PAEDIATRIC HOSPITAL LEVEL STANDARD TREATMENT GUIDELINES AND ESSENTIAL MEDICINES LIST
CHAPTER 21: PALLIATIVE CARE
NEMLC 23 FEBRUARY 2023

For Final Ratification

SECTION	MEDICINE	ADDED/DELETED/NOT ADDED
21.1.2.1 DYSPNOEA	Midazolam, oral	Units corrected
	Midazolam, buccal/intranasal	
	Midazolam, IV/SC	

General

Mg/mcg consistency

An external commenter indicated that there was a lack of consistency with dosing units used for the medications in this chapter. The Paediatric Committee recommended that chapter be updated to indicate doses without leading zeros, and to utilise the same unit for both dose and maximum dose. Where confusion is anticipated both mg and mcg doses will be included.

21.1.2.1 Dyspnoea

Midazolam dosing

An external commenter indicated that there were some errors within the dose and maximum doses indicated. These were corrected and units updated as discussed above.

- Midazolam

Route	Dose
Oral	• 125-250mcg~~mg~~/kg [maximum 20 mg (20 000 mcg)] as a single dose.
Buccal/ Intranasal	• 6 months to 9years: 50-150 mcg~~mg~~/kg [maximum 5 mg (5000 mcg)] as a single dose. • 10 to 17 years: 1.5-3.5 mg as a single dose.
IV or SC injection	• 1 month to 5 years: Initially 6.25–25 mcg ~~mg~~/kg, to be administered over 2–3 minutes, dose can be increased if necessary in small steps to maximum total dose of 3000 mcg/dose (3 mg/dose). • 6 to 11 years: Initially 6.25–25 mcg ~~mg~~ /kg, to be administered over 2–3 minutes, dose can be increased if necessary in small steps to maximum total of 3750 mcg (3.75 mg). • 12 to 17 years: Initially 6.25–25 mcg ~~mg~~ /kg, to be administered over 2–3 minutes, dose can be increased if necessary in small steps to maximum of 5000 mcg (5 mg).
IV or SC infusion	• 250-1500mcg ~~0.25 -1.5mg~~/kg/24 hours as starting dose titrating upwards against symptoms and sedation. (Equates to: 10 – 60mg/kg/hour)

21.1.3.2 Depression

The description was updated as follows for clarity:

DESCRIPTION

~~Around 10-30% of chronically ill children are depressed.~~

Low mood in children and adolescents who become aware of their impending death is often congruent and appropriate and does not always warrant treatment.

However, around 10 – 30% of chronically ill children are depressed. DSM 5 criteria instruct clinicians to exclude 'symptoms that are clearly due to a general medical condition' BUT this may lead to an under diagnosis of depression in this population.

~~Depression in children and adolescents who become aware of their impending death is often congruent and appropriate and does not always warrant treatment~~

21.1.4.2 Malodorous fungating wounds/tumours

Metronidazole, topical

At the NEMLC meeting in December 2022, it was a proposed that metronidazole gel products be investigated for use in this indication rather than using crushed tablets.

One topical gel and one vaginal gel available in South Africa. The 0.75% metronidazole topical gel has a single exit price of R268.85/30g. The table below shows comparison to metronidazole tablets.

Product	Price*	Price per gram
Metronidazole Gel 30g 0.75%	R268.85	R8.96
Product	**Price****	**Price per tablet**
Metronidazole; 200mg; Tablet; 21 Tablets	R3.55	R0.17
Metronidazole; 400mg; Tablet; 14 Tablets	R3.70	R0.26
Metronidazole; 400mg; Tablet; 21 Tablets	R5.50	R0.26
Metronidazole; 400mg; Tablet; 5 Tablets	R1.89	R0.38
Metronidazole; 200mg; Tablet; 28 Tablets	R4.20	R0.15
Metronidazole; 200mg; Tablet; 21 Tablets	R3.70	R0.18

**Single Exit Price*

***Master Health Product List – February 2023*

There is a large cost difference between the metronidazole gel and tablets. Sensitivity analysis was conducted to estimate a proposed contract price, from a conservative 80% of SEP to a desirable 40% of SEP. See table below.

			80% of SEP		60% of SEP		40% of SEP	
Product	**SEP Price**	**Price per gram**	**Price per 30g**	**price/ gram**	**Price per 30g**	**price/ gram**	**Price per 30g**	**price/ gram**
Metronidazole Gel 30g 0.75%	R268.85	R8.96	R215.08	R7.17	R161.31	R5.38	R107.54	R3.58

At 40% SEP, the cost of 1 gram of gel far exceeds that of a metronidazole tablet. It is proposed that the recommendation to use crushed metronidazole tablets be retained.

Subcutaneous morphine

Appendix: Subcutaneous morphine

Advice on subcutaneous morphine usage will be added as an annexure.

PREVIOUS ACCEPTED AMENDEMENT

SECTION	MEDICINE	ADDED/DELETED/NOT ADDED
21.1.1.1 ODYNOPHAGIA	Chlorhexidine 0.2% mouth wash	Added
	Paracetamol, oral	Added
	Morphine	Added
21.1.1.2 NAUSEA AND VOMITING	Lorazepam	Added
	Betamethasone	Added
	Haloperidol	Added
	Hyoscine butylbromide	IM added and dose amended
	Omeprazole/PPI	Added
21.1.1.3 INTRACTIBLE DIARRHOEA	Loperamide	Dose amended
	Morphine oral	Not added
	Morphine SC	Not added
	Calcium gluconate:	Added for acute hypocalcaemia associated with tetany
21.1.1.4 CONSTIPATION	Sorbitol	Added
	Glycerine suppositories	Added
	Phosphate enema	Added
	Polyethylene glycol	Added
21.1.2.1 DYSPNOEA	Morphine, SC	Added
	Midazolam, oral	Added
	Midazolam, buccal/intranasal	Added
	Midazolam, IV/SC	Added
21.1.2.2 CHRONIC COUGH	Morphine	Added
21.1.3.1 ANXIETY	Fluoxetine	Added
	Citalopram	Added
21.1.3.2 DEPRESSION	Citalopram	Added
21.1.3.3 DYSTONIA/MUSCLE SPASMS/SPASTICITY	Biperiden	Removed
	Diazepam	Retained
	Baclofen	Not added
	Ibuprofen	Added

	Morphine, oral	Added
	Gabapentinoids	Referral to tertiary added
21.1.3.4 INTRACTABLE SEIZURES	Midazolam, SC/IV	Added
	Morphine SC/IV	Added
21.1.4.1 PRURITUS	Ondansetron	Added
Opioid related	Rifampicin	Not added
uraemic	Gabapentinoids	Referral to tertiary
Cholestasis	Rifampicin	Not added
	Phenobarbitone	Added
Burn wounds	Sedating or non-sedating antihistamines	Added
	Ondansetron	Added
	Gabapentinoids	Referral to tertiary
21.1.4.2 MALODOROUS FUNGATING WOUNDS/TUMOURS	Metronidazole, topical	Added
	Activated charcoal dressings	Added
	Lidocaine/prilocaine	Added
21.2.1 CATASTROPHIC BLEEDS	Tranexamic acid, topical	Added
	Tranexamic acid oral/IV	Not added
	Adrenaline, topical	Added
21.2.2 SPINAL CORD COMPRESSION	Dexamethasone, IV	Added
21.2.3 RESPIRATORY PANIC	Midazolam, buccal	Added
	Morphine, buccal	Added
21.3.1 TERMINAL CARE	Midazolam IV/SC	Added

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NEMLC 20 OCTOBER 2022

MEDICINE AMENDMENTS

SECTION	MEDICINE	ADDED/DELETED/NOT ADDED
21.1.1.1 ODYNOPHAGIA	Chlorhexidine 0.2% mouth wash	Added
	Paracetamol, oral	Added
	Morphine	Added
21.1.1.2 NAUSEA AND VOMITTIMG	Lorazepam	Added
	Betamethasone	Added
	Haloperidol	Added
	Hyoscine butylbromide	IM added and dose amended
	Omeprazole	Added
21.1.1.3 INTRACTIBLE DIARRHOEA	Loperamide	Dose amended
	Morphine oral	Added
	Morphine SC	Added
	Calcium gluconate:	Added for acute hypocalcaemia associated with tetany
21.1.1.4 CONSTIPATION	Sorbitol	Added
	Glycerine suppositories	Added
	Phosphate enema	Added
	Polyethylene glycol	Added
21.1.2.1 DYSPNOEA	Morphine, SC	Added
	Midazolam, oral	Added
	Midazolam, buccal/intranasal	Added
	Midazolam, IV/SC	Added
21.1.2.2 CHRONIC COUGH	Morphine	Added
21.1.3.1 ANXIETY	Fluoxetine	Added
	Citalopram	Added
21.1.3.2 DEPRESSION	Citalopram	Added
21.1.3.3 DYSTONIA/MUSCLE SPASMS/SPASTICITY	Biperiden	Removed
	Diazepam	Retained
	Baclofen	Not added
	Ibuprofen	Added
	Morphine, oral	Added
	Gabapentinoids	Referral to tertiary added
21.1.3.4 INTRACTABLE SEIZURES	Midazolam, SC/IV	Added
	Morphine SC/IV	Added
21.1.4.1 PRURITUS	Ondansetron	Added
Opioid related		
uraemic	Gabapentinoids	Referral to tertiary
Cholestasis		
	Phenobarbitone	Added

Burn wounds	Sedating or non-sedating antihistamines	Added
	Ondansetron	Added
	Gabapentinoids	Referral to tertiary
21.1.4.2 MALODOROUS FUNGATING WOUNDS/TUMOURS	Metronidazole, topical	Added
	Activated charcoal dressings	Added
	Lidocaine/prilocaine	Added
21.2.1 CATASTROPHIC BLEEDS	Tranexamic acid, topical/oral/IV	Added
	Adrenaline, topical	Added
21.2.2 SPINAL CORD COMPRESSION	Dexamethasone, IV	Added
21.2.3 RESPIRATORY PANIC	Midazolam, buccal	Added
	Morphine, buccal	Added
21.3.1 TERMINAL CARE	Midazolam IV/SC	Added

General

- Description updated in line with WHO definition
- Principles for safe and effective prescribing of medicines in paediatric palliative care patients added
- Restructured to divide type of symptoms and management

New section added:

- Paediatric palliative care emergencies added (catastrophic bleeds, spinal cord compression, respiratory panic)

Subcutaneous (SC) morphine

SC morphine added as a route option to various areas of this chapter. Venous depletion is a concern with the elderly and patients with long-term complex co-morbidities, such as in palliative care settings.[1] It is proposed that an appendix be added to outline the use and administration of SC morphine.

21.1.1.1 Odynophagia

Expanded from mucositis management section.

Chlorhexidine 0.2% mouthwash: Added

Paracetamol: Added

[1] Broadhurst D, Cooke M, Sriram D, Gray B. (2020) Subcutaneous hydration and medications infusions (effectiveness, safety, acceptability): A systematic review of systematic reviews. PLoS ONE 15(8): e0237572. https://doi.org/10.1371/journal.pone.0237572

Morphine: Added with referral to Pain Chapter

All agents previously included in the chapter.

21.1.1.2 Nausea and vomiting

Targeted antiemetic therapy added, with a table outlining the cause, site and anti-emetic of choice.
Lorazepam: Added
Betamethasone: Added
Haloperidol: Added
Hyoscine butylbromide: IM added, and dose amended
Omeprazole: Added

Additional medications were added, as listed above, to allow for management to be based on cause and site. The dosing recommendations are in line with the Association of Paediatric Palliative Medicine 2020 formulary.[2] All these agents (with exception of betamethasone) were already listed as treatment options within the STGs and EML. The use of corticosteroids as part of preventative therapy for chemotherapy induced nausea and vomiting since the 1980's[3] and recommended as an antiemetic adjuvant or to be used in highly emetogenic cytotoxic therapies in the APPM. Betamethasone included, as dexamethasone only available as a Section 21.

21.1.1.3 Intractable Diarrhoea

Formally titled: persistent diarrhoea

Loperamide: Dose amended
Updated in line with the British National Formulary for children 2020-2012, and APPM.[2]

Morphine oral: Added
Morphine SC: Added

Morphine included on first principles for utilisation of its side effects.

Calcium gluconate: Added for acute hypocalcaemia associated with tetany
The use of calcium gluconate is included with the recommendations in the Endocrine Chapter for management of hypocalcaemia.

The following text was added:

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[2] Association of Paediatric Palliative Medicine (AAPM). APPM Master Formulary, 5th Edition, 2020. www.appm.org.uk
[3] Van Ryckeghem. Corticosteroids, the oldest agent in the prevention of chemotherapy-induced nausea and vomiting: what about guidelines. Journal of Translational Medicines. 2016, 4(1): 46-51.

- Loperamide: 0.1mg/kg 6 hourly increasing up to 2mg/kg/day.

OR

- Morphine, oral
  - If 0–1 month of age: 0.05 mg/kg 6 hourly.
  - If > 1–12 months of age: 0.1 mg/kg/dose 4 hourly.
  - If > 12 months of age: 0.2–0.4 mg/kg/dose 4 hourly.
- Morphine SC in instances where oral absorption is questionable (see Appendix)

For acute hypocalcaemia associated with tetany

- Calcium Gluconate:
  - Loading intravenous bolus: 10% calcium gluconate 0.5 ml/kg (0.11 mmol/kg) to a maximum of 20 ml over 10 minutes (maximum rate 0.5 mmol/minute) followed by a continuous intravenous infusion over 24 h of 0.5 -1.0 mmol/kg (maximum 8.8 mmol)

21.1.1.4 Constipation

Sorbitol: Added

Sorbitol was added as an alternative osmotic laxative, as it was reported that lactulose is not always available at all facilities.

Glycerine Suppositories: Added

Addition of glycerine suppositories for where oral route is not possible was added in line with the Adult STGs and EML.[4]

Phosphate enema: Added

Polyethylene glycol: Added

Added in line with the Alimentary Tract Chapter.

21.1.2.1 Dyspnoea

Morphine SC/IV: Added

Midazolam: oral/buccal/intranasal/IV/SC: Added

Various routes options added to ensure options are available to minimise causing extra pain. Buccal, subcutaneous and intranasal routes are new to the Paediatric STGs and EML. Both buccal and SC routes are included in the Adults STGs and EML.[4] Intranasal midazolam has been included in the updated Paediatric Anaesthetic Chapter. This route provides for an alternative, effective, non-invasive

[4] National Department of Health. Adult Hospital Level STGs and EML, 2019, 5th Edition.

administration route of midazolam; is safe and fast acting, and a practical route for administration to children. [5,6]

For excessive secretions

Atropine ophthalmic solution 1% used sublingually: Added

First principles, utilisation of adverse effect. *Off-label use*

A retrospective chart review of patients treated in paediatric intensive care or pulmonology and urology wards who received sublingual atropine was undertaken in a facility for a 1-year period. Twenty patients were included in the assessment and response rates were measured using the Teacher Drooling Scale (TDS). Prior to sublingual atropine, the median TDS was 5, which decreased to 3 on the second day of treatment ($p < 0.001$). No adverse events were observed.[7]

A case study of a 14-year-old boy with metachromatic leukodysrophy experiencing excessive oral secretions was given a trial of sublingual atropine. Family and nursing staff observed a meaningful reduction in oral secretions after first day of therapy with no obvious adverse effects. Need for suctioning, drooling and noisy respiration was almost completely eliminated, and when it occurred triggered the need for the next dose. The dosage used was 1-2 drops SL of 0.5% atropine ophthalmic solution every 4-6 hours.[8]

The following text was added:

For excessive secretions

- Atropine ophthalmic solution 1%
  - Starting dose (all ages): 1 drop sublingual every 6 hours.
  - Increase to 2 drops sublingual every 6 hours.
  - Stop if mouth becomes too dry.
  - Note: this may cause pupils to dilate.

Hyoscine butylbromide, oral: Removed

Hyoscine butylbromide, SC: Added

[5] Pansini V, Curatola A, Gatto A, Lazzareschi I, Ruggiero A, Chiaretti A. Intranasal drug administration for analgesia and sedation in children admitted to pediatric emergency department. A narrative review. Annals of Translational Medicine. 2021. 9(2):189.

[6] South African Society of Anaesthesiologists (SASA). SASA Paediatric Guidelines for the safe use of procedural sedation and analgesia for diagnostic and therapeutic procedures in children: 2021-2026. https://doi.org/10.36303/SAJAA.2021.27.4.S2.2635

[7] Azapağsi E, Kendirili T, Perk O, Kutluk G, Tunçer GO, Teber S, Çobanogly N. Sublingual atropine sulphate use for sialorrhea in pediatric patients. J Pediatr Intensive Care. 2020, 9: 196-200.

[8] Case study: Rapoport A, Sublingual Atropine Drops for the Treatment of Pediatric Sialorrhea, Journal of Pain and Symptom Management, V4 (5) 783-788, 2010. https://doi.org/10.1016/j.jpainsymman.2010.02.007.

It was noted that the oral formulation was not effective. Subcutaneous route added in line with that Adult Hospital Level STGs and EML[9] together with IV route that was previously there.

21.1.3 Neuropsychiatric symptoms

Depression and Anxiety

Recommendations aligned with: Chapter 14: Paediatric Psychiatry.

21.1.3.3 Dystonia/Muscle spasms/spasticity

Sections merged together as treatment recommendations are the same.

Biperiden: removed

Not commonly used in palliative care setting.

Baclofen: Not added as per previous NEMLC decision

Diazepam: Retained

In line with previous NEMLC recommendations, baclofen was not added, and diazepam was retained.

Ibuprofen: Added

In line with pain chapter recommendations.

21.1.3.4 Intractable seizures

Midazolam SC/IV: Added

Morphine SC/IV: Added

Dosage recommendations added in line with APPM.

21.1.4.1 Pruritus

Opioid related	Ondansetron	Added
Uraemic	Gabapentinoids	Referral to tertiary

[9] Hyoscine butylbromide, SC/IM, (respiratory secretions): National Department of Health: Affordable Medicines, EDP-Adult Hospital Level. Medicine Review: Hyoscine butylbromide for management of respiratory secretions in adult palliative care patients, December 2017. http://www.health.gov.za/

Cholestasis	Phenobarbitone	Added
Burn wounds	Sedating or non-sedating antihistamines	Added
	Ondansetron	Added
	Gabapentinoids	Referral to tertiary

Opioid Related

Rifampicin has been shown to be effective in the management of morphine-induced pruritus in the palliative care setting.[10] Its action is thought to be related to inhibition of bile acid update by hepatocytes. [11] Ondansetron has been demonstrated to be beneficial in opioid-induced pruritus management in randomised controlled trials of patients receiving morphine. [12, 13]

Uraemic

As for burn wounds. A referral to tertiary for consideration of gabapentinoids was added.

Cholestasis

Rifampicin is an inducer of phases I and II enzymes in transformation in liver and intestines and thus may alter metabolism and increase the excretion of potential pruritogens. It is usually recommended as second line management of cholestasis pruritus (cholestyramine usually listed as first line – not currently included on EML). [14] Phenobarbitone is less effective than rifampicin however has been used in the management of pruritus. [14] It was recommended by NEMLC that rifampicin not be included for this indication, as it would not be in line with good antibiotic stewardship.

Burns

The pruritus in burn wound management has been aligned with recommendations in the Paediatric Emergencies and Trauma Chapters. [15,16]

[10] Mercadante S, Villari P, Fulfaro F. Rifampicin in opioid-induced itching. Support Care Cancer 2001; 9: 467-8

[11] Ganesh A, Maxwell LG. Pathophysiology and Management of Opioid-Induced Pruritus. Drugs. 2007, 67 (16): 2323-2333.

[12] Borgeat A, Stirnemann HR. Ondansetron is effective to treat spinal or epidural morphine-induced pruritus. Anesthesiology 1999; 90: 432-6

[13] Charuluxananan S, Somboonviboon W, Kyokong O, et al. Ondansetron for treatment of intrathecal morphine-induced pruritus after cesarean delivery. Reg Anesth Pain Med 2000; 25: 535-9

[14] Düll MM, Kermer AE. Newer approaches to the management of pruritus in cholestatic liver disease. Current Hepatology Reports. 2020, 19: 86-95.

[15] Ahuja RB, Gupta R, Gupta G, Shrivastava P. A comparative analysis of cetirizine, gabapentin and their combination in relief of post-burn pruritus. Burns. 2011: 203-207

[16] Chung BY, Kim HB, Jung MJ, Kang SY, Kwak IS, Park CW, Kim HO. Post-Burn Pruritus. International Journal of Molecular Sciences. 2020, 21, 3180.

21.1.4.2 Malodorous fungating wounds/tumours

Metronidazole, topical: Added

Crushed metronidazole tablets were recommended for management of malodorous fungating wounds. A systematic review of topical treatments to control the odour of malignant fungating wounds[17] found that metronidazole yielded a B grade level of evidence (moderate level of evidence). Metronidazole was cited in 10 studies, with application varying from gel or solution to use of crushed tablets; usually applied once daily for 14 days. All studies showed a reduction in odour based usually on assessment by visual analogue assessment.

The following text was added:

- Crushed metronidazole tablets can be used either as a solution (mixed with normal saline) for cleaning, applied directly to the wound as a powder or mixed with aqueous cream.

Activated charcoal dressings: Added

A randomised controlled trial compared activated charcoal dressings to hydrocolloid dressings for reduction of wound area of chronic wounds (n=66). Activated charcoal dressings were demonstrated to be more effective initially with better tolerability, however effects at 4 weeks were comparable between groups. [18] Activated charcoal was proposed as a better tolerated product.

Lidocaine/prilocaine: Added

21.2.1 Catastophic bleeds

Tranexamic acid topical/oral/IV: Added for small mucosal bleeds

Tranexamic acid had been used particularly topically in mucosal bleeds such as epistaxis. [19] A randomised controlled trial found tranexamic acid nasal topical packing resulted in cessation of bleeding in 73% of patients, compared to 29% taking placebo. [20]

Adrenaline topical: Added for bleeding wounds

[17] De Costa Santos CM, de Mattos Pimenta CA, Cuce Nobre MR. A systematic review of topical treatments to control the odor of malignant fungating wounds. Journal of Pain and Symptom Management. 2010, 39 (6):1065 – 1076.

[18] Kerihuel, Jean Charles. (2010). Effect of activated charcoal dressings on healing outcomes of chronic wounds. Journal of wound care. 19. 208, 210-2, 214. 10.12968/jowc.2010.19.5.48047.

[19] Cai J et al. The many roles of tranexamic acid: An overview of the clinical indications for TXA in medical and surgical patients Eur J Haematol. 2020 February ; 104(2): 79–87. doi:10.1111/ejh.13348.

[20] Zahed R, Mousavi Jazayeri MH, Naderi A, et al. Topical tranexamic acid compared with anterior nasal packing for treatment of epistaxis in patients taking antiplatelet drugs: randomized controlled trial. Acad Emerg Med. 2018;25(3):261–266. [PubMed: 29125679]

Recommended for topical vasoconstriction to minimise local bleeding. [21]

21.2.2 Spinal cord compression

Dexamethasone IV: Added[22]

21.2.3 Respiratory Panic

Midazolam, buccal: Added
Morphine, buccal: Added

21.3.1 Terminal Care

Midazolam IV/SC: Added

[21] Recka et al. 'Management of bleeding associated with bleeding malignant wounds.' Journal of Palliative Medicine Volume 15, Number 8, 2012
[22] Rautenbach K, Stones DK. Spinal cord disease in children with malignancies: Clinical cases and literature review. SAJCH JULY 2011 VOL. 5 NO. 2 51 – 55