University Hospital Southampton
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Sedation on the Paediatric Intensive Care Unit

Version 1

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Description	Guidance on the initiation and ongoing maintenance of sedation on PICU including monitoring, scoring and safe practice recommendations.		
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1 Version control

Date	Author(s)	Version created	Approval committee	Date of approval	Date next review due	Key changes made to document
3/6/25	Jo Thirsk and Michael Edwards	1				

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3 Introduction

Admission to a paediatric intensive care unit (PICU) is a life changing event for a family and children may experience pain and anxiety for a wide variety of reasons (1). A fundamental principle for any healthcare professional of any discipline working in PICU must be to ensure that their patient has adequate pain control with minimum anxiety during their stay in ICU (2).

The aim of sedation and analgesia is to keep a child comfortable and safe. This can be achieved with a combination of pharmacological and non-pharmacological measures. Children with inadequate sedation/analgesia are at risk of loss of vascular access, self-extubation, self-injury and post-traumatic stress. Non-pharmacological methods can make a big difference to comfort but are rarely sufficient to facilitate invasive mechanical ventilation. Pharmacological methods may include continuous infusions, intravenous boluses and enteral medications. This can lead to excess amounts of either sedative or analgesic being given resulting in problems with delirium and withdrawal (iatrogenic withdrawal syndrome) thereby complicating the patient's stay and subsequent recovery (1).

It has been shown that the appropriate choice of agent in conjunction with validated scoring systems to assess pain and discomfort facilitates sedation, minimises complications and reduces length of stay (3).

4 Scope

This document applies to all health care professionals caring for patients receiving sedation on PICU.

5 Aim/purpose

To provide recommendations for starting and continuing sedative medication in patients on PICU to provide adequate analgesia, anxiolysis and sedation while also using good practice principles and non-pharmacological methods to minimise side effects. This guideline contains recommendations for a 'standard' patient but also has recommendations for specific patient groups. The aim is so standardise practice locally as there are currently wide variations nationally due to a lack of strong evidence-based recommendations on the optimal sedation in PICU.

6 Definitions (if necessary)

BIS	Bispectral index
BP	Blood pressure
CAPD	Cornell Assessment of Paediatric Delirium
ECMO	Extracorporeal Membrane Oxygenation
ETT	Endotracheal tube
HR	Heart Rate
ICP	Intracranial pressure
IWS	Iatrogenic Withdrawal Syndrome
NMB	Neuromuscular blockade
NPS	Numerical Pain Scale
PRIS	Propofol Infusion Syndrome
R-FLACC	Revised FLACC (Face, Legs, Arms, Cry, Consolability)
TBI	Traumatic Brain Injury
WAT-1	Withdrawal Assessment Tool – Version 1

7 Good practice for all patients

7.1.1 Simple non-pharmacological adjuncts

The following steps should be taken for all children (4):

- Sympathetic care from staff and family
- Parental involvement in care
- Comforting touch/massage or rocking
- Reducing environmental noise and light to promote sleep and day–night orientation
- Minimising unnecessary procedures during sleep time
- Relaxation/distraction therapy
- Considering swaddling and non-nutritive sucking in infants
- Addressing feeding and hydration needs wherever possible
- Addressing essential cares e.g. mouth & eye care, body wash
- Regular turns to prevent pressure sores
- Considering play and music therapy

Consider the following:

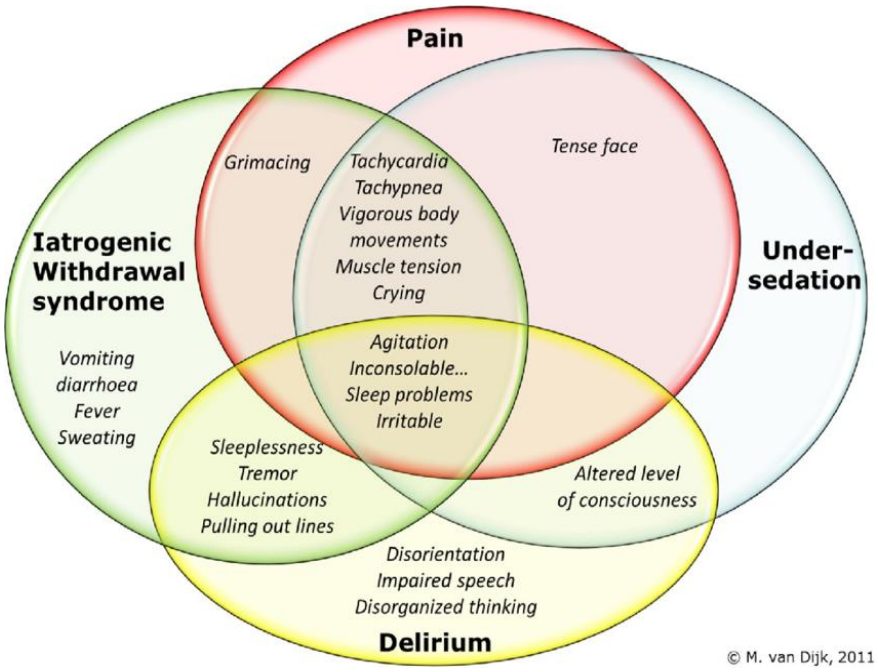
- Nasal endotracheal tube (ETT) – Often better tolerated than an oral ETT.
- Splints – May prevent excessive sedative doses required to limit risk of self-extubation and removal of vascular access devices.

7.1.2 Assessment of sedation and pain

Regular monitoring of pain and sedation level are vital to optimise care for patients, allowing the clinical team to monitor the efficacy of any treatment decisions. The effectiveness of pharmacological interventions should be monitored because expected pharmacodynamic and pharmacokinetic behaviour may be significantly altered in the critically unwell child (5).

If a child is unable to self-report their pain/distress (e.g. due to endotracheal intubation), healthcare professionals must observe the child's physiological and behavioural responses. It may be difficult to discriminate between pain, under-sedation, Iatrogenic Withdrawal Syndrome (IWS) and delirium in critically ill children because the behavioural cues will overlap (Figure 1)(2).

Figure 1: Overlap of behavioural cues in pain, sedation, withdrawal syndrome and delirium



Assessment of sedation:

Comfort-B score: To assess sedation the Comfort-B score is used (Figure 2). This gives a child a score between 6-30 based on a combination of behaviours and physiological responses. The score reflects whether the child is over- or under-sedated. The PICU team should set a daily target score (usually 12-17). The bedside nurse will calculate the score every 4 hours as a minimum. Based on the Comfort-B score, the bedside nurse should adjust the child's sedation as per flowcharts 1 & 2 (see pages 6 and 7).

Assessment of pain:

To assess pain within PICU, the (Revised) FLACC score and Numerical Pain Scale (NPS) are used. The child's age and cognitive status will determine the choice of scoring method. Each scale gives a score from 0-10. Scores should be calculated 4-hourly or more frequently if the child has ongoing pain.

(Revised) FLACC score: R-FLACC is an observed behaviour scale that is validated for assessing pain (Figure 3). It is most validated in children aged 2 months until 7 years, but is often used in intubated children above or below this age range. It is also validated in any age for children with cognitive impairment and/or development disability.

Numerical Pain Score (NPS): NPS is a self-reported method of pain assessment that is validated in children aged 4-17 years, but is most appropriate in those 6 years or older.

Important! These are all screening ⚠ tools, not diagnostic tools ⚠

Figure 2: Comfort-B score (6)

COMFORT B Score

Alertness	1 - Deeply asleep (eyes closed, no response to changes in environment) 2- Lightly asleep (eyes mostly closed, occasional responses) 3 - Drowsy 4 - Awake & alert 5 - Awake & hyper-alert	How responsive is the patient to the ambient light, sound and activity around them? Monitors, phones, talking
Calm/ Agitation	1 – Calm 2 - Slightly anxious 3 - Anxious 4 - Very anxious 5 - Panicky	How would you rate the patient's level of anxiety?
Respiratory response ***(Intubated & ventilated)***	1 - No spontaneous respiration, no cough 2 - Spontaneous breathing no resistance to ventilator 3 – occasional cough or resistance to ventilator 4 - Actively breathes against ventilator or coughs 5 - Fights ventilator coughing or choking	How comfortable and compliant is the patient with ventilation via ET tube?
Respiratory response ***(crying & self ventilated)***	1 – Quiet breathing, no crying sound 2 – Occasional sobbing or moaning 3 – Whining or monotonous sound 4 – Crying 5 – Screaming or shrieking	How would you score the intensity of verbal response? *Significance should be given to the characteristics of the cry not to the presence of tears*
Physical Movement	1 - No movement 2- Occasional (three or fewer) slight movements 3 - Frequent, (> 3) slight movements 4 - Vigorous movements limited to extremities 5 - Vigorous movements include torso & head	What is the intensity & frequency of the patient's movements?
Muscle Tone	1 - Muscles totally relaxed; no muscle tone 2 - Reduced muscle tone; less than normal 3 - Normal muscle tone 4- Increased muscle tone, increased flexion of fingers & toes 5- Extreme muscle rigidity & flexion of fingers & toes *In cases of complex needs/CP/underlying neuromuscular condition assess with a parent for the 1st assessment.*	How does the patient's muscle tone compare to a normal awake & alert child of the same age/stage of development? Flex /extend limb. *(Assess this section last)*
Facial Muscles	1 – Facial muscles totally relaxed 2 – Normal facial tone 3 – Tension evident in some muscles (not sustained) 4- Tension evident throughout muscles (sustained) 5- Facial muscles contorted and grimacing	How does the patient's facial movement/ tension compare to that of an awake & alert child of the same age/stage of development?

POCKET GUIDE Comfort B Explanation v2.0 Final 10th September 2018

Figure 3: (Revised) FLACC score (7, 8)

	Scoring		
Categories	O	1	2
Face	No particular expression or smile.	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to; distractable	Difficult to console or comfort

7.1.3 Daily discussion of sedation requirement

On the 4pm PICU ward round there will be a discussion of the child's sedative/analgesic needs. Particular emphasis will be on whether the prior set target is appropriate for that child and whether the bedside nurse is struggling or succeeding to reach that target. This will also be the time to discuss whether the child is at a point where sedatives need to be weaned/rotated (see Sedation weaning, withdrawal and delirium guideline).

7.1.4 WAT-1 and CAPD screening

After 3 days on PICU, patients should be screened with the Withdrawal Assessment Tool (WAT-1) every 12 hours at 2am and 2pm. Abrupt reductions in medications can lead to IWS. If sedative dose changes are made in response to a high WAT-1 score then the score should be done 4-hourly until WAT-1 score <3.

CAPD screening should be performed on all children admitted to PICU if their Comfort-B score is more than 11. It is carried out alongside WAT-1 screening every shift. If CAPD is 9 or more then follow the paediatric delirium pathway (see Sedation weaning, withdrawal and delirium guideline).

8 Important principles for safe practice

8.1.5 Adequate analgesia

Not all sedative agents provide analgesia. If a child is in pain, then adequate sedation will not be achieved. Hence a combination of analgesic and sedative is the standard approach to ensure the child is comfortable and accepting of mechanical ventilation.

8.1.6 Neuromuscular blockade

Children may require neuromuscular blockade (NMB) as part of their clinical care. Neuromuscular blockers act on the neuromuscular junction's post-synaptic membrane to prevent muscle contraction.

The key significance of this is:

- Behavioural clues to a patient's discomfort will no longer be present
- NMB does not offer **any** sedation and a child can be fully awake but unable to move

Other negative effects of NMB include impaired airway protective reflexes, reduced effectiveness of physiotherapy (as patient is unable to cough), critical care myopathy and masking of seizures (9). If neuromuscular blockade is used, a mandatory ventilation mode is required.

NMB use should be kept to a minimum and the child should be adequately sedated (Comfort-B score <10) prior to their use. The use of neuromonitoring (BIS) should be strongly considered if continuous NMB is being used (see SORT Procedural GA guideline) and Train of Four monitoring should be carried out every 2 hours aiming for 2-3 twitches. NMB pauses should happen daily to assess the child's underlying sedation level. Sedation

should only be reduced in these children after careful consideration and discussion with PICU consultant.

NMB is often used intermittently for a variety of clinical situations such as pulmonary hypertensive crises, severe cardiovascular/respiratory instability, open chest, whilst on ECMO to achieve oxygenation, or to facilitate mandatory mechanical ventilation. These patients must always be heavily sedated to avoid awareness whilst paralysed. Patients who are regularly or continuously given NMB should be prescribed eye drops/ointments to prevent corneal injury.

8.1.7 Propofol

Propofol is a drug used for anaesthesia. It is largely avoided in PICU due to Propofol Infusion Syndrome (PRIS) but it may be running when a child is transferred from theatres. It may be acceptable to continue this if the child is likely to be extubated in <12 hours and should be run at a maximum dose of 4mg/kg/hr (including boluses). Higher doses of propofol may be indicated during procedural general anaesthesia (see SORT Procedural GA guideline). Starting propofol is a consultant-led decision and infusions should not be continued for longer than 48 hours unless in specific circumstances. In this situation, monitoring for PRIS should be carried out which includes blood gases, triglycerides, CK, liver function tests, U&Es, amylase, lactate and ECG (10).

Children on infusions for <5 days can normally have their infusions stopped without consequence of IWS. However, withdrawal should be assessed from ≥3 days stay in PICU as IWS can occur after short infusions. Please see the Sedation weaning, withdrawal and delirium guideline

Propofol can lead to severe hypotension so caution is needed, particularly in neonates post-cardiac surgery. Avoid boluses in this group.

Propofol boluses in other patient groups should only be given after discussion with PICU consultant.

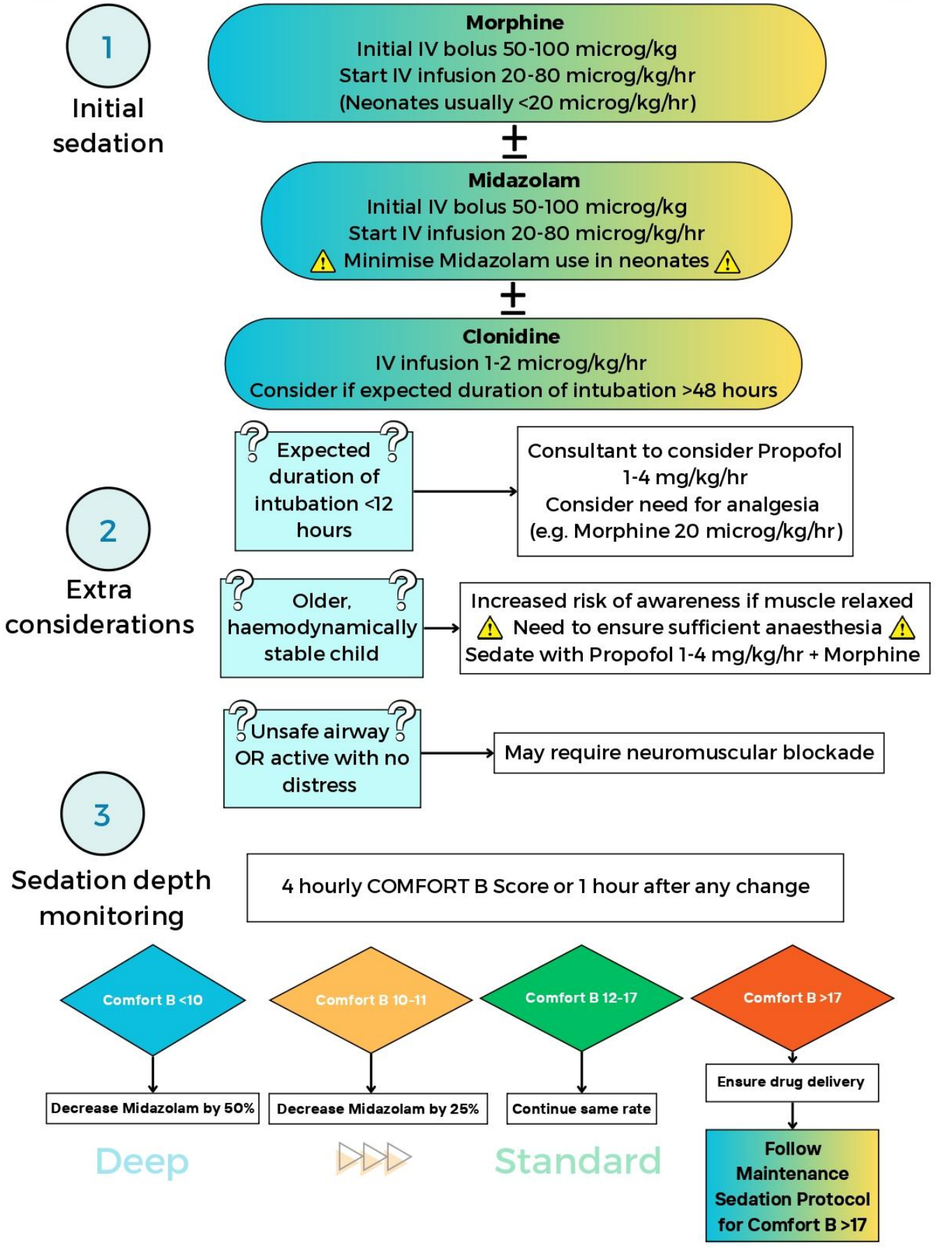
9 Flow charts for sedation protocols

For the vast majority of intubated patients, their sedation/analgesia can be managed with the following flow charts. Some groups of patients may require alternative sedative regimes (see Special patient groups) whilst some patients will require more individualised sedation prescriptions.

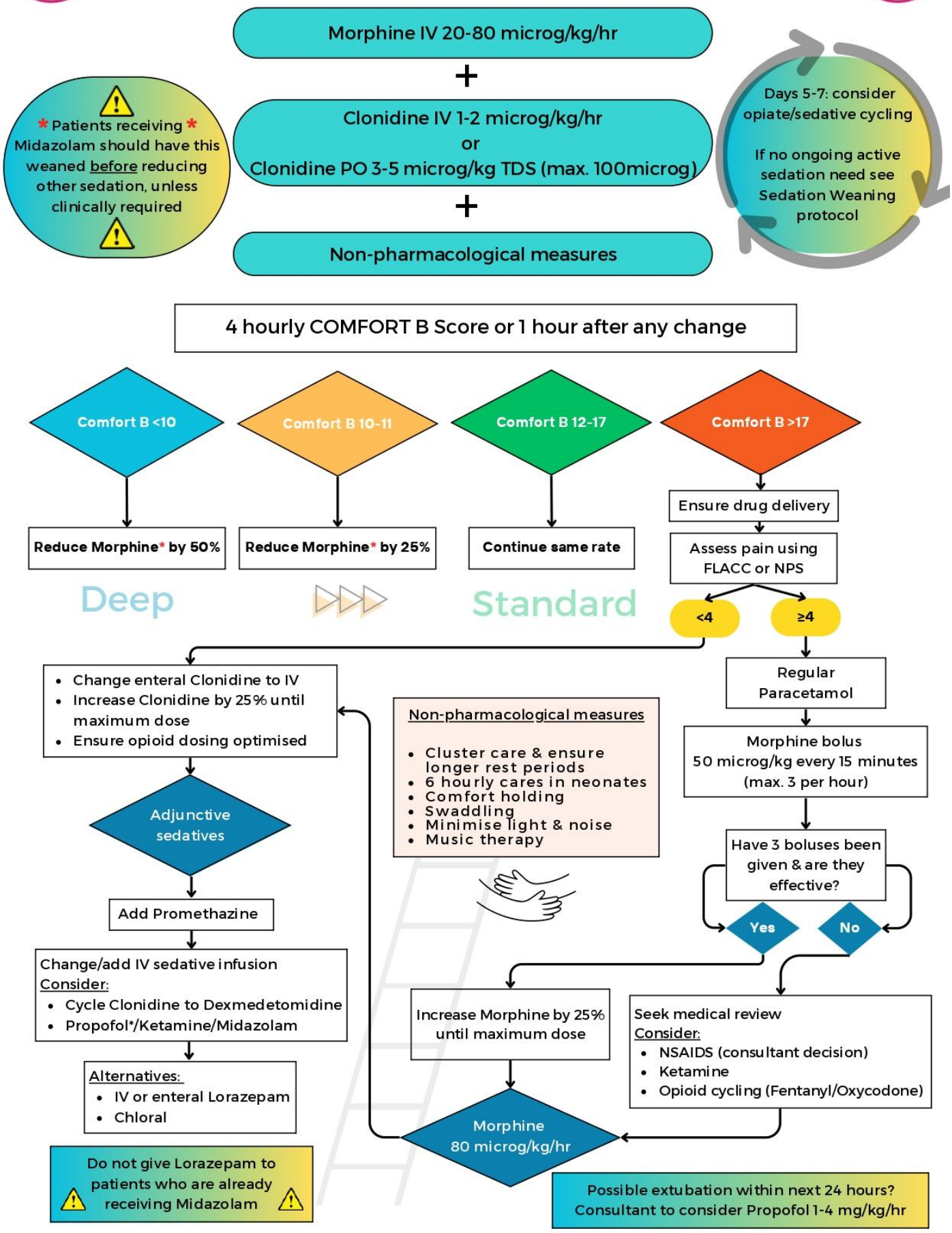
Admission Sedation Protocol – For use during retrieval and PICU admission, until patient reviewed by senior PICU doctor.

Maintenance Sedation Protocol – For ongoing sedation of PICU patients after initial stabilisation period.

Admission Sedation Protocol



Maintenance Sedation Protocol



10 Special patient groups

There are some patient groups who require different sedative and analgesic approaches. In some cases, high levels of sedation may be a core component of the patient's treatment. Escalation and weaning of sedation in these patient groups may be challenging, requiring support from senior PICU staff.

Neonates
This group can be managed as typical PICU patients except extended use of high dose benzodiazepines should be avoided as much as possible due to concerns about neurodevelopment (11). Their sedative requirements are often lower than older children.

Congenital cardiac disease
This group can be managed as typical PICU patients however if bradycardia and/or hypotension are causing problems, dexmedetomidine (8x more specificity for alpha-2 receptors) may be preferred to clonidine (12).

Post-Cardiac Arrest
This group will need to be heavily sedated to minimise cerebral oxygen demand and facilitate targeted temperature control ± neuro-muscular blockade over the first 24-48 hours. They may require higher doses of morphine and ongoing use of midazolam.

Traumatic Brain Injury (TBI)
This group will need heavy sedation to reduce spikes in intra-cranial pressure (ICP) from normal care such as suctioning, log rolls, turns, and coughing. Some patients will require very high doses of midazolam and opioid infusions. Refer to guideline for management of TBI.

11 Sedation and analgesia medication formulary

Listed below are the common medications used on PICU for sedative and/or analgesic purposes. The formulary should be used in conjunction with the recommendations made above in the guideline and provides further information on each agent. The monographs are not exhaustive and only include common or important information about each drug – please see BNFc or summary of product characteristics for further information. Sometimes medication is used outside of the recommendations below as per consultant / specialist advice.

The information below has been extracted from various resources including BNFc, electronic medicines compendium, Evelina formulary and UpToDate and modified where required to match local practice and experience. Please note many medications listed below are off-license or off-label, please prescribe with caution and consider the most appropriate choice for each patient.

Drug	Chloral Hydrate	Clonidine	Dexmedetomidine
Indications and dosing	**<u>Sedation</u>** Sedation adjunct – only use if other agents ineffective, use PRN and review need regularly. IF NEEDING REGULAR DOSES DICUSS SEDATION PLAN WITH CONSULTANT **Enteral:** 25-50mg/kg (max 2g) up to every 4 hours	**<u>Sedation/ pain / opiate + benzodiazepine withdrawal</u>** 1st line sedation in most patients **IV infusion**: 0.5-2microg/kg/hr **Enteral**: 3microg/kg (max 50microg) test dose - if switched from IV test dose not required Dose range: 3-5microg/kg (max 100microg/dose) TDS **Dystonia** **IV infusion**: 1-9microg/kg/hr	**<u>Sedation where use of clonidine has failed/ not appropriate</u>** May be used for post-op cardiac patients in preference to clonidine where HR/BP or arrythmias are an issue **IV infusion**: 0.2-1.4microg/kg/hr For procedural sedation see separate guideline *Non-formulary – use should be reserved for when other treatments have failed or are inappropriate*
Mode of action	Chloral hydrate is metabolised by the liver to active metabolite trichloroethanol. This enhances activity of GABA in the CNS to produce sedative effect.	Stimulates pre-synaptic alpha-2 and imidazoline receptors which decreases noradrenaline release from central and peripheral sympathetic nerves. Reduces blood pressure and heart rate as well as inducing sedation, anxiolysis and analgesia.	Selectively stimulates pre-synaptic alpha-2 adrenoceptors which decreases noradrenaline release in sympathetic nerve endings. Sedative effects due to decreased firing of locus coeruleus. Has analgesic and anaesthetic sparing effects. Dexmedetomidine is 8x more specific to α2 receptors than clonidine
Pharmacokinetics (+ renal and hepatic considerations)	Onset of action 30-60 mins t ½ in children 4-12 hours (significantly prolonged elimination in neonates). Accumulation can occur in renal and hepatic dysfunction, avoid where possible – if used start at lower dose and increase time between doses.	Good oral bioavailability (65-90%) t ½ 8 -12 hours (up to 44-72 hours in neonates) Metabolised extensively by the liver and excreted in urine, dose reduction may be required in renal or hepatic impairment (t ½ increases up to 41 hours in adults with severe renal impairment)	t ½ 2 hours (4.5hrs in neonates) Decreased clearance and prolonged elimination in hepatic impairment– start low and increase to effect No adjustment needed for renal impairment
Contraindications, side effects and interactions	Caution in cardiac disease – can induce arrythmias, especially at high doses SEs: GI upset, delirium Use with other sedating drugs adds to CNS depressant effects	Increased risk of bradycardia/ hypotension with other HR and BP lowering drugs Beta blockers may enhance rebound hypertensive effects on abrupt discontinuation Side effects: QT prolongation, dry mouth, restlessness, Raynard's phenomenon Use with other sedating drugs adds to CNS depressant effects	Side effects: hyperthermia, hallucination, agitation, thirst, hypo/hyperglycaemia, hypoalbuminemia Contraindications: acute cerebrovascular disorder Increased risk of bradycardia/ hypotension with other HR and BP lowering drugs. Beta blockers may enhance rebound hypertensive effects on abrupt discontinuation. Use with other sedating drugs adds to CNS depressant effects
Other considerations	Prolonged use (>2 weeks) may require weaning, abrupt discontinuation can lead to delirium AVOID in neonates Enteral clonidine or sedating antihistamines should be used in preference to chloral hydrate Use lowest dose possible for shortest period of time.	**Switching IV to PO (sedation only)** - use >14 days will require weaning ≤0.5microg/kg/hr = 3microg/kg (max 100microg) TDS >0.6-1 microg/kg/hr= 5microg/kg (max 100microg) TDS >1 microg/kg/hr = 5microg/kg (max 100microg) TDS (consider QDS if not providing adequate effect) **Switching from IV clonidine to dexmedetomidine:** Clonidine dose x 0.7 to switch to dexmedetomidine then titrate to effect i.e. if clonidine 1.5microg/kg/hr = 1 microg/kg/hr dexmedetomidine	Use >14 days will require weaning, **use enteral clonidine if oral switch suitable:** ≤0.4microg/kg/hr= 3microg/kg (max 100 microg) TDS 0.5-0.9 microg/kg/hr = 5 microg/kg (max 100microg) TDS 1-1.4microg/kg/hr = 5 microg/kg (max 100microg) TDS consider QDS if not giving adequate effect **Switching from IV dexmedetomidine to clonidine:** Dexmedetomidine dose x 1.4 to switch to clonidine then titrate to effect i.e. if dexmedetomidine 1.4microg/kg/hr = 2 microg/kg/hr clonidine

Drug	Diazepam (Schedule 4 controlled drug)	Fentanyl (Schedule 2 controlled drug)	Gabapentin (Schedule 3 controlled drug)
Indications and dosing	**Weaning benzodiazepines** **Enteral:** see sedation withdrawal guideline for switch from midazolam to diazepam	**Sedation/ pain (when morphine not suitable or for sedation rotation purposes)** **IV bolus** 0.5-1micrograms/kg, repeat as necessary **IV infusion** 1-6 micrograms/kg/hr	**Neuropathic pain (unlicensed indication)** **Enteral:** **Day 1** 5mg/kg (max 300mg) OD **Day 2** 5mg/kg (max 300mg) BD **Day 3** 5mg/kg (max 300mg) TDS May be increased to maximum 10mg/kg TDS (max 3.6g/day)
Mode of action	Long-acting benzodiazepine – see midazolam Very lipid soluble – crosses blood brain barrier	Synthetic opiate which binds to stereospecific opiate mu receptors throughout the CNS. Around 50-100 x more potent than morphine.	Mode of action for neuropathic pain not fully known - analgesic effect from blockade of voltage gated calcium channels in the CNS reducing release of excitatory neurotransmitters. Specifically, interaction with the a2d-1 calcium channel subunit, which is involved in nociception and descending pain inhibitory pathways.
Pharmacokinetics (+ renal and hepatic considerations)	Good oral absorption (>90%) t ½ 18 hours, up to 2-5 days for active principal metabolite desmethyldiazepam. Proportion of diazepam metabolised to desmethyldiazepam increases on long-term administration. t ½ is significantly prolonged in neonates, renal and hepatic impairment (consider a benzodiazepine with a shorter half-life).	Rapid onset of action – 3-5 minutes Short duration of action – 30-60 minutes t ½ in neonates 4-6 hours t ½ 6 months – 5 years 2.5hrs t ½ > 6months 21 hrs (reduces to 2-4hrs in teenagers) >90% hepatically metabolised and primarily eliminated in urine (start low and titrate to effect). Highly lipophilic so redistributes into muscle and fat	Peak plasma concentration 2-3hrs after dose t ½ in children 4.7hrs t ½ in adults 5-7hrs Excretion is proportional to renal function (not hepatically metabolised). Clearance in infants is highly variable and higher in children <5 yrs compared to those >5. Dose adjustment required in renal impairment
Contraindications, side effects and interactions	Side effects: mood and behavioural changes, agitation, ataxia, dysarthria, nystagmus, hypotension. Paradoxical increases in hostility and aggression are seen more commonly in children. Use with other sedating drugs adds to CNS depressant effects Contraindications: unstable myasthenia gravis Interactions: Fluconazole moderately increases exposure to diazepam (may require lower dose)	Side effects: nausea (less so than morphine), constipation, respiratory depression, hypotension, urinary retention High doses associated with chest wall rigidity Several drugs can alter fentanyl exposure such as clarithromycin, some antiepileptics and antifungals – see BNFc Also see morphine	Gabapentin has been associated with a rare risk of severe respiratory depression even without concomitant opioids. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, and concomitant use of central nervous system (CNS) depressants might be at higher risk – consider lower dose
Other considerations	See midazolam – avoid use in neonates Liquid is intermittently unavailable, use tablet size closest to dose and crush and mix with a small volume of water, dosing is unreliable as poor water solubility	**Patients on ECMO may require higher doses** as fentanyl is sequestered by circuit Consider need for laxatives or antiemetics Tolerance and dependence can develop quickly requiring escalating doses – consider sedation rotation. Fentanyl 1microg/kg/hr = Morphine 10-20 microg/kg/hr	Gabapentin liquid contains large amount of propylene glycol – capsules preferred for higher doses. Capsules may be opened but taste very bitter, if giving orally may need to mask taste with squash or soft food e.g. yoghurt

Drug	**Ibuprofen-** ask consultant before prescribing	Ketamine (Schedule 2 controlled drug)	Lorazepam (Schedule 4 controlled drug)
Indications and dosing	**Pain/ inflammation** **Enteral**: 1-2 months 5mg/kg TDS or QDS >2 months - <40kg 5-10mg/kg TDS (max 30mg/kg/day) >40kg 400mg TDS (up to max 2.4g/day) **Pericarditis** 10mg/kg TDS (max 600mg/dose)	**Sedation prior to painful/ invasive procedure** **IV bolus:** 0.5-2mg/kg **Analgesia for moderate to severe pain or as adjust for sedation in difficult to sedate patients** **IV infusion** 2-40microg/kg/min	**Sedation** **IV/enteral**: 25-100microg/kg (max 4mg) 6-12 hrly **Weaning benzodiazepines** Discuss with pharmacist
Mode of action	Non-steroid anti-inflammatory which inhibits cyclo-oxygenase (COX) enzymes responsible for prostaglandin synthesis. Inhibition of COX-1 has anti-inflammatory and analgesic effect. Also blocks COX-2 which is responsible for maintaining gastric mucosa and influences kidney and platelet function.	Potent analgesic and dissociative anaesthetic. Phencyclidine derivative with direct action on cortex and limbic system, binds to opioid receptors. Blockade of NMDA receptors which produce the analgesic and amnesic effect. Sympathomimetic activity may result in tachycardia and hypertension.	Short-acting benzodiazepine – see midazolam Lipid soluble – crosses the blood brain barrier Despite being labelled as short acting, due to differences in distribution, the duration of sedation after a lorazepam dose is longer than that after an equivalent diazepam dose
Pharmacokinetics (+ renal and hepatic considerations)	Rapid absorption, peak plasma concentration within 2 hours of tablets and 1 hour for suspension. t ½ in adults 2-4 hours t ½ in children 1-2 hrs Metabolised in liver and mostly eliminated in urine AVOID in AKI and severe hepatic impairment	IV injection rapid onset of action (within 1 min) Anaesthetic effect lasts 5-10 minutes t ½ in children 2-3 hrs Extensive hepatic metabolism, excreted in urine. No renal dose adjustment required, risk of prolonged action in hepatic impairment, consider using a lower dose in moderate to severe impairment	Almost completely absorbed following oral administration. Peak effect is reached in <2 hrs. There are no major active metabolites. The elimination half-life is 12-15 hours and there is minimal risk of excessive accumulation. Lower doses and longer intervals recommended in renal/hepatic impairment and in neonates, however lorazepam may be favourable to longer acting benzodiazepines
Contraindications, side effects and interactions	Contraindications: bleeding, hx of GI bleeds or ulceration, thrombocytopenia, varicella infection. Cautions: asthma, renal or cardiovascular disease Side effects: haemorrhage, renal failure, thrombocytopenia (more common in neonates) Interactions: can reduce antiplatelet effect of aspirin – limit use to 48 hours. Caution with other meds which increase risk of bleeding e.g. antiplatelets, anticoagulants or nephrotoxicity e.g. diuretics, ACE inhibitors. May increase digoxin levels. See BNFc	May produce laryngospasm in infants. Contraindications: severe cardiac disease, raised intracranial pressure, stroke, acute porphyria's, head trauma Cautions: psychotic disorders, seizures, shock, hypovolaemia Side effects: tachycardia, hypertension, hypotension, hypersalivation, nightmares and hallucinations (more likely in older children) Interactions: additive CNS depressant effects with other sedatives- effects may be prolonged	Contraindications: unstable myasthenia gravis Side effects: Apnoea, extrapyramidal symptoms, mood and behavioural changes, ataxia, dysarthria, nystagmus, hypotension. Paradoxical increases in hostility, agitation and aggression are seen more commonly in children. Use with other sedating drugs adds to CNS depressant effects
Other considerations	Should be given with food but post-op 1 or 2 doses while still NBM benefit may outweigh risk Consider proton pump inhibitor if planned course length > 7 days	May be a preferred sedative in patients admitted with severe asthma attack due to bronchodilation properties At lower doses useful for severe pain refractory to other analgesics.	See midazolam – avoid in neonates Insoluble in water – round doses to the nearest ¼ of a tablet (250microg), Part dosing from tablets is not advised, therefore administration is not practical in patients <5kg. 'Normal' 1mg tablets can be given sublingually in older patients

Drug	Melatonin	Midazolam (schedule 3 controlled drug)
Indications and dosing	**<u>Establishing day-night rhythm after non-pharmacological methods have failed</u>** **Enteral**: Initially 2-3mg 30 mins to 1 hr before bedtime, increased if necessary up to 10mg Crush tablets in preference to using liquid. *Non-formulary – use only when non-pharmacological methods have failed, review after starting and only continue if benefit seen*	**<u>Sedation</u>** 2nd line sedative in those difficult to sedate with other agents. Traumatic head injury and seizing patients should usually have midazolam as standard **IV infusion:** 10-80microg/kg/hr Higher doses may be required for neuroprotection in TBI or refractory seizures up to 300 microg/kg/hr (with consultant approval even higher doses may be used) **IV bolus:** 50-100 microg/kg (max 2mg)
Mode of action	Melatonin is involved in the synchronisation of circadian rhythms to the diurnal light-dark cycle. Melatonin taken without additional environmental measures (darkened room/quiet environment/minimal disruption) will have poor/no effect.	Binds at the GABA-A receptor site in the central nervous system including the limbic system and reticular formation. Enhances the main inhibitory neurotransmitter GABA with inhibition at all levels of the CNS, to provide anxiolysis and sedation. Short-acting imidazobenzodiazepine with rapid onset. Midazolam does not provide any analgesic effect – do not use alone for sedation
Pharmacokinetics (+ renal and hepatic considerations)	Melatonin is well absorbed and undergoes extensive 1st pass metabolism. Peak plasma levels occur approximately 1 hour after administration of immediate release formulations. Melatonin undergoes extensive metabolism and has a short (45minutes) half-life, accumulation is of minimal concern Avoid in severe renal/hepatic impairment.	Rapid onset of action around 1-5 minutes and short duration of action t ½ in neonates 6-12 hrs t ½ in children 2.9-4.5hrs (as low as 1 hr in 3-10 yrs old) t ½ can be prolonged by up to 6 x in critically ill children Accumulation occurs in renal impairment – start low and titrate to effect Extensive hepatic metabolism to active metabolites, avoid in severe impairment, midazolam preferred benzodiazepine in mild to moderate impairment due to short half-life. Dose reduction advised.
Contraindications, side effects and interactions	Exacerbations of autoimmune disease and seizures has been reported in patients with a history of these disorders. Use with other sedating drugs adds to CNS depressant effects Side effects: Arthralgia, behaviour abnormal, mood altered, pain, anxiety, asthenia, chest pain, hyperbilirubinemia, hypertension.	Contraindications: unstable myasthenia gravis Cautions: hypothermia, hypovolaemia, neonates, vasoconstriction Potentially fatal respiratory depression, especially when used with opioids Side effects: Apnoea, vasodilation, angioedema, mood and behavioural changes, agitation, ataxia, dysarthria, nystagmus, hypotension, paradoxical increases in hostility and aggression are seen more commonly in children. Interactions: Macrolides inhibit metabolism increasing plasma concentrations. Itraconazole & fluconazole increase plasma concentrations of midazolam. Theophylline, carbamazepine, phenytoin antagonises sedative effects. Theophylline patients require larger midazolam doses, reduce midazolam if theophylline is discontinued. Enhanced sedative effect when used with opiates, anticonvulsants, antipsychotics, antidepressants and other anxiolytics/sedative agents.
Other considerations	Modified release tablets can be crushed to make an immediate release dispersion. Should be stopped on discharge from PICU, do not send patients home on melatonin for this indication. No clear evidence of benefit, especially in patients <1 year as not fully developed natural circadian rhythm.	Tolerance and withdrawal significant with all benzodiazepines – keep use as short term as possible. See sedation guideline for IV to enteral conversion. AVOID in neonates and limit use in those under 6 months. Midazolam accumulates in adipose tissue, which can significantly prolong sedation, especially in obesity, hepatic or renal impairment. Variable information but midazolam may be sequestered in the ECMO circuit and impacted by larger volume of distribution – higher doses may be required

Drug	Morphine (schedule depends on formulation)	Olanzapine
Indications and dosing	**Sedation/ analgesia** **IV bolus:** 50-100microg/kg **IV infusion:** 10-80 microg/kg/hr (higher doses may be required for neuroprotection in TBI) **Enteral:** 100-300microg/kg up to 4 hourly (higher doses may be required if switching from IV to enteral for sedation wean)	***Discuss with consultant / pharmacist before starting*** **Acute delirium in PICU-** ensure non-pharmacological methods optimised **Enteral:** 0-1years – 0.625mg OD to BD 1-3 years – 1.25mg OD to BD 4-10 years – 2.5mg OD to BD >10 years – 2.5-5mg OD to BD Initial course: 3 days and review (note may need extended course) Start at once daily at night and only increase after 48-72 hours to allow time to have effect
Mode of action	Potent opioid analgesic. Binds to mu-opioid receptors in CNS causing inhibition of ascending pain pathways and activation of descending pain pathways and altering perception and response to pain.	Second generation antipsychotic with a broad range of targets including serotonin, dopamine, cholinergic antimuscarinic, adrenergic and histamine receptors. Antagonism of dopamine and serotonin sites thought to be responsible for its role in delirium. Olanzapine can have an immediate sedative action but may take days to weeks for its antipsychotic action to reach full effect.
Pharmacokinetics (+ renal and hepatic considerations)	Onset of action IV: 5-10 minutes Oral: 30 mins, peak action at 1hr t ½: Neonates 2.6 hrs Infants <6 months 4-6 hrs Child 3hrs Undergoes extensive 1st pass metabolism in liver and excreted mainly in urine (some in bile and faeces). Oral bioavailability around 50%. t ½ prolonged in renal impairment, reduced clearance, reduce dose. In moderate to severe renal impairment consider alternative such as fentanyl or oxycodone.	Adult data unless specified Well absorbed orally, 40% removed by 1st pass metabolism t ½ 10-18 yrs 37 hrs, time to peak 4.7 hrs Clearance approx. 30% lower in women Highly metabolised by liver, eliminated in urine and faeces. Discuss with pharmacist if renal or hepatic impairment (lower starting dose advised)
Contraindications, side effects and interactions	Potentially fatal respiratory depression, especially when used with benzodiazepines Side effects: nausea, pruritus, constipation, respiratory depression, hypotