERVENTION

Comparison	Number of studies
1. Olanzapine vs Haloperidol	2 systematic reviews, 3 RCTs (one is quasi-randomised)
2. Olanzapine vs Benzodiazepines	0 studies identified
3. Olanzapine vs Placebo	1 systematic review

Comparison 1: Olanzapine vs Haloperidol

Efficacy

Critical outcomes: None of the 5 included studies reported on the following outcomes:

- change in agitation score,
- use of physical restraint,
- hospital/ICU length of stay,
- hospital discharge disposition and
- health related quality of life

Important outcomes

1. **Duration of delirium (days):**
   - *NICE review 2010 (updated in 2019):* The effect of haloperidol compared to olanzapine on duration of delirium is uncertain. Mean Difference (MD) 0.62 days, 95% CI 0.06 to 1.18, one RCT, n = 146, 1 trial, very low certainty evidence due to study quality, and imprecision
   - *Jain 2017:* The mean duration of treatment (days) was similar, 3.57 days (+- 0.92 days) in the olanzapine arm and 3.37 days (+- 0.71 days) in the haloperidol arm.

2. **Change in delirium severity:**

   Results were reported from three studies at different time points and using different measures. Overall, they found there was no difference in delirium severity between olanzapine and haloperidol.

   - *Finucane 2020:* Change in delirium severity: there may be little or no difference in change in delirium severity with olanzapine compared to haloperidol (Very low certainty evidence due to critical imprecision)
     1) within 24 hours: the mean difference (MD) between treatment arms was 2.36 (95% CI -0.75 to 5.47).
     2) between 24 and 48hrs: MD 1.90 (95% CI -1.50 to 5.30)
   - *NICE review:* There may be no difference in change in delirium severity score (delirium Rating Scale – DRS) comparing haloperidol and olanzapine. MD 0.7, 95% CI 0.45 to 1.85, n =146, 1 trial, moderate certainty evidence rated down due to poor study quality)
   - *Skrobik 2004:* There was a comparable reduction in the DI score in both groups over time (ANOVA time effect p 0.02, group effect p 0.83, interaction effect p 0.64)
   - *Jain 2017:* the mean MDAS score at baseline was 18.49 in the olanzapine group and 17.79 in the haloperidol group (the groups were comparable at baseline, p 0.791). The mean MDAS score at the end of the study period was 8.43 in the olanzapine group and 8.00 in the haloperidol group.
   - *Van der Vorst 2020:* The delirium response rate (DRR) was in the Olanzapine arm was 45% (95% CI 31 to 59) and 57% (95% CI 43 to 71) in the haloperidol arm (ΔDRR −12%; odds ratio [OR], 0.61; 95% CI, 0.2–1.4)

3. **Delirium resolution** (defined as reduction of delirium rating scale below a target set by the authors or complete resolution of symptoms): Results were reported from three studies. Overall, they found there was little or no difference in delirium resolution between olanzapine and haloperidol.
   - *NICE review:* There may be little to no difference comparing haloperidol and olanzapine. Risk Ratio (RR) 0.99, 95% CI 0.8 to 1.21, p=0.24, I^2=27%, n = 218, 2 trials (low certainty evidence due to poor study quality and indirectness from delirium assessment).
   - *Van der Vorst 2020:* The TRR (time from randomisation to resolution) was 4.5 days (95% CI 3.2 to 5.9) in the Olanzapine and 2.8 days (95% CI 1.9 to 3.7) in the haloperidol arm.

Safety

1. **Mortality**
   - Not reported.
2. **Extrapyramidal side effects (EPS):**
   - *NICE review:* We are uncertain about the difference in occurrence of EPS between haloperidol and olanzapine groups, RR 8.2, 95% CI 0.48 to 140.09, n = 73 , 1 quasi-RCT (very low certainty evidence due to study design limitations, and imprecision). Six participants rated low scores on extrapyramidal symptom testing (1 for the Ross Chouinard, 1–4 for the Simpson-Angus scale) in the haloperidol arm. There were no extrapyramidal manifestations in the olanzapine arm.
   - *Van der Vorst 2020:* six participants (12.2%) experienced EPS in the haloperidol group (three with tremors, two with muscle stiffness and one with QTc prolongation), compared to four (8.2%) in the olanzapine group (two with tremors, one with dizziness and one with muscle stiffness).

3. **Requiring anticholinergic medication:**
   - *Skrobik 2004:* no participants in either the haloperidol or olanzapine groups received prophylactic or therapeutic antiparkinsonian therapy.

4. **Adverse events:**
   - *Jain 2017:* There were two participants in the olanzapine group with adverse effects (one with excessive sedation, one with akathisia), and three in haloperidol group (drug-induced parkinsonism). All side effects were mild in severity. EPS were not defined separately but included under adverse events and as such have been reported here.
   - *Van der Vorst 2020:* 13 out of 46 patients (26.5%) in the olanzapine arm and 16 out of 49 patients (32.7%) in the haloperidol arm reported treatment-related adverse effects of any grade. Five patient (10.2%) in the olanzapine group and 10 patients (20.4%) in the haloperidol group reports Grade 3 or above TRAEs (OR 0.4, 95% CI 0.1 to 1.4, p=0.16). There were no treatment-related deaths.

Comparison 2: Olanzapine vs Benzodiazepines

None of the included studies compared olanzapine to benzodiazepines

Comparison 3: Olanzapine vs Placebo (NICE review)

Efficacy

Critical outcomes: The NICE review did not report on the following outcomes:

- change in agitation score
- use of physical restraint, hospital/ICU length of stay
- hospital discharge disposition and
- health related quality of life.

Less critical outcomes:

1. **Duration of delirium (days):** We are uncertain of the effect of olanzapine compared to placebo on duration of delirium MD=-2.4, 95% CI -3.51,-1.29, n = 103, 1 trial. (Low certainty evidence due to very poor study quality and imprecision)

2. Change in delirium severity: There is probably a reduction in the delirium rating scale (DRS) in favour of olanzapine compared to placebo MD = -11.1, 95% CI -15.51 to -7.69, n=103, 1 trial. (Moderate certainty evidence due to poor study quality and imprecision)

3. **Delirium resolution** (defined as reduction of delirium rating scale below a target set by the authors or complete resolution of symptoms): Outcome "Complete Response" reported that there is probably a more rapid resolution of delirium symptoms in favour of the olanzapine compared to placebo, RR=3.68, 95% CI 1.63 to 8.33, n=103, 1 trial. (Moderate certainty evidence due to poor study quality, indirectness and imprecision)

Safety

For this comparison, the NICE review did not report on extrapyramidal side-effects, if anticholinergic medication was required, drug-related adverse events or mortality.

Conclusion

We identified two reviews and three trials addressing the outcomes of interest, comparing olanzapine to haloperidol. In patients with delirium, there is probably little or no difference in olanzapine compared to haloperidol in the outcomes of interest. We are uncertain about the difference in occurrence of extrapyramidal side-effects and other adverse events in olanzapine compared to haloperidol.

We identified one review addressing the outcomes of interest, comparing olanzapine to placebo. In patients with delirium, we are uncertain of the effect of olanzapine compared to placebo in duration of delirium. There is probably a reduction in the delirium rating scale and a more rapid resolution of delirium symptoms in favour of olanzapine compared to placebo. There were no data on any safety outcomes.

Due to small study sizes and methodological limitations in the studies, the evidence was generally of low to very low certainty. This indicates a research gap. Larger rigorous RCTs are needed.

Table 2: Characteristics of Included Systematic Reviews: Delirium

CITATION	STUDY DESIGN	POPULATION (N)	INTERVENTION *vs* COMPARATOR	OUTCOMES & MAIN FINDINGS	COMMENTS
Comparison 1: Haloperidol compared to Olanzapine					
Finucane AM, Jones L, Leurent B, Samson EL, Stone P, Tookman A, et al. Drug therapy for delirium **in terminally ill adults**. Cochrane Database Sys. Rev. 2020;1. Doi: 10.1002/14651858.CD004770.pub3	Systematic review	Terminally ill adults (18 years or older) with delirium symptoms Included studies: RCTs	Haloperidol compared to Olanzapine	Delirium symptoms within 24 hours n= 28, one trial mean difference (MD) 2.36 (95% CI -0.75 to 5.47, p=0.14) Delirium symptoms between 24 and 48 hours n=24, one trial MD 1.9 (95% CI -1.5 to 5.3, p=0.27) **Very low certainty** (both outcomes), downgraded by 3 levels due to so few data that the results were highly susceptible to chance	AMSTAR – Moderate quality • Study design not explained • No meta-analysis
NICE Review (within CPG) National Institute for Health and Care Excellence (NICE). **Delirium: diagnosis, prevention and management** [Internet]. [London]: NICE; 2010 [updated July 2020]. (Clinical guideline 103 [CG103]). Available from: https://www.nice.org.uk/Guidance/CG103	Systematic review	Adult patients (18 years or older) in a hospital setting (surgical, medical, ICU, or emergency departments) or in long-term residential care with delirium. Included studies: RCTs and quasi randomized trials. Non-randomised studies (NRS) were included only if no other evidence, with preference to large cohort studies and comparative non-randomised designs. Exclusion criteria: Younger than 18 years Receiving end-of-life care Intoxication and or acute withdrawal from drugs or alcohol, with associated delirium	Haloperidol compared to olanzapine	Complete response (resolution) n=219, 2 trials RR=0.99 (95% CI 0.8 to 1.21, p=0.24, I^2=27%) **Low certainty** downgraded due to poor study quality (not blinded, inadequate sequence generation and allocation concealment, funding and outcome possibly inadequate) and imprecision. Duration of delirium n=146, 1 trial MD=0.62 (95% CI 0.06 to 1.18) **Very low certainty**, downgraded for very poor study quality, imprecision and reported as “time to take effect” in responders only, likely to be biased Severity of Delirium n=146, 1 trial MD=0.7 (95% CI 0.45 to 1.85) **Moderate certainty,** downgraded due to poor study quality (not blinded) and imprecision (number of patients < 400)	AMSTAR – High quality • Data extraction not in duplicate

				Adverse events n=73, 1 included trial RR=8.2 (95% CI 0.48 to 140.09) **Very low certainty**, downgraded due to very poor study quality (quasi-randomised, not blinded) and imprecision(wide confidence interval)	
Comparison 2: Olanzapine vs placebo					
NICE Review (within CPG) National Institute for Health and Care Excellence (NICE). **Delirium: diagnosis, prevention and management** [Internet]. [London]: NICE; 2010 [updated July 2020]. (Clinical guideline 103 [CG103]). Available from: https://www.nice.org.uk/Guidance/CG103	Systematic review	Adult patients (18 years or older) in a hospital setting (surgical, medical, ICU, or emergency departments) or in long-term residential care with delirium. Included studies: RCTs and quasi randomized trials. Non-randomised studies (NRS) were included only if no other evidence, with preference to large cohort studies and comparative non-randomised designs. Exclusion criteria: Younger than 18 years Receiving end-of-life care Intoxication and or acute withdrawal from drugs or alcohol, with associated delirium	Olanzapine compared to placebo	Complete response n=103, 1 included trial RR=3.68 (95% CI 1.63 to 8.33) **Moderate certainty** due to poor study quality (not blinded) indirectness (indirect outcome through delirium assessment method) and imprecision (number of events < 300). Duration of delirium n=103, 1 included trial MD=-2.4 (95% CI 3.51 to -1.29) **Very low certainty** due to poor study quality (evidence of confounding and not blinded) and imprecision (wide confidence interval). Severity of Delirium n=103, 1 included trial MD=-11.1 (95% CI 14.51 to -7.69) **Moderate certainty** due to poor study quality (not blinded) and imprecision (number of patients < 400).	AMSTAR – High quality • Data extraction not in duplicate

Table 3: Characteristics of Included Randomised Controlled Trials: Delirium

CITATION	STUDY DESIGN	POPULATION (N)	INTERVENTION *vs* COMPARATOR	OUTCOMES & MAIN FINDINGS	RISK OF BIAS
Comparison 1: Haloperidol versus Olanzapine					
Skrobik YK, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs haloperidol: treating delirium in a **critical care setting**. Intensive Care Med. 2004;30:444-9. Doi: 10.1007/s00134-003-2117-0	Design Prospective quasi-randomized trial. Single blinding (treating nurses and physician not blinded to assigned drug) Duration July 2000 to September 2001. Funding Peer-reviewed grant from the Zyprexa fund, Eli-Lilly, North America Ethics Protocol approved by the institutional scientific and ethics committee	Adults aged 18 to 75 years admitted to medical-surgical ICT in Montreal. All patients with delirium (as defined below) were considered eligible for the study. Sample size 73 included in final analysis (Haloperidol n=45, Olanzapine n=28) 103 considered eligible, 80 informed consent obtained, 3 withdrawn, 2 status changed to "no active treatment", 1 suspected drug interaction, 1 data lost Inclusion criteria Admitted for more than 24 hours, participants screened 3 times daily for delirium with the ICU Delirium Screening Checklist (ICU-DSC). In participants with a score >= 4 or with clinical manifestations of delirium, diagnosis confirmed by physician using DSM-IV criteria. Exclusion criteria Pregnant patients who received antipsychotic medication within 10 days prior to admission; Pregnant patients with contraindications to haloperidol or olanzapine; Gastrointestinal dysfunction that did not allow oral or enteral drug administration; Neurological status did not allow neuropsychiatric examination e.g. coma Other caveats Patients who developed agitation were allowed intravenous haloperidol ("rescue haloperidol")	Intervention Enteral olanzapine 5mg daily (>60yrs: 2.5mg daily) Comparator Enteral haloperidol 2.5 to 5mg every 8 hours (>60yrs: 0.5 to 1 mg 8 hourly) Subsequent titration based on clinical judgement. Benzodiazepine use noted as adjuvant therapy.	Outcomes 1. Change in mean daily delirium scores (delirium index (DI) scores) 2. Adjunct benzodiazepine use requirements over time 3. Use of rescue haloperidol, opiates, sedatives, Ramsay scores, vital signs and liver function tests in both groups. 4. Presence of extrapyramidal side effects (EPS) Results 1. Comparable reduction in DI score over time was noted in both groups, with no difference (ANOVA time effect p=0.02, group effect p=0.83 interaction effect p=0.64) 2. Benzodiazepines: Analysis of variance did not identify any difference between the two groups, at any of the 5 measurement times (interaction effect p=0.94 group effect p=0.9). 3. " The dose of rescue haloperidol, opiates, sedatives other than benzodiazepines, Ramsay scores, vital signs, and liver function tests were no different between groups." 4. Haloperidol: 6 rated low scores on extrapyramidal symptom testing (1 for the Ross Chouinard, 1–4 for the Simpson-Angus scale). Olanzapine: no extrapyramidal manifestations or adverse effects	**HIGH RISK OF BIAS** All outcomes: **High risk of bias** in domain 1 due to quasi-randomisation of allocation sequence and baseline differences between allocation groups, **some concerns** in domain 2 due to no information around participant blinding and effects of assignment, and **some concerns** in domain 5 due to no information around a prespecified plan or protocol. **Low risk of bias** in domains 3 and 4.

Jain R, Arun P, Sidana A, Sachdev A. Comparison of efficacy of haloperidol and olanzapine in the treatment of delirium. Indian J Psychiatry. 2017;59(4):451-6. Doi: 10.4103/psychiatry.IndianJ Psychiatry_59_17	Design Open label, randomized controlled study. Randomisation through computer-generated random number table Duration December 2011 to December 2012. Patients assessed every 24 hours until delirium resolution. Trial registry Registered with the Clinical Trial Registry-India CTRI/2016/10/007331 Ethics Approved by local institutional ethics committee Funding None Other Assessment of delirium through Confusion Assessment Method (CAM), and diagnosis using DSM-IV criteria. Delirium severity assessed with Memorial Delirium Assessment Scale (MDAS). Simpson-Angus Scale (SAS) used to assess EPS	Delirious patients admitted to medicine emergency ward and referred to the Department of Psychiatry for consultation at the Government Medical College and Hospital, Chandigarh, India. Sample Size 100 132 enrolled; 32 dropped out after randomization and were not included in the final analysis; Olanzapine n=47 Haloperidol n=53 Inclusion criteria Delirious patient plus >18 years old; Verbally responsive; No dementia Exclusion criteria Mechanically ventilated; Mute; Currently on antipsychotics for any reason; Experiencing alcohol or benzodiazepine withdrawal delirium; Hypersensitivity to either olanzapine or haloperidol in the past.	Intervention Olanzapine, enteral only, 2.5 to 10mg daily orally or via nasogastric tube (NGT) Comparator Haloperidol, enteral only, 1 to 4mg orally or via NGT tube Doses based on MDAS scores of mild, moderate or severe delirium.	Outcomes 1. Efficacy of olanzapine and haloperidol in delirium 2. Tolerability of olanzapine and haloperidol in delirium 3. Phrenology of delirium and pattern of symptom improvement with treatment Results • Delirium severity – mean MDAS score (baseline) 18.49 olanzapine group, 17.79 haloperidol group (groups comparable at baseline, p=0.791). mean MDAS score (end study period) 8.43 olanzapine group, 8.00 haloperidol group; 54.7% reduction in mean MDAS scores (54.4% in olanzapine group and 55% in haloperidol group • Pattern of symptom improvement ○ Severity of attention on day 2 and severity of disorganized thinking on days 2 and 3 were less in the olanzapine group (p<0.05). ○ Severity of perceptual disturbances on day 4, and severity of psychomotor disturbances on days 3 and 4 were less in the haloperidol group (p<0.05). • Duration of treatment– mean duration of treatment (days) 3.57 olanzapine (+- 0.92 days), 3.37 haloperidol (+- 0.71 days), (p=0.233) • Drug-related adverse effects – 2 in olanzapine group (1 with excessive sedation, 1 with akathisia), 3 in haloperidol group (drug-induced parkinsonism). All side effects were mild in severity.	**HIGH RISK OF BIAS** All outcomes: **Some concerns** in domain 1 due to this being a single-blind study, **some concerns** in domain 2 due to single-blind study and limited information on statistical methods, **high risk of bias** in domain 3 due to no information around data available for all participants and missingness, **high risk of bias** in domain 4 due to potential bias from researchers not being blinded, and **some concerns** domain 5 due to no information around a pre-specified analysis plan.
Van der Vorst MJDL, Neefjes ECW, Boddaert MSA, Verdegaal BATT, Beeker A, Teunissen SCC, et al. Olanzapine versus haloperidol for treatment of delirium in patients with advanced cancer: a phase III randomized clinical trial. Oncologist.	Design Multicentre, randomized controlled, phase III trial. Conducted at five sites in the Netherlands. Study terminated early as unlikely to reach the predefined efficacy criteria. Trial registry	Patients ≥ 18 years old with advanced cancer, admitted to a medical oncology ward or high-care hospice facility Sample size 100 50 allocated to each group	Intervention Olanzapine, po or IMI Comparator Haloperidol, po or sc	Outcomes: *Primary endpoint:* Delirium Response Rate (DRR) on days 1 to 7 after randomization as defined by DRS-R-98 assessment *Secondary endpoints:* TRR (time from randomization to resolution of delirium in days) TRAEs (treatment related adverse events), according to the CTCAE version 4.03	**SOME CONCERNS** All outcomes: **Some concerns** in domain 5 due to no information around pre-specified plan or protocol. **Low risk of bias** in domains 1 to 4.

2020; 25:e570-7. Doi: https://doi.org/10.1634/theoncologist.2019-0470	NCT01539733 Duration January 2011 to July 2016 Funding Netherlands Organization for Health Research and Development (ZonMw) Palliative Care Program (No. 11510011). Ethics Written informed consent	Olanzapine – 9 discontinued treatment. Analysis – Intention-to-treat (ITT) n=49, per protocol n = 40 Haloperidol – 8 discontinued treatment. Analysis – ITT n = 49, per protocol n = 41 Inclusion criteria 18 years or older; Advanced cancer; Admitted to medical oncology ward or high-care hospice facility; Fluent in the Dutch language; Diagnosed with delirium. Exclusion criteria Diagnoses of glaucoma, Parkinson's disease, dementia or psychiatric disorders interfering with delirium assessment; history of neuroleptic malignant syndrome or convulsions; delirium due to substance withdrawal cardiac conduction abnormalities; Currently using other neuroleptic medication or lithium.		Delirium-related distress for patients and their caregivers assessed by DEQ Results DRR: Olanzapine 45% (95% CI 31 to 59) Haloperidol 57% (95% CI 43 to 71) (ΔDRR −12%, odds ratio [OR] 0.61, 95% CI 0.2–1.4 p = 0.23) (ITT) TRR: Olanzapine 4.5 days (95% CI 3.2 to 5.9) Haloperidol 2.8 days (95% CI 1.9 to 3.7) (p = 0.18) DRR for motor subtypes (ITT) Hyperactive OR 0.5, 95% CI 0.1 to 2.1, p=0.50 Hypoactive OR 0.2, 95% CI 0.04 to 1.5, p=0.12 Mixed OR 1.8, 95% CI 0.4 to 7.9, p=0.49 Safety TRAEs of any grade Olanzapine arm: 13 patients (26.5%) Haloperidol arm: 16 patients (32.7%) Grade ≥3 TRAEs Olanzapine arm: 5 patients (10.2%) Haloperidol arm: 10 patients (20.4%) (OR 0.4, 95% CI 0.1 to 1.4, p=0.16) No treatment related deaths Delirium-Related Distress Sixteen patients completed this DEQ in each treatment arm. Mean delirium-related distress level (0 – 4 numerical rating scale) Olanzapine 2.1 (SD 1.4) Haloperidol 2.3 (SD 1.4) Mean delirium-related distress level (spouse/caregiver) Olanzapine 3.0 (SD 1.2) Haloperidol 2.7 (SD 1.1) Mean delirium-related distress level (nurses) Olanzapine 1.1 (SD 1.1) Haloperidol 0.9 (SD 0.9)	

Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☒ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	For important outcomes there were limitations in the data: small study sizes, methodological limitations in the studies, the evidence was generally of low to very low certainty. No data on critical outcomes.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☒ None ☐	Olanzapine vs haloperidol: no difference (none) Olanzapine vs placebo: probably better efficacy (small and low levels of certainty) Olanzapine vs benzodiazepines: no data
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☒ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	For important outcomes there were limitations in the data: small study sizes, methodological limitations in the studies, the evidence was generally of low to very low certainty. No data on critical outcomes
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge ☐ Moderate ☐ Small ☒ None ☐	Olanzapine vs haloperidol: no difference (none) Olanzapine vs placebo: probably better efficacy (small) Olanzapine vs benzodiazepines: no data
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☐ Favours control ☐ Intervention = Control ~~*or* Uncertain~~ ☒	Olanzapine vs haloperidol: no difference (intervention = control) Olanzapine vs placebo: probably better efficacy (favours intervention) – but very low level of certainty of evidence Olanzapine vs benzodiazepines: no data
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: N/A	
FEASABILITY	**Is implementation of this recommendation feasible?** Yes ☒ No ☐ Uncertain ☐	Olanzapine is not specifically registered for delirium; however, olanzapine oral is available in the public sector for other indications (bipolar disorder, schizophrenia). All formulations are available on the South African market. The loss of IM haloperidol is disruptive in the change of clinical practice.
RESOURCE USE	**How large are the resource requirements?** More intensive ☐ Less intensive ☐ Uncertain ☐	**Price of medicines:** **Medicine** | **Tender price (ZAR)*** | **100% OF SEP (ZAR)**** | **60% OF SEP (ZAR)** Haloperidol 5mg tablets, 500 | 23.23 | n/a | n/a

Haloperidol 5mg/5ml injection, single (discontinued)	n/a	45.68***	n/a
Olanzapine 10 mg injection	n/a	72.84	43.71
Olanzapine 5mg orodipersible (ODT, 30	n/a	267.41	160.45
Olanzapine 2.5mg tablet (SOT), 28	13.80	n/a	n/a

* Contract circular HP09-2021SD, August 2022
**SEP database, July 2022
***SEP database, February 2021 (Haloperidol injection discontinued)

Background:

- *Adult Hospital Level STG and EML, 2019 edition*

Recommends haloperidol IM injection, but this has been discontinued from the South African market.

- *NICE Guideline 2010 (updated in March 2019)*

Recommendations for olanzapine include:

- IM injection: 2.5–10 mg per day, depending on response; the effect was observed for one week; delirium had 3 occurred from 30 min to 17 days (Hu 2006)
- Orally or by enteral tube: given within 2 h of the diagnosis of delirium, initially 5 mg per day (patients over 60 years 2.5 mg) then titrated based on clinical judgement for up to 5 days (Skrobik 2004)
- Orally/ sublingually: initial dose 1.25–2.5 mg then adjusted, depending on response, to 1.25–20 mg per day; the effect was observed for one week; delirium had occurred from 30 min to 17 days (Hu 2006)

- *NEMLC report (Adult Hospital 2019 review of palliative care chapter)*

Haloperidol, oral: added
Haloperidol, SC/IV: added
Lorazepam, oral: added
Midazolam, SC/IV: added
Antipsychotic (haloperidol), oral/IV/SC: Low doses are generally recommended as 1strst line in guidelines, due to associated side-effects. However, a RCT (Agar,2017) showed that oral haloperidol and risperidone was less effective in reducing delirium symptoms than placebo and shortened overall survival. Limitations included the oral route of administration (possibly contributing to increased extrapyramidal side effects); increased administration of midazolam to the antipsychotic groups (possibly increasing paradoxical agitation and variable baseline demographics and precipitants of delirium were not reported in all groups. Cochrane review concluded that there is insufficient evidence to determine the role of medicine treatment for delirium in terminally ill patients; thus recommendations aligned with expert consensus.
***Recommendation:** Low dose haloperidol as 1st line treatment for delirium in palliative care at secondary level of care.*
Rationale: Aligned with guidelines.
Level of Evidence: III Guidelines

- *Pharmacokinetic study by Markowitz et al, 2006*

Both routes of ODT administration (above the tongue and sublingually) resulted in more measurable early concentrations relative to SOT. However, there were no statistically significant differences observed between any of the olanzapine exposures for observed pharmacokinetic parameters (C(max), T(max), AUC(0-8h)).

- *Medicines.org.uk: Olanzapine 5mg ODT tablets - Summary of Product Characteristics (SmPC)*

Olanzapine ODT should be placed in the mouth, where it will rapidly disperse in saliva, so it can be easily swallowed. Removal of the intact ODT from the mouth is difficult. Since the ODT is fragile, it should be taken immediately on opening the blister. Alternatively, it may be dispersed in a full glass of water or other suitable beverage (orange juice, apple juice or milk) immediately before administration. Olanzapine ODT is bioequivalent to olanzapine film-coated tablets, with a similar rate and extent of absorption. It has the same dosage and frequency of administration as olanzapine film-coated tablets. Olanzapine ODT may be used as an alternative to olanzapine film-coated tablets.

- *Pharmacokinetic parameters:*

On review of the pharmacokinetic properties of olanzapine ODT and SOT formulations, bioequivalence can be assumed.

	Tmax	T1/2	
Haloperidol, IM	10 minutes	13 to 35 hrs	*SAMF, 2022*
Olanzapine ODT	4 to 6 hrs	33 hrs	*Markowitz, 2006*
Olanzapine SOT	5 to 8 hrs	33 hrs	*Callaghan JT, 1999*
Olanzapine, IM	14 to 45 minutes	33 hrs	*FDA PI (drugs.com)*

Comparative cost analysis per treatment course *(comparing direct medicine prices):*

- **Haloperidol 0.5-1mg inj,** immediately 30 minutes later and 4-hourly to a max of 10mg per 24 hours *(Using the max dose of 2 x 5 mg inj per day for 3 days = 6 x 10 mg inj):* **R274.08** (Historic SEP price accessed through State S21)

- **Olanzapine 2.5-5mg inj**, immediately 30-60 minutes later and 4-hourly to a max of 20mg per 24 hours *(Using the max dose of 2 x 10 mg inj per day for 3 days = 6 x 10 mg inj):* **R437.06** (100% SEP) and **R262.24** (60% SEP).

- **Olanzapine 2.5-5mg SOT via NGT,** immediately 30-60 minutes later and 4-houlry to a max of 20mg per 24 hours *(Using the max dose of 8 x 2,5 mg tablets per day for 3 days = 24 x 2.5 mg tablets):* **R11.83** (Contract price)

- **Olanzapine 2.5-5mg ODT**, immediately 30-60 minutes later and 4-hourly to a max of 20mg per 24 hours *(Using the max dose of 4 x 5mg ODTs per day for 3 days = 12 x 5 mg ODT):* **R106.96** (100% SEP) and **R64.18** (60% of SEP)

NB: It is concerning to note that haloperidol injection had only been added to the NICE guidelines in 2019, as haloperidol was registered with the MHRA for delirium. Global vs local availability of medicines warrants investigation.

Other resources: n/a

VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [X]	There is no information available about the acceptability of olanzapine to stakeholders. However, given the absence of other options in the management of delirium, it could be a viable and acceptable alternative.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [X]	There is no available local survey data – based on expert opinion.

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	18 August 2022	LR, SM, TK, NG, MM, TL	Olanzapine (all formulations) suggested as an option to haloperidol to manage delirium where non-pharmacological management is not sufficient (conditional recommendation, low to very low certainty evidence).
V1.0	28 Mar 2024	LR	Updated to reflect erratic supplies of haloperidol IM

References

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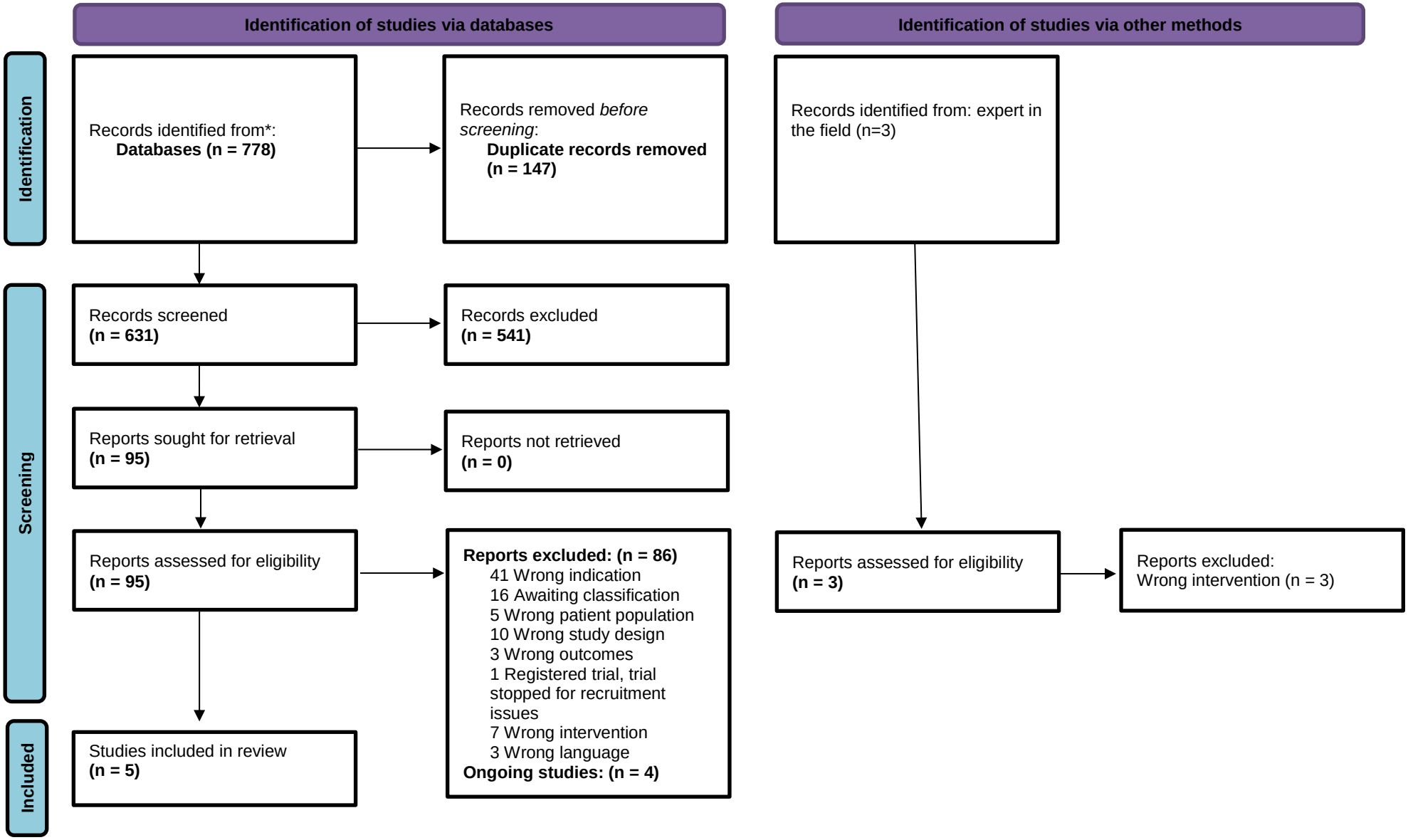
Appendix 1: Search Strategy

#9	#1 AND #2 AND #8
#8	#3 OR #4 OR #5 OR #6 OR #7
#7	schizophrenia[mh] OR schizophreni*[tiab]
#6	dementia[mh] OR dementia*[tiab]
#5	confusion[mh] OR confus*[tiab] OR disorientat*[tiab] OR bewilderment[tiab] OR delirium*[tiab]
#4	paranoid disorders[mh] OR paranoi*[tiab]
#3	psychotic disorders[mh] OR psychosis[tiab] OR psychotic[tiab] OR psychoses[tiab] OR psychiatric disorder*[tiab] OR mental disorders[mh] OR mental illness*[tiab] OR mental disorder*[tiab] OR mood disorders [mh] OR mood disorder*[tiab] OR affective disorder*[tiab] OR bipolar disorder[mh] OR bipolar[tiab] OR mania*[tiab] OR manic[tiab]
#2	Search: aggression[mh] OR aggress*[tiab] OR disruptive behavior*[tiab] OR disruptive behaviour*[tiab] OR agitat*[tiab] OR violent behavior*[tiab] OR violent behaviour*[tiab]
#1	Search: olanzapine[mh] OR olanzapine*[tiab] OR zyprexa*[tiab] OR zolafren*[tiab] OR LY 170053[tiab] OR LY170053[tiab] OR LY 170052[tiab]

Appendix 2: PRISMA Flow Chart



Modified From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Appendix 3: AGREE II Appraisal Summary

Guideline	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	OA
NICE: DELIRIUM: diagnosis, prevention and management	94%	81%	88%	100%	67%	63%	83%
SIGN 157: Risk reduction and management of delirium	94%	97%	65%	81%	73%	58%	67%
Management of delirium in older people	100%	89%	72%	89%	50%	79%	83%

Domain 1: Scope and purpose
Domain 2: Stakeholder involvement
Domain 3: Rigour of development
Domain 4: Clarity of presentation
Domain 5: Applicability
Domain 6: Editorial independence
OA: overall assessment

Appendix 4: Table of excluded studies, with reasons

Author, date	Type of study	Reason for exclusion
1. Bak, 2019	SR*	Wrong indication
2. Belgamwar, 2005	SR	Wrong indication
3. Burry, 2018	SR	Wrong intervention
4. Burry, 2019	SR	Wrong intervention
5. Dundar, 2016	SR	Wrong indication
6. Fernández Sánchez, 2009	SR	Wrong indication
7. Huf, 2009	SR	Wrong language
8. Huf, 2016	SR	Wrong indication
9. Lacasse, 2016	SR	Wrong intervention
10. Maglione, 2011	SR	Wrong indication
11. Mühlbauer, 2021	SR	Wrong patient population
12. Nikooie, 2019	SR	Wrong intervention
13. Paris, 2021	SR	Wrong indication
14. Pelland, 2009	SR	Wrong language
15. Seida, 2012	SR	Wrong patient population
16. Shoptaw, 2009	SR	Wrong indication
17. Tulloch, 2004	SR	Wrong indication
18. Williamson, 2019	SR	Wrong indication
19. Yildiz, 2003	SR	Wrong language
20. Yildiz, Sachs 2003	SR	Wrong study design
21. Yunusa, 2019	SR	Wrong indication
22. Zaman, 2017	SR	Wrong indication
23. Baldaçara, 2011	RCT#	Wrong indication
24. Battaglia, 2003	RCT	Wrong indication
25. Battaglia, 2005	RCT	Wrong outcomes
26. Beasley, 1996	RCT	Wrong indication
27. Belgamwar, 2005	RCT	Wrong indication
28. Bozzatello, 2017	RCT	Wrong patient population
29. Breier, 2000	RCT	Awaiting classification
30. Breier, 2001	RCT	Awaiting classification
31. Breier, 2002	RCT	Wrong indication
32. Chan, 2014	RCT	Wrong indication
33. Clark, 2001	RCT	Wrong indication
34. David, 2001	RCT	Awaiting classification
35. Eli, 2005	RCT	Awaiting classification
36. Faay, 2020	RCT	Wrong indication
37. Fontaine, 2003	RCT	Wrong patient population
38. Gareri, 2004	RCT	Wrong indication
39. Hsu, 2010	RCT	Wrong indication
40. Huf, 2009	RCT	Wrong intervention
41. Huang, 2015	RCT	Wrong indication
42. Hwang, 2012	RCT	Awaiting classification
43. Jin, 2009	RCT	Awaiting classification
44. Katagiri, 2013	RCT	Wrong indication
45. Kinon, 2000	RCT	Wrong indication
46. Kinon, 2001	RCT	Wrong outcomes
47. Kinon, 2004	RCT	Wrong indication
48. Kittipeerachon, 2016	RCT	Wrong intervention
49. Kong, 2009	RCT	Awaiting classification
50. Krakowski, 2014	RCT	Wrong indication
51. Lindbord, 2003	RCT	Wrong outcomes
52. Meehan, 2001	RCT	Awaiting classification
53. Meehan, 2001 (1)	RCT	Awaiting classification
54. Meehan, 2001 (2)	RCT	Awaiting classification

55. Meehan, 2001 (3)	RCT	Wrong indication
56. Meehan, 2002	RCT	Wrong indication
57. Mintzer, 2002	RCT	Awaiting classification
58. Ono, 2008	RCT	Awaiting classification
59. Raveendran, 2007	RCT	Wrong indication
60. Schneider, 2006	RCT	Wrong indication
61. Smith, 2003	RCT	Awaiting classification
62. Street, 2000	RCT	Wrong patient population
63. Svestka, 2002	RCT	Awaiting classification
64. Verhey, 2006	RCT	Wrong indication
65. Villari, 2009	RCT	Wrong intervention
66. Wright, 2001	RCT	Awaiting classification
67. Wright, 2003	RCT	Wrong indication
68. Hirsch, 2019	Narrative review	Wrong study design
69. Houston, 2019	Narrative review	Wrong study design
70. Wagstaff, 2005	Narrative review	Wrong study design
71. Pascual, 2007	Observational study	Wrong study design
72. Walther, 2014	Observational study	Wrong study design
73. ACTRN12610000033044	Ongoing trial	Wrong indication
74. NCT00316238	Ongoing trial	Wrong indication
75. NCT00485810	Ongoing trial	Wrong indication
76. NCT00485901	Ongoing trial	Wrong indication
77. NCT011234082	Ongoing trial	Wrong indication
78. NCT00649510	Ongoing trial	Wrong indication
79. NCT00797277	Ongoing trial	Wrong indication
80. NCT00833300, 2009	Registered trial	Registered trial, trial stopped for recruitment issues
81. NCT00970281	Ongoing trial	Wrong indication
82. Elsayem, 2010	Pilot study	Wrong study design
83. Citrome, 2007	Quantitative review	Wrong study design
84. Srivastava, 2010	Summary of review	Wrong study design
85. deAlmeida, 2017	Review of reviews	Wrong study design
86. Jones, 2001	Summary of RCTs	Wrong study design

*SR = systematic review, #RCT = randomized controlled trial

Appendix 5: Table of Ongoing Trials

Citation	Study Design	Population (n)	Treatment
Arak University of Medical Sciences. IRCT20141209020258N114, first registered 3 July 2019, recruiting.	RCT with parallel assignment	50	Patients randomised to haloperidol 2.5mg (max 40mg) intramuscular injection (IMI) every 6 hours or olanzapine 2.5 to 10mg (max 20mg) orally
Arak University of Medical Sciences. IRCT20200927048852N1, first registered 13 October, recruiting.	Phase III RCT with parallel assignment	90	Patients randomised to haloperidol 2.5mg per day for up to 10 days or olanzapine 2.5mg to 10mg per day for up to 10 days or quetiapine 12.5 to 75mg per day
HCA Hospice Care. NCT04750395, first registered 11 February 2021, ongoing	RCT with parallel assignment	80	Patients randomised to transmucosal haloperidol, two doses of 2.5mg every 24 hours with up to two breakthrough doses or transmucosal olanzapine, two doses of 5mg with up to two breakthrough doses
Tan Tock Seng Hospital. NCT04833023, first registered 6 April 2021.	RCT with parallel assignment	72	Patients randomised to haloperidol oral solution 1mg (max 6mg in 24 hours), 2 hourly until max reached with midazolam 2mg as rescue dose (2mg q2h prn) or olanzapine orodispersible tablet 2.5mg (max 15mg in 24 hours), 2 hourly until max reached with midazolam 2mg as rescue dose (2mg q2h prn)

South African National Essential Medicine List
Adult Hospital Level and PHC Medication Review Process
Component: Emergencies and injuries

MEDICINE REVIEW

Executive Summary

Date: May 2022
Medicine (INN): Morphine
Medicine (ATC): N02AA01
Indication (ICD10 code): J81 (The relief of moderate to severe pain in patients with acute pulmonary oedema).
Patient population: Adult patients with acute pulmonary oedema with distress, anxiety, or restlessness
Prevalence of condition: According to the Global Health Data Exchange (GHDx) registry, a search with the keyword "heart failure", the current worldwide prevalence of HF is 64.34 million cases (8.52 per 1,000 inhabitants), or 0.8%. The overall prevalence of clinically identified heart failure is estimated to be 3–20 cases/1000 population, but rises to > 100 cases/1000 population in those aged ⩾65 years. The PICO population ONLY includes those patients with distress, anxiety or restlessness - there is limited prevalence data for this cohort but it is estimated as a small proportion of the total APE cohort.[28]
The average incidence of hospitalized ADHF was 11.6 per 1,000 persons, aged ≥55 years, per year.[29,30,31] Considering only the population with anxiety, restlessness and distress, no prevalence of these symptoms cold be found in literature. As approximately 15% of patients with acute decompensated heart failure has morphine prescribed - one can assume that anxiety could be present in around 15% of acute decompensated heart failure. So, 15% of 0.8% is approximately 0.12%.
Level of Care: PHC, Adult Hospital Level
Prescriber Level: Clinician (Doctor)
Current standard of Care: SL or IV Nitrates; IV or PO Furosemide, IV Morphine
Efficacy estimates: (preferably NNT): 67 NNH (mortality)
Motivator/reviewer name(s): Michael McCaul, Clint Hendrikse, Gustav Thom, Idriss Kallon, Veranyuy Ngah, Rephaim Mpofu Trudy Leong.
PTC affiliation: Gustav Thom – KZN PTC

Key findings

- We conducted a rapid review of clinical evidence on whether intravenous/intra-osseus morphine should be used in the treatment of acute pulmonary distress
- We identified four systematic reviews of observational studies. The two most relevant, up-to-date, and highest quality reviews were used to inform recommendations for critical outcomes.
- Morphine may increase in-hospital and all-cause mortality (OR 1.78; 95% CI 1.01 to 3.13; 15 more per 1000, from 0 fewer to 40 more; n=151 735 participants) and may result in a large increase in need for invasive mechanical ventilation (OR 2.72; 95% CI 1.09 to 6.80; 45 more per 1000, from 2 more to 136 more; n=167 847 participants) compared to not using morphine.
- No available data could be sourced on whether morphine increases non-fatal adverse events, ICU or hospital length of stay.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		x			

Recommendation: The PHC/Adult Hospital Level Committee suggests not to use morphine for the treatment of acute pulmonary distress.
Rationale: Available evidence shows that morphine may increase in-hospital and all-cause mortality and may result in a large increase in invasive mechanical ventilation compared to not using morphine. No available data could be found on whether morphine increases non-fatal adverse events, ICU or hospital length of stay.
Level of Evidence: Low certainty of evidence
Review indicator: New high-quality evidence of a clinically relevant benefit

NEMLC RECCOMENDATION – 23 JUNE 2022:

NEMLC MEETING OF 23 JUNE 2022:

NEMLC accepted the proposal to amend the remove morphine the treatment of acute pulmonary distress. However, recommended that a caution be included in the STG, accordingly:

CAUTION

Do not use morphine for pulmonary oedema, as there is observational data providing a signal of harm.

Furthermore, once the respetive chapter is finalised, it was recommended that a circular be drafted and disseminated regarding the harms associated with use of morphine for distress in pulmonary oedema.

Monitoring and evaluation considerations

Research priorities

Authors: Idriss Kallon[1], Veranyuy Ngah[1], Clint Hendrikse[2, 5], Gustav Thom[3, 5], Michael McCaul[1,4, 5], Rephaim Mpofu[5,6], Trudy Leong [7,8]

[1]Division of Epidemiology and Biostatistics, Department of Global Health, Stellenbosch University
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[4]SA GRADE Network
[5] PHC/Adult Hospital Level Committee (2019-2023)
[6] Department of Medicine, Division of Clinical Pharmacology, Groote Schuur Hospital, University of Cape Town
[7]Essential Drugs Programme, National Department of Health
[8] Secretariat to the PHC/Adult Hospital Level Committee (2019-2023); Secretariat to the National Essential Medicines List Committee (2021-)

Declarations of interest: IK, VN, GT, MM and TL have no interests pertaining to morphine.

Acknowledgments: Rephaim Mpofu (affiliated to University of Cape Town, Groote Schuur Hospital, Adult Hospital Level Committee, National Department of Health, South Africa and PHC/Adult Hospital Level Committee, 2019-2023) assisted with the costing analysis.

Background

Morphine has been prescribed for patients with acute decompensated heart failure, but there is little evidence for safety and efficacy when used for this indication. The suggested mechanism is that morphine may assist with anxiolysis and reduce preload (Ellingsrun, 2016). However, a mortality benefit has not been demonstrated, and recent evidence suggests increase in adverse events and 30-day mortality. Morphine is included in both the Adult and PHC EML/STG for the management of pulmonary oedema/acute decompensated heart failure, specifically for patients who are experiencing anxiety. In the Adult Hospital EML/STG it is recommended under Acute Pulmonary Oedema "if distressed. Consider adding Morphine". In the PHC EML/STG, it is recommended "if patient is very anxious or restless". The evidence to support this is unclear/lacking (expert opinion) and recent evidence of harm has emerged (Gao *et al*, 2021 and Lin *et al*, 2021).

Research Question

Should intravenous morphine be used in the treatment of acute pulmonary distress?

Methods

We conducted a rapid review of evidence for the use of intravenous morphine in patients with acute pulmonary oedema. We systematically searched Ovid MEDLINE, Embase and the Cochrane Database of Systematic Reviews on February 12, 2022 for Randomised Controlled Trials (RCTs) and Systematic Reviews (SRs) of RCtTs or observational studies. Additionally, we searched the Pan African Clinical Trial registry for any ongoing studies from 2021. The search strategy can be seen in Appendix 1. Screening of title and abstracts and full text screening, selection of studies and data extraction was conducted

independently and in duplicate by two reviewers (IK and VN). Title and abstract, including full text screening was done using the Covidence systematic review software. AMSTAR II was used to appraise all the systematic reviews included in the study by a single reviewer (VN), checked by a second reviewer (IK). GRADE was applied to determine the certainty of evidence and the GRADEPro software was used to generate evidence profiles. Relevant study data were extracted into a narrative table of results. MM, IK, VN and CH reviewed the overall report. Where multiple eligible SRs were included, we reported evidence from the most relevant, recent and high-quality review or reviews in order to provide evidence across all *a priori* outcomes.

Eligibility criteria for review

Population:	Adult 18 years and older patients with acute pulmonary oedema with distress, anxiety, or restlessness in-hospital or prehospital. **Exclusion**: post-op complications, non-cardiogenic, congested cardiac failure*
Intervention:	Standard of care without Morphine: Standard of care includes IV and Sublingual nitrates and IV and PO Furosemide)
Comparator:	Standard of care with intravenous/intra-osseus Morphine: Standard of care includes IV and Sublingual nitrates and IV and PO Furosemide
Outcomes:	Mortality, AEs, SAEs, ICU length of stay, Hospital length of stay
Studies:	RCTs and SRs

**This question is restricted to acute pulmonary oedema*

Results

The search produced 709 records where 683 reports were irrelevant. We included 25 reports for full text review, excluded 21, and included four systematic review reports for data extraction and synthesis. See the PRISMA (Appendix 2) for further details, which include reasons for exclusions. Also, refer to table of excluded studies with reasons (Table 2). Gao *et al*., (2021) and Zhang *et al* (2021) were assessed to be of moderate quality (according to AGREE II) of the four included systematic reviews and were considered most relevant and up-to-date. AMSTAR II assessment results in Appendix 4. Relevant pooled outcomes from Gao and Zhang were re-GRADED (see Appendix 5)

Description of included studies

We found no RCTs addressing this question. The four included studies were systematic reviews of observational studies, with three using meta-analyses to aggregate results. The effect estimates in the meta-analysis were adjusted. Standard of care was not stated in the reviews.

Gao *et al* (2021) investigated the risk of mortality associated with opioid use in acute heart failure. They included 6 observational retrospective studies, with 15 1735 participants in total. Treatment given to the control groups was not described. The authors report extracting adjusted measures of effect from primary studies for meta-analysis where reported, however do not report on which factors were adjusted for. Gil *et al* (2019) assessed morphine use in the treatment of acute cardiogenic pulmonary edema. They included seven studies (one randomized controlled trial, one non-randomized control trial and five observational studies), and 150639 participants. Lin *et al* (2021) studied intravenous morphine in heart failure and Zhang *et al* (2021) investigated the safety of morphine in patients with acute heart failure. Lin *et al* (2021) included five studies (three propensity-matched cohorts and two retrospective analysis (one unpublished) with 14 9967 participants. Zhang *et al* (2021) included seven retrospective case-control studies and 172 226 participants, including adjusted measures of effect similar to Gao (2011). The treatment given to control groups in included studies was not stated.

See Table 1 for detailed information on included studies.

Internal validity of the systematic reviews, GRADE and absolute effects

AMSTAR II was used to determine the internal validity of included SRs (Appendix 5). In an effort to reduce duplication of effort in synthesis, we used the most relevant (to the PICO), up-to-date and highest quality SRs, among those, we prioritized reviews using GRADE. If a selected review did not report on all relevant outcomes, the next best review with relevant outcomes reported was used. Where needed outcomes were re-GRADED accounting for differencing in contextual/clinical interpretation such as indirectness and imprecision. Gao et al., (2021) included one secondary analysis of a previously conducted RCT which was excluded from our list of included studies to avoid double counting.

Gao and Zang had the highest AMSTAR II scores overall (moderate quality review), however Goa was considered overall to be the most relevant, up-to-date and internally valid as they also used GRADE. Gao did not report their reasons for the selection of type of studies included in the review neither did they report on the funding sources of each study included in the review hence scored as moderate quality. The Lin and Gil reviews were of critically low quality.

Absolute effects were calculated from pooled effect data where possible. In the absence of baseline event data (control event rates for pooled effects), absolute effects were calculated using reported baseline events either (where available) from pooled baseline event data from included reviews across the same outcome or large risk observational studies for that outcome to determine baseline prevalence. This was done for mortality and SAEs.

Effect of interventions

Mortality (in-hospital mortality and 30-day mortality)

Morphine may increase in-hospital mortality (OR 1.78; 95% CI 1.01 to 3.13, low certainty of evidence, six observational studies, n=151 735 participants) resulting in 15 more per 1000, from 0 fewer to 40 more in hospital deaths (Evidence Profile in Appendix 5 and Figure 1). (Gao, 2021) Gao *et al* (2021) did not report any baseline event rates for standard of care or for the intervention arms, thus to calculate absolute effects we assumed a baseline control event rate of 2% for overall mortality based on Lin (2019).

Zhang *et al* (2021) found no association between morphine and in-hospital mortality (OR: 1.94; 95% CI 0.93 to 4.03; p = 0.08, Figure 2) however the direction of effect is still in line with Gao *et al* (2021).

Figure 1: Forest plot of the pooled analysis evaluating in-hospital and 30-day mortality according to opioid use. IV, inverse variance (Gao, 2021)

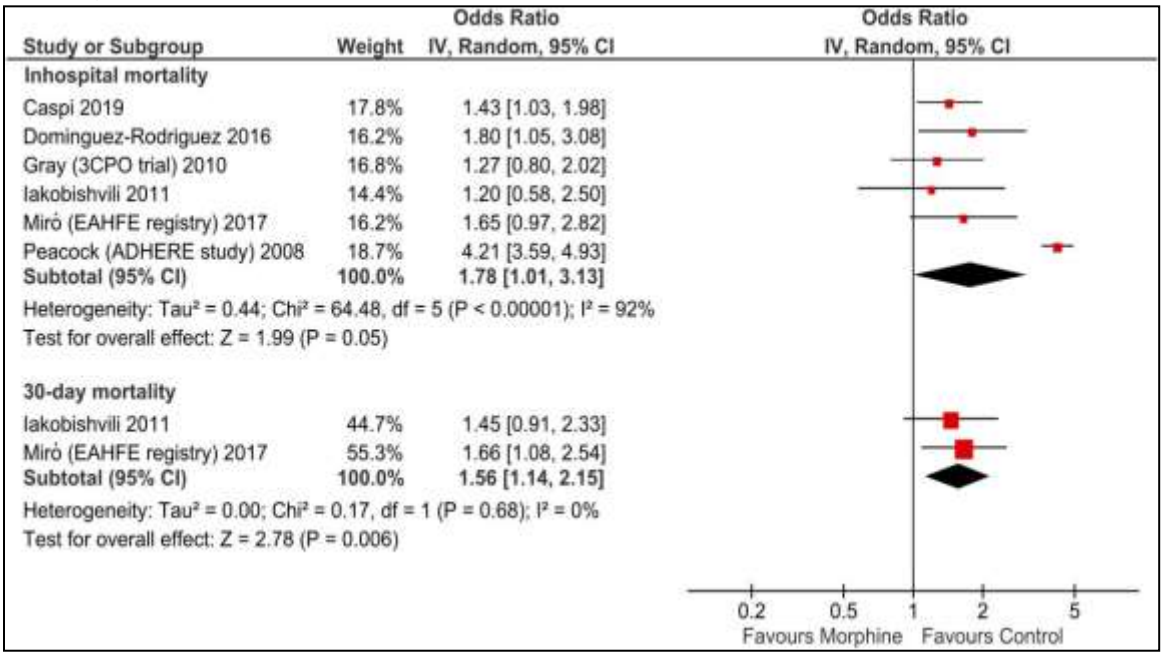


Figure 2: Forest plot of in-hospital mortality (Gao, 2021)

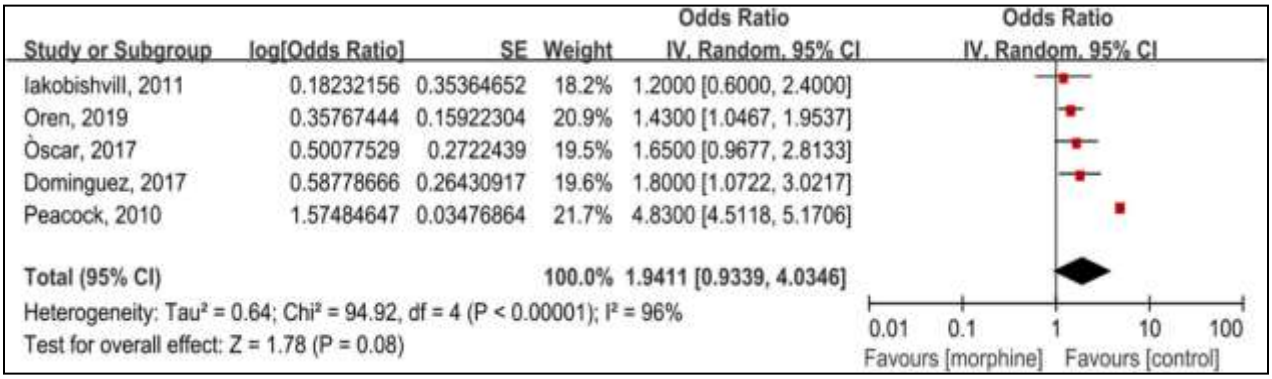
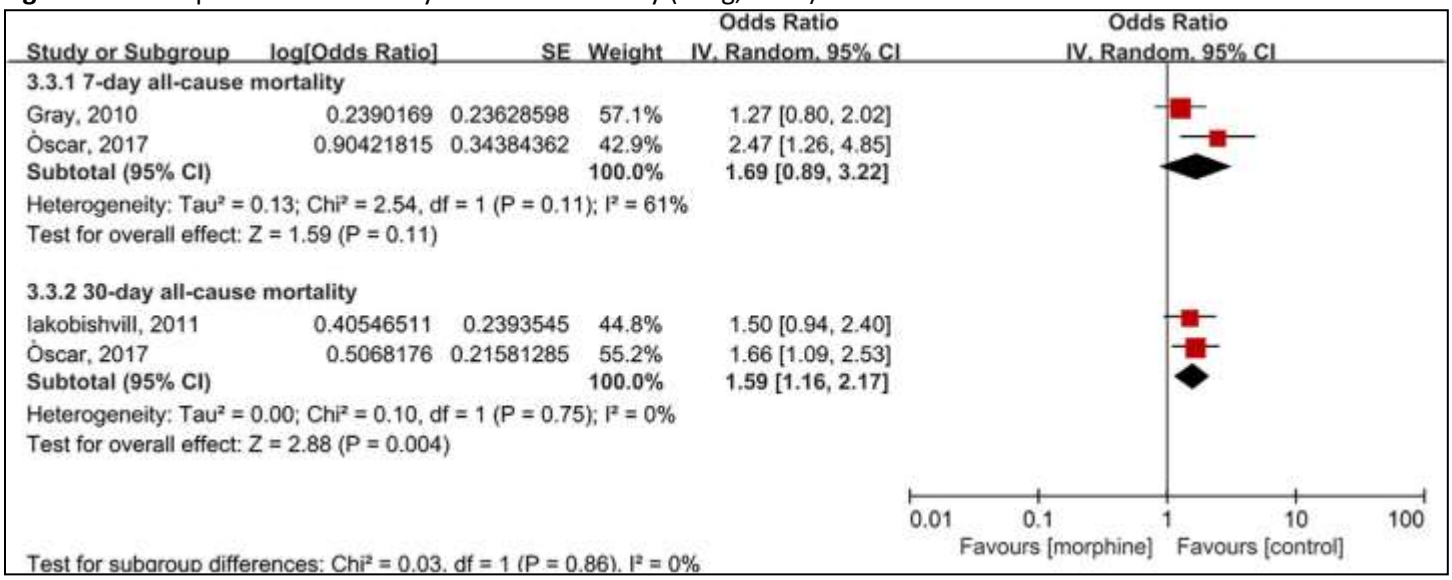


Figure 3: Forest plot of 7 and 30-day all-cause mortality (Zang, 2021)

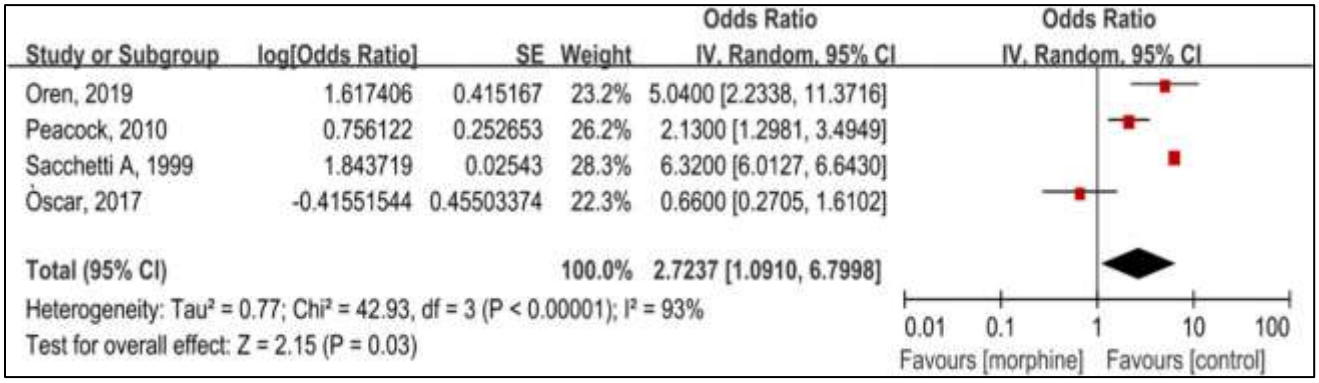


Zhang et al (2021) found that morphine treatment was associated with an increased significant 30-day all-cause mortality (OR 1.59; 95% CI 1.16 - 2.17) from three studies (n=9 904). Gao et al (2021) reported a similar association between morphine use and 30-day mortality (OR 1.56; CI 1.14 -2.15) from two studies (n=986) (Figure 3).

SAE (need for invasive mechanical ventilation)

Morphine may result in a large increase in invasive mechanical ventilation (OR 2.72; 95% CI 1.09-6.80, low certainty of evidence, four observational studies, n=167 847 participants) (Figure 4) (Zang, 2021). Baseline event rate not reported in review thus calculated from estimates of mechanical ventilation baseline event rate based on Gray (2008, NEJM).[27]

Figure 4: Forest plot of invasive mechanical ventilation



Adverse events
Not measured.

ICU or hospital length of stay
Not measured.

Conclusion

This evidence review of use of intravenous morphine in the treatment of acute pulmonary distress included four systematic reviews of observational studies. This review focuses on adjusted pooled evidence from two high-quality, relevant and up-to-date reviews pooling more than 150 000 participants, with direction and magnitude of effects consistent across other included systematic reviews. Based on the most recent, relevant, and highest quality reviews, morphine may increase in-hospital and all-cause mortality and may result in a large increase in invasive mechanical ventilation compared to not using morphine. We have no data on whether morphine increases non-fatal adverse events, ICU or hospital length of stay.

Evidence to Decision Framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty of evidence?** High [ ] Moderate [ ] Low [X] Very low [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Observational evidence (using ROBINS-1) downgraded by one level for risk of bias and by one level for inconsistency. Goa (2021) judged indirectness as serious (for unclear reasons), thus scoring very low certainty. The committee did not consider this evidence as indirect as evidence has clear alignment to PICO and is across various settings, including HIC and LIMCs.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [ ] Small [ ] None [x]	The review identified no beneficial anticipated effects.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large [ ] Moderate [x] Small [ ] None [ ]	• Morphine may increase in-hospital mortality (OR 1.78; 95% CI 1.01 to 3.13, low certainty of evidence, six observational studies, n=151 735 participants) resulting in 15 more per 1000, from 0 fewer to 40 more in hospital deaths (NNH 67) • Morphine may result in a large increase in invasive mechanical ventilation (OR 2.72; 95% CI 1.09-6.80, low certainty of evidence, four observational studies, n=167 847 participants) 45 more per 1,000 (from 2 more to 136 more) baseline event rate based on Gray (2008, NEJM)[27] • Absolute effects for mortality based on baseline event rates provided by Lin (assuming 2% mortality rate)
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention (No Morphine) [x] Favours control (Morphine) [ ] Intervention = Control *or* Uncertain [ ]	**Desirable effects** (of morphine): None **Undesirable effects** (of morphine): moderate
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: n/a Yes [ ] No [ ]	n/a
FEASABILITY	**Is implementation of this recommendation feasible?** Yes [x] No [ ] Uncertain [ ]	No evidence of feasibility was reviewed/sought. The Committee was of the opinion that not giving morphine is standard practice in most settings and clinicians would accept such a recommendation.

RESOURCE USE

How large are the resource requirements?

More intensive	Less intensive	Uncertain
	x	

The Committee was of the opinion that removing a medicine would result in cost savings, with less mechanical ventilation.

Price/treatment course of morphine, IV per patient *(direct medicine prices only)*

Medicine	Tender price (ZAR)*
Morphine 10mg/mL ampoule	4.03**
Sodium chloride 0.9% 10 ml	1.56**
Total	**5.59**

**Weighted average tender prices*

*** Contract circular HP06-2021SVP, June 2022*

Prevalence assumptions:

- According to the Global Health Data Exchange (GHDx) registry, the current worldwide prevalence of HF is approximately 0.8%.
- Meta-analysis by Platz et al (2015) showed that the prevalence of pulmonary oedema in heart failure and reduced ejection fraction (HF-REF) trials ranged from 75% to 83% (though the criteria defining HF varied across trials).
- Experts suggest that approximately 15% of HF-REF patients are administered morphine (as per the 2019 Adult Hospital and 2020 PHC STGs and EML recommendations).

Other assumptions:

- Adult population estimated to be >19 years of age (38189762); based on StatsSA mid-year population estimates of 2021.
- 85.04% of the population is uninsured (>19 years = 32476574)
- Most patients would use a maximum dose of morphine, IV (10 mg).
- Patients would only have one episode per year.

Estimated annual budget impact (medicine costs only):

1: Lower prevalence of HF-REF 75%:
Administered morphine: 0.09 % of 32 476 574 = 28 449
Estimated medicine cost per annum: R159 033

2. Upper prevalence of HF-REF of 83%:
Administered morphine: 0.1 % of 32 476 574 = 32 347
Estimated medicine cost per annum: R180 818

Therefore, disinvesting morphine IV for the treatment of anxiety in adult patients with pulmonary oedema would result in a saving of R159 000 to R180 000 per year.

References:

- Council for Medical Schemes Annual report, 2018/9. Available at: https://www.medicalschemes.com/files/Annual%20Reports/CMSAR2018_19.pdf
- StatsSA mid-year population estimates of 2021.
- Platz E, et al. Assessment and prevalence of pulmonary oedema in contemporary acute heart failure trials: a systematic review. Eur J Heart Fail. 2015 Sep;17(9):906-16.
- Contract circular HP06-2021SVP, June 2022

VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [x] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [x]	No evidence of values and acceptability was reviewed/sought. The Committee expects minor variability in how patients value critical outcomes such as death and avoiding serious adverse events. Acceptable to stakeholders in the hospital setting (district level). However, removing morphine from practice for pulmonary oedema may result in some resistance or lack of behavior change, especially in the prehospital setting.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [x] Uncertain [ ]	Removing morphine will likely result in increased equity across settings where morphine was not available or had unequal access.

Version	Date	Reviewer(s)	Recommendation and Rationale
1.0	13 April 2022	ID, VN, CH, GT, MM, TL	

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Appendix 1: Search Strategy

Ovid MEDLINE

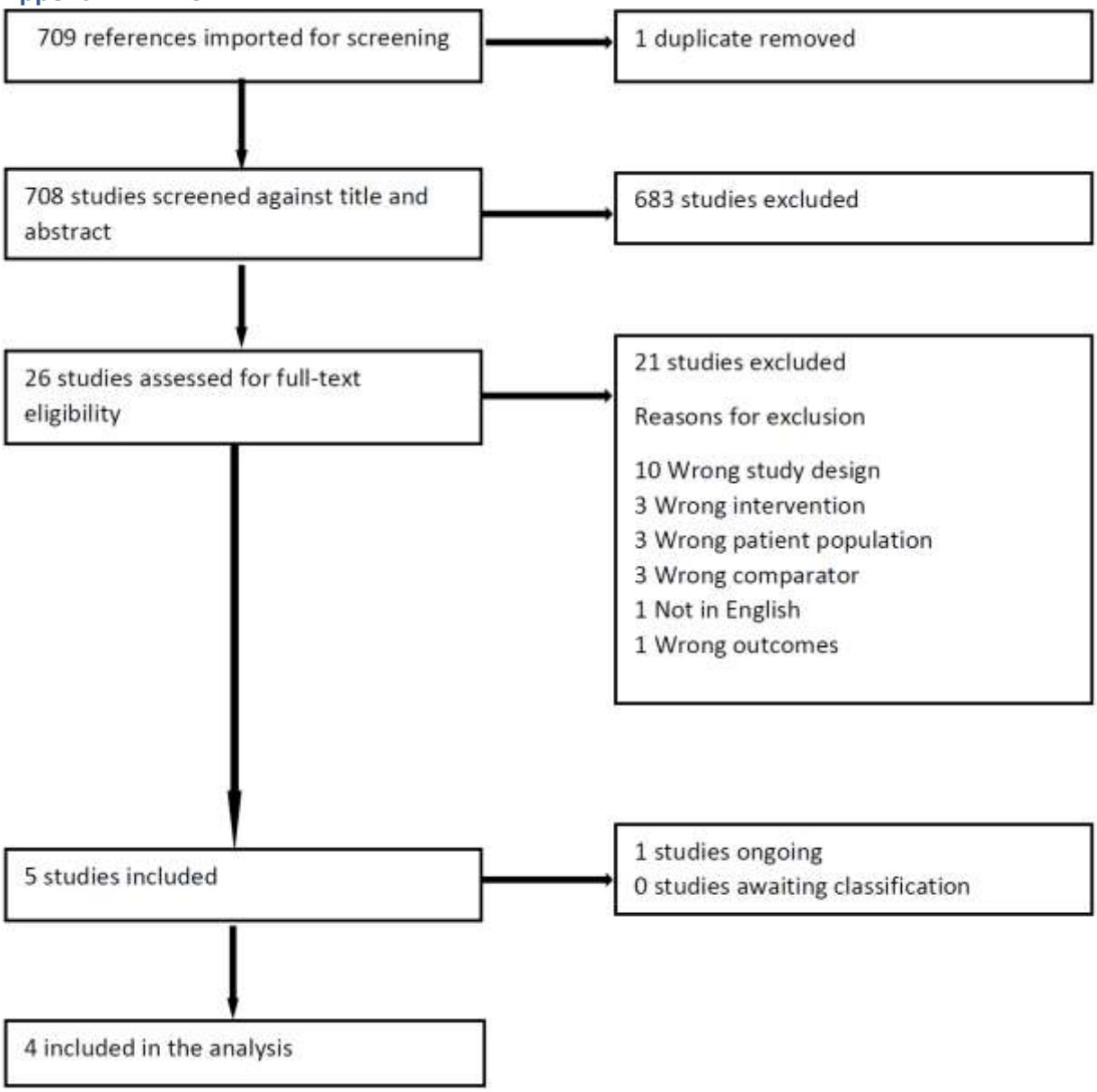
1	Pulmonary Edema/	17628
2	(pulmonary adj2 (edema or oedema)).tw.	19427
3	decompensated heart failure.mp.	3870
4	decompensated cardiac failure.mp.	37
5	exp Heart Failure/	135224
6	1 or 2 or 3 or 4 or 5	161564
7	Morphine/	39357
8	morphin*.tw.	55512
9	7 or 8	62460
10	6 and 9	332
11	randomized controlled trial.pt.	558117
12	controlled clinical trial.pt.	94685
13	(randomized or placebo or randomly or trial or groups).ab.	3175308
14	drug therapy.fs.	2440064
15	11 or 12 or 13 or 14	5255383
16	exp animals/ not humans.sh.	4955382
17	15 not 16	4572999
18	10 and 17	152
19	Meta-Analysis as Topic/	20787
20	meta-analysis/ or "systematic review"/	257861
21	meta analy*.tw.	223648
22	metaanaly*.tw.	2381
23	(systematic adj (review* or overview*)).tw.	232823
24	19 or 20 or 21 or 22 or 23	389013
25	10 and 24	7
26	18 or 25	152

Embase

1	lung edema/	51465
2	(pulmonary adj2 (edema or oedema)).tw.	31414
3	decompensated heart failure.mp.	8216
4	decompensated cardiac failure.mp.	73
5	exp Heart Failure/	597104
6	1 or 2 or 3 or 4 or 5	641888
7	Morphine/	116360
8	morphin*.tw.	78128
9	7 or 8	130930
10	6 and 9	3362
11	(random* or factorial* or placebo* or assign* or allocat* or crossover*).tw.	2281083
12	((blind* or mask*) and (single or double or triple or treble)).tw.	301379
13	crossover procedure/	69726
14	double blind procedure/ or single blind procedure/	237518
15	randomization/ or placebo/	471387
16	parallel design/ or Latin square design/	15682
17	randomized controlled trial/	697078
18	exp ANIMAL/ or exp NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp ANIMAL MODEL/	32230501
19	exp human/	24589730
20	18 not 19	7640771
21	11 or 12 or 13 or 14 or 15 or 16 or 17	2588211
22	21 not 20	2254143
23	10 and 22	360
24	exp Meta Analysis/	237876
25	((meta adj analy*) or metaanalys*).tw.	289477
26	(systematic adj (review* or overview*)).tw.	283463

27	"systematic review"/	331371
28	24 or 25 or 26 or 27	559508
29	10 and 28	106
30	23 or 29	417
Cochrane Database of Systematic Reviews		
#231	MeSH descriptor: [Pulmonary Edema] explode all trees	273
#232	(pulmonary edema):ti,ab,kw	1925
#233	("pulmonary œdema"):ti,ab,kw	262
#234	MeSH descriptor: [Heart Failure] explode all trees	10224
#235	(decompensated heart failure):ti,ab,kw	1337
#236	(decompensated cardiac failure):ti,ab,kw	407
#237	#231 or #232 or 233 or #234 or #235 or #236	25707
#238	MeSH descriptor: [Morphine Derivatives] explode all trees	7372
#239	(morphin*):ti,ab,kw	15665
#240	#238 or #239	17651
#241	#240 and #237	208

Appendix 2: PRISMA



Appendix 3

Table 1: Characteristics of included studies

Citation	Study design	Population	Treatment	Main Findings	Comments
Lin Y, Chen Y, Yuan J, Pang X, Liu H, Dong S, Chen Q. Intravenous morphine use in acute heart failure increases adverse outcomes: a meta-analysis. Rev. Cardiovasc. Med. 2021 Sep 24;22(3):865-72.	Systematic review and Meta-analysis	5 studies (3 propensity-matched cohorts, 2 retrospective analysis (1 unpublished)). Total n=149,967 (intravenous morphine group, n=22,072; no-morphine group, n=127,895) All studies provided the primary clinical endpoints, 4 studies provided secondary endpoints; 3 studies had follow-up durations from 30 days to 12 months Patients with AHF	Intravenous morphine used in treatment group (dosage≥0.5 mg/kg) vs no morphine used in the control group.	**In-hospital mortality** OR = 2.14, 95% CI: 0.88–5.23, p = 0.095, I^2 = 97.1 %; Very low certainty of evidence <u>Total group:</u> 2899/22072 in intervention group 3180/127895 in control group. <u>Sub group analysis in score matching studies</u>: 178/1165 in intervention group 132/1165 in control group (OR=1.41, 95% CI: 1.11–1.80, p =0.005, I^2 = 0%) **ICU Length of stay** Not reported **Hospital Length of stay** Not reported	All included studies represented a low risk of bias in selective outcome reporting and outcome assessment. The scores of NOS for study quality assessment of included studies ranged from 7 to 9. However, the funnel plot asymmetry for in-hospital mortality and invasive mechanical ventilation indicated publication bias. Between-study heterogeneity in in-hospital mortality was $I2$ = 97.1%. Accordingly, subgroup analyses including score-matching studies only were conducted, for which in-hospital mortality was $I2$ = 0%, suggesting low heterogeneity.
Gao D, David C, Rosa MM, Costa J, Pinto F, Caldeira D. The Risk of Mortality Associated With Opioid With Acute Heart Failure: Systematic Review and Meta-analysis. J Cardiovasc Pharmacol Volume 77, Number 2, February 2021	Systematic Review and Meta-analysis	6 studies (observational retrospective studies) Total n=151735 Patients with AHF defined as acute signs/or symptoms of low cardiac output and/or congestion, either de novo or as a heart failure exacerbation, or as reported by investigators irrespective of the details reported.	Treatment: IV morphine Control: Standard of care was not stated.	**In-hospital mortality** OR 1.78; 95% CI 1.01–3.13. very low certainty of Evidence, 151 735 participants, 6 studies Sensitivity analysis (OR 1.46; 95% CI 1.19–1.79; I^2= 0%. Total n=151735 Intervention n=22649 Control n=129086 **30-day mortality** OR 1.56; 95% CI 1.14–2.15 Very low certainty of evidence, 986 participants, 6 studies Total n=986 Intervention n=493 Control n=493 **ICU length of stay** No reported **Hospital length of stay** Not reported	Opioids seem to be associated with a higher risk of in-hospital mortality; however, the true effect may be substantially different from the estimated effect. Opioids seem to be associated with a higher risk of 30-d mortality, however the true effect may be substantially different from the estimated effect.

Gil V, Domínguez—Rodríguez A, Masip J, Peacock WF, Miró O. Morphine Use in the Treatment of Acute Cardiogenic Pulmonary Edema and its Effects on Patient Outcome: A Systematic Review. Current Heart Failure Reports (2019) 16:81–88 https://doi.org/10.1007/s11897-019-00427-0	Systematic Review (7 studies)	1 randomized controlled trial 1 non-randomized controlled trial 5 observational studies Total n=150639 Intervention n=22080 Control n=128559 Unable to determine total number of males and females as not all studies provide this information	Treatment: Morphine with or without other drugs Control: Other drugs without morphine, but the drugs were not stated.	All studies with the exception of Sachetti et al. evaluated mortality in the patients. The conclusion from the review was that administration of morphine to patients with acute pulmonary oedema could lead to worse outcomes in the patients ranging from increased length of hospital stay to death	A meta-analysis not performed but a narrative review of each study was done
Zhang D, Lai W, Liu X, Shen Y, Hong K. The safety of morphine in patients with acute heart failure: A systematic review and meta-analysis. Clin Cardiol. 2021;44(9):1216-1224. https://doi.org/10.1002/clc.23691	Systematic review and meta-analysis	Seven studies (all retrospective case-control studies) Total n=172226 Morphine group n=22967 Control group n=149259 Mean age range from 73 to 81 years Sample size range from 181 to 147 362.	Treatment Morphine and intravenous morphine. Dosage not stated Control treatment was not stated.	**In-hospital mortality** Five studies Total n=170993 Morphine n=22338 Control n= 148655 (OR: 1.94; 95% CI 0.93 to 4.03; p = 0.08, I^2 = 96%) **7-day and 30-day all-cause mortality** Three studies included Total n= 9904 Morphine n= 1175 Control n=8729 **For 7 day all-cause mortality** (OR: 1.69; 95% CI 0.89 to 3.22; p = 0.11, I^2 = 61%) **For 30-day all-cause mortality** OR: 1.59; 95% CI 1.16 to 2.17; p = 0.004, I^2 = 0% **SAE** Risk of invasive mechanical ventilation 4 studies Total n=167847 Morphine n=22047 Control n= 145800 OR 2.72; 95% CI 1.09 to 6.80; p = 0.03, I^2 = 93% **ICU length of stay** Not reported **Hospital length of stay** Not reported	Publication bias could not be ascertained as the number of included studies was less than 10 The Newcastle-Ottawa Scale (NOS) for observational studies was used to assess the quality of the studies based on selection of the population, the comparability of the study, and the assessment of the outcome. The study scored an average of 6.43 For the in-hospital mortality, risk of invasive mechanism and 7-day all-cause mortality outcomes the results showed significant heterogeneity There was no heterogeneity for the 30-day all-cause mortality outcome

Appendix 4

Table 2: Characteristics of excluded studies

Citation	Type or record	Reason for exclusion
Agewall S. *Morphine in acute heart failure*. J Thorac Dis 2017;9(7):1851-1854.	Journal article	Wrong study design
Berger PE, et al.. *ARE narcotics harmful in the treatment of acute pulmonary edema? A critically appraised topic*. Scientific Abstracts (163). CJEM.JCMU 2010;12(3): 277.	Conference abstract	Wrong study design
Dominquez-Rodriquez A, , et al. Study Design and Rationale of *A"Multicenter, Open-labelled, Randomized Controlled Trial Comparing Midazolam Versus Morphine in Acute Pulmonary Edema":* MIMO Trial. Cardiovasc Drugs Ther 2017; 31:209-213	Protocol	Wrong comparator
Dominquez-Rodriquez A, et al. *Influence of morphine treatment on in-hospital mortality among patients with acute heart failure*. Med Intensiva 2017;41:382-384.	Letter	Wrong comparator
Ellingsrud C, et al *Morphine in the treatment of acute pulmonary edema*. Tidsskr Nor Legeforen 23-24, 2014; 134:2272-2275.	Journal article	Wrong study design
Graham CA, et al. *Morphine should be abandoned as a treatment for acute cardiogenic pulmonary oedema*. Emergency Medicine Australasia 2009;21:160.	Letter	Wrong study design
Hall M, et al. *Is Morphine indicated in acute pulmonary oedema*. Emerg Med J 2005; 22:391-392.	Letter	Wrong study design
Herlitz J, et al. *Is pre-hospital treatment of chest pain optimal in acute coronary syndrome? The relief of both pain and anxiety is needed*. International Journal of Cardiology 2011;(149): 147–151.	Journal article	Wrong study design
Holm M, et al.. *The Movement Trial*. J Am Heart Assoc. 2019;8:1-11.	Journal article	Wrong intervention
Johnson MJ, et al.. *Morphine for the relief of breathlessness in patients with chronic heart failure – a pilot study*. The European Journal of Heart Failure 2002; (4):753–756.	Journal article	Wrong patient population
Johnson MJ, et al. *Oral modified release morphine for breathlessness in chronic heart failure: a randomized placebo-controlled trial*. ESC Heart Failure 2019: 6:1149-1160.	Journal article	Wrong intervention
Kubica J, et al.. *Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial*. European Heart Journal 2016; 37:245–252.	Journal article	Wrong patient population
León-Delgado M, et al.. *Opioids for the management of dyspnea in patients with heart failure: a systematic review of the literature*. Colombian Journal of Anesthesiology 2019; 47(1): 49-56	Journal article	Wrong comparator
Mattu A, et al. *Prehospital Management of Congestive Heart Failure*. Heart Failure Clin 5 2009; 19–24.	Journal article	Wrong study design
Orso D, et al. *Is morphine safe in acute decompensated heart failure? A systematic review of the literature*. European Journal of Internal Medicine 2019; 69:e8–e10.	Journal article	Wrong study design
Oxberry SG, et al.. *Short-term opioids for breathlessness in stable chronic heart failure: a randomized controlled trial*. European Journal of Heart Failure 2011;13:1006–1012.	Journal article	Wrong patient population
Oxberry SG, et al.. *Minimally clinically important difference in chronic breathlessness: Every little helps*. American Heart Journal 2012; 164(2):229-235.	Journal article	Wrong outcomes
Oxberry SG, et al. *Repeat Dose Opioids May Be Effective for Breathlessness in Chronic Heart Failure if Given for Long Enough*. Journal of Palliative Medicine 2013; 16(3): 250-255.	Journal article	Wrong intervention
Poole-Wilson PA. *Treatment of Acute Heart Failure. Out with the Old, in With the New*. JAMA 2002; 287(12):1578-1580.	Journal article	Wrong study design
Triposkiadis F, et al.. *Current drugs and medical treatment algorithms in the management of acute decompensated heart failure.* Expert Opin Investig Drugs 2009; 18(6):695-707.	Journal article	Wrong study design
Vicicevic Z. Is it necessary to use Morphine in acute pulmonary edema? Lijec Vjesn 2003; 125(47):1-2.	Journal article	Not in English

Appendix 5: Certainty assessment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsist-ency	Indirectness	Imprecision	Other considerations	Morphine	SOC	Relative (95% CI)	Absolute (95% CI)		
In-hospital mortality												
6	observational studies	serious[a]	serious[b]	not serious	not serious[c]	none	794/22649 (3.5%)	2582/129086[g] (2.0%)	**OR 1.78 (1.01 to 3.13)**	**15 more per 1,000 (from 0 fewer to 40 more)**	⊕⊕◯◯ Low	CRITICAL
SAE												
4	observational studies	not serious[d]	serious[e]	not serious	serious[f]	none	1632/22047 (7,4%)	4083/145800[g] (2,8%)	**OR 2.72 (1.09 to 6.80)**	**45 more per 1,000 (from 2 more to 136 more)**	⊕⊕◯◯ Low	CRITICAL

CI: confidence interval; **OR:** odds ratio; **SOC:** standard of care

Explanations

a. Serious risk of bias: At least one domain of bias in most studies was graded as serious according to ROBINS-I tool

b. With the exception of Peacock, confidence intervals show overlapping, point estimates have a some variation and there is a significant heterogeneity in the pooling. Peacock is a study that comprises a greater sample size (147k vs. 6k, the 2nd greatest) in comparison with the aforementioned studies, and is the only study conducted in a nation that does not abide by ESC guidelines. Inconsistency may be dampened with the exclusion of Peacock as observed following the jackknife sensitivity analysis, however as no concrete justification for the discrepancy was found

c. No imprecision: Not downgraded, very low baseline risk (rare events <2%), further changes in relative effects are unlikely to result in meaningful changes in absolute effects. Furthermore, not downgrading for imprecision as to not double downgrade/penalise for both inconsistency and imprecision.

d. No serious ROB: NCOS was used, low risk of bias for this outcome of included studies

e. Serious inconsistency: Significant heterogeneity across studies specifically Oscar (2017) and Sacchetti (1999)

f. Serious imprecision: Absolute effect does not cross the null threshold, potentially large relative effect (OR >2.5) with IOS met, however absolute effect ranges from trivial harms to possible large harms.

g. Baseline risk calculated from references 16 (for in-hospital mortality)and 27 (for SAE) as this data was not provided as generic inverse variance methods was used

Appendix 6: Overall AMSTAR score for each of the included studies

STUDY	AMSTAR RESULT
Lin Y, Chen Y, Yuan J, Pang X, Liu H, Dong S, Chen Q. Intravenous morphine use in acute heart failure increases adverse outcomes: a meta-analysis. Rev. Cardiovasc. Med. 2021 Sep 24;22(3):865-72.	Critically Low quality review
Gao D, David C, Rosa MM, Costa J, Pinto FJ, Caldeira D. The risk of mortality associated with opioid use in patients with acute heart failure: systematic review and meta-analysis. Journal of Cardiovascular Pharmacology. 2021 Feb 1;77(2):123-9.	Moderate quality review
Gil V, Domínguez-Rodríguez A, Masip J, Peacock WF, Miró Ò. Morphine use in the treatment of acute cardiogenic pulmonary edema and its effects on patient outcome: a systematic review. Current heart failure reports. 2019 Aug;16(4):81-8.	Critically Low quality review
Zhang D, Lai W, Liu X, Shen Y, Hong K. The safety of morphine in patients with acute heart failure: A systematic review and meta-analysis. Clinical cardiology. 2021 Sep;44(9):1216-24.	Moderate quality review

Appendix 7: Ongoing studies

Ongoing studies

A Multicenter, Open-Labeled, Randomized Controlled Trial Comparing Midazolam Versus Morphine in Acute Pulmonary Edema": MIMO Trial(26)

Brief Summary: Acute pulmonary edema (APE) is a common condition in the emergency room, associated with considerable mortality. The use of intravenous morphine in the treatment of APE remains controversial and Benzodiazepines have been suggested as an alternative for morphine to relieving dyspnoea and anxiety in the patients with APE. The Midazolam versus Morphine in APE trial (MIMO) is a multicenter, prospective, open-label, randomized study designed to evaluate the efficacy and safety of morphine in patients with APE.
Study type: Interventional (Clinical Trial)
Estimated enrollment: 136 participants
Allocation: Randomized
Intervention model: Parallel assignment
Masking: None (Open Label)
Primary purpose: Treatment

South African National Essential Medicine List
Primary Healthcare EML review process
Component: Emergencies & injuries

RAPID SCOPING REVIEW

Date: 21 October 2021

Key findings

- The purpose of this rapid scoping review was to determine if there is any new evidence since the previous review of the evidence in 2018 for burn dressings and mupirocin to trigger a formal review.
- No additional RCTs or relevant evidence from SRs since 2018 of burns dressings was found.
- No evidence signal to indicate any change to original 2018 NEMLC recommendations for local wound care (Povidone iodine, silver sulfadiazine, mupirocin, nano-crystalline dressings, *melaleuca alternifolia*) in patients with burns.
- No evidence for the effectiveness mupirocin.
- 2018 and 2019 recommendations remain unchanged.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			

Recommendation: Current standard of care in the STG to be retained – topical povidone iodine for infected burns.
Rationale: No new evidence could be identified for alternative treatment options for septic burns.
Level of Evidence: Low to very low certainty
Review indicator: New evidence sufficient to change the recommendation

NEMLC RECOMMENDATION (MEETING OF 23 JUNE 2022):
NEMLC accepted the review and proposed recommendation, but recommended that the PHC/Adult Hospital Level Committee consider reviewing other dressings for wounds, noting that this topic would be prioritised in the topic prioritisation project plan and may be reviewed in the next review cycle. Furthermore, it was noted that wound dressings are not funded from the Provincial Pharmaceutical budgets.

Monitoring and evaluation considerations

Research priorities

1. Executive Summary

Date: 21 October 2021
Medicine (INN): Dressings for burns (antibiotics and chemotherapeutics for dermatological use)
Medicine (ATC): D06
Indication (ICD10 code): Burns T30.0-3/T31.0-9 + (Y34.99)
Patient population: Adults and paediatrics
Level of Care: Primary Healthcare
Prescriber Level: Nurse prescriber
Current standard of Care: Povidone iodine 5% cream
Efficacy estimates: n/a
Motivator/reviewer name(s): Dr Michael McCaul, Dr Clint Hendricks, Dr Gustav Thom
PTC affiliation: GT – KZN PPTC

2. Name of reviewer(s) : Michael McCaul (1), Clint Hendricks (2), Gustav Thom (3)

1) Division of Epidemiology and Biostatistics, Department of Global Health, Stellenbosch University. SA GRADE Network
2) Division of Emergency Medicine, University of Cape Town. Emergency Physician, Cape Town
3) District Clinical Specialist Team, Amajuba District, KZN

MM, CH, GT have no interests pertaining to topical preparations for management of burns.

3. Introduction/ Background

A proposal was made to add topical mucopirocin to the Adult Hospital Level and PHC STG for the management of septic burns. As the issue of topical preparations had been investigated and not added during the 2017-19 NEMLC review cycle it was necessary to ascertain whether new evidence had emerged since that would necessitate a new review.

4. Purpose/Objective:

To determine if new evidence has emerged since the 2018 (PHC, 21.3.2) and 2019 (Adult, 20.15) EML for dressings for burn care, specifically:

- Povidone iodine
- Silver sulfadiazine
- Mupirocin
- Nano-crystalline dressings
- Melaleuca alternifolia

5. Methods:

We conducted a rapid scoping review of the literature to determine whether there is any new evidence to trigger a formal review of burn dressings for adult and PHC level.

a. **Data sources** : Searched https://www.epistemonikos.org/ for updated or new systematic review of effect on 13 October 2021. Search terms included all intervention terms (as above, including dressings) and terms linked to the population (i.e. burns).

b. **Search strategy :** Title and abstract, and full text screening was done individually by MM, with a 2nd reviewer checking excluded studies (GT). Search strategy in Appendix 1. We used the search filers for systematic reviews and then for trials. We only included evidence (systematic reviews or RCTs) from 2018 onwards and checked CENTRAL for updated systematic reviews that originally supported the 2018 and 2019 Adult and PHC reviews.

c. **Search Yield:** We screened 74 articles, of which 10 were included in full text screening. Seven SRs were included in the narrative summary.

d. Excluded studies:

Author, date	Type of study	Reason for exclusion
Rahimi 2021	SR	Biosynthetic Dressings not relevant
Li, 2020	SR	Nano-silver dressing combined with recombinant human epidermal growth factor. Not relevant.
Harshman, 2019	SR	Acute Emergency care (pre-burn center)
Wormald, 2020	SR	Hydrosurgical debridement. Not relevant

e. Evidence synthesis

Description of included SRs

We found 4 Cochrane Systematic Reviews and 3 non-Cochrane reviews. Three SRs were included (<2018) as they were part of the original evidence review in 2018/2019 (See Table 11: Characteristics of included reviews). Below we include original evidence from the 2018/2019 review, and additional evidence, with references.

Results of Systematic Reviews

We found no new RCTs addressing burn dressings. The 2013 Cochrane review informing the previous recommendations has not been updated. New SRs across topics provide no new evidence for povidone iodine, silver sulfadiazine, mupirocin, nano-crystalline dressings and melaleuca alternifolia.

Silver Sulfadiazine

Silver sulphadiazine was consistently associated with poorer healing outcomes than biosynthetic (skin substitute) dressings, silver-containing dressings and silicon-coated dressings. (Wasiak, 2013, Cochrane Review).

Silver sulfadiazine was associated with a statistically significant increase in burn wound infection vs. dressings/skin substitute (OR = 1.87; 95% CI: 1.09 to 3.19, I2 = 0%). Though, RCTs were at high, or unclear, risk of bias. Silver sulfadiazine was also associated with significantly longer length of hospital stay vs dressings/skin substitute (MD = 2.11 days; 95% CI: 1.93 to 2.28) (Barajas-Nava, 2013, Cochrane Review)

Similar results found in other SRs for SSD (Nimia, 2019 and Maciel, 2019). Moderate quality evidence indicates that there is no significant difference in wound healing between silver-containing foam dressing and SSD dressing (Chaganti, 2019).

Povidone iodine:

Cochrane review showed that there is probably no difference in infection rates between an iodine-based treatment vs moist exposed burn ointment (moderate certainty evidence) – Mean time to healing for wounds treated with povidone iodine vs chlorhexidine: MD - 2.21 days, 95% CI 0.34 to 4.08. (Norman, 2017, Cochrane Review)

Melaleuca alternifolia:

No available evidence could be sourced for cooling burns with Melaleuca alternifolia (tea tree oil) for the first 12 hours. There is also the associated risk of hypothermia for large burn wounds, if this is practiced

Nano-crystalline dressings:

Cochrane review showed that, "There is moderate certainty evidence that, on average, burns treated with nanocrystalline silver dressings probably have a slightly shorter mean time to healing than those treated with Vaseline gauze (difference in means -3.49 days, 95%CI -4.46 to -2.52; I2 = 0%; 2 studies, n=204), but low certainty evidence that there may be little or no difference in numbers of healing events at 14 days between burns treated with silver xenograft or paraffin gauze (RR 1.13, 95% CI 0.59 to 2.16 1 study; n=32) (Norman, 2017, Cochrane Review).

Mupirocin:

We found no RCTs or SRs of Mupirocin.

Facial Burns

Topical antimicrobial agents versus topical non-antimicrobial agents *(Hoogewerf, 2020)*

There is moderate-certainty evidence that there is probably little or no difference between antimicrobial agents and non-antimicrobial agents (SSD and MEBO) in time to complete wound healing (hazard ratio (HR) 0.84 (95% confidence interval (CI) 0.78 to 1.85, 1 study, 39 participants).

Topical antimicrobial agents versus other topical antimicrobial agent *(Hoogewerf, 2020)*

There is very low-certainty evidence regarding whether topical antimicrobial agents make a difference to wound infection (RR 0.73, 95% CI 0.46 to 1.17; 1 study, 15 participants).

Skin substitutes versus topical antimicrobial agents *(Hoogewerf, 2020)*

There is low-certainty evidence that a skin substitute may slightly reduce time to partial (i.e. greater than 90%) wound healing, compared with a non-specified antibacterial agent (MD –6.00 days, 95% CI –8.69 to –3.31; 1 study, 34 participants).

We are uncertain whether skin substitutes in general make any other difference in effects as the evidence is very low certainty. Outcomes included wound infection, pain, scar quality, adverse effects of treatment and length of hospital stay.

Table of included studies

Author, date	***Type of study***	**n**	**Population**	**Comparators**	**Primary outcome**
Wasiak, 2013[1] (in original review)	Cochrane Systematic Review	30 RCTs, poor quality	Any age with superficial or partial thickness burns	hydrocolloid dressings; polyurethane film dressings; hydrogel dressings; silicon-coated nylon dressings; biosynthetic skin substitute dressings; antimicrobial (silver and iodine containing) dressings; fibre dressings; wound dressing pads	Time to healing No of dressings Pain QOL LOS Infection AE
Barajas-Navam 2013[2] (in original review)	Cochrane Systematic Review	36 RCTs (2117 participants)	People of any age or gender, with any type of burn injury	Systemic antibiotics given orally or parenterally Selective intestinal decontamination with antibiotics **Topical antibiotics, such as topical antimicrobial dressings or ointments** Local airway prophylaxis, such as aerosolised antibiotics.	Burn wound infection Invasive infection Infection-related mortality Adverse events wound healing rate Antibiotic resistance All-cause mortality LOS
Nimia, 2019[3]	Systematic Review	24 RCTs Low to unclear ROB	People with burns	SSD vs other dressings (with or without silver)	Infection control and wound healing
Marciel, 2019[4]	Systematic Review	11 RCTS	Burn patients hospitalized in the burn ward	New treatments vs SSD	Complete healing

Chaganti, 2019[5]	Systematic Review	3 RCTS	Patients with partial thickness burns	foam dressing vs SSD and non-foam dressing	Wound healing
Norman, 2017[6] (in original review)	Cochrane Systematic Review	56 RCTs (5807 participants)	people with any burn wound	topical treatments with antiseptic properties.	time to complete wound healing proportion of wounds completely healed during follow-up AEs QOL Pain Resource use
Hoogewerf, 2020[7]	Cochrane Systematic Review	12 RCTs (507 participants)	People with facial burns of any depth	Topical antimicrobial agents topical non-antimicrobial agents Skin substitutes Miscellaneous treatments	time to complete wound healing proportion of wounds completely healed during follow-up AEs QOL Pain Resource use

f. Evidence quality: Overall certainty of the evidence in the included SRs were low.

Appendix 1 – Search strategy

(title:(burn OR burns) OR abstract:(burn OR burns)) AND (title:(dressings OR dresssing OR "povione iodine" OR "silver sulfadiazine" OR mupirocin OR "nano-crystalline" OR "melaleuca alternifolia") OR abstract:(dressings OR dressing OR "povione iodine" OR "silver sulfadiazine" OR mupirocin OR "nano-crystalline" OR "melaleuca alternifolia"))

Version	Date	Reviewer(s)	Recommendation and Rationale
1	21 October 2021	MM, CH, GT	Povidone iodine, topical retained for management of septic burns, as no new evidence could be identified for alternative treatment options for septic burns.

References:

Included studies

1. Wasiak J, Cleland H, Campbell F, Spinks A. Dressings for superficial and partial thickness burns. *Cochrane Database Syst Rev*. 2013;2013(3). doi:10.1002/14651858.CD002106.pub4
2. Barajas-Nava LA, López-Alcalde J, Roqué i Figuls M, Solà I, Bonfill Cosp X. Antibiotic prophylaxis for preventing burn wound infection. *Cochrane Database Syst Rev*. 2013;2013(6). doi:10.1002/14651858.CD008738.pub2
3. Nímia HH, Carvalho VF, Isaac C, Souza FÁ, Gemperli R, Paggiaro AO. Comparative study of Silver Sulfadiazine with other materials for healing and infection prevention in burns: A systematic review and meta-analysis. *Burns*. 2019;45(2):282-292. doi:10.1016/j.burns.2018.05.014
4. Siqueira BS, Zanette GF. Versus Other Treatments : a Systematic Review and Meta-Analysis of. *An Bras Dermatol*. 2019;94(2):204-210.
5. Chaganti P, Gordon I, Chao JH, Zehtabchi S. A systematic review of foam dressings for partial thickness burns. *Am J Emerg Med*. 2019;37(6):1184-1190. doi:10.1016/j.ajem.2019.04.014
6. Norman G, Christie J, Liu Z, et al. Antiseptics for burns. *Cochrane Database Syst Rev*. 2017;2017(7). doi:10.1002/14651858.CD011821.pub2
7. Hoogewerf CJ, Hop MJ, Nieuwenhuis MK, Oen IMMH, Middelkoop E, Van Baar ME. Topical treatment for facial burns. *Cochrane Database Syst Rev*. 2020;2020(7). doi:10.1002/14651858.CD008058.pub3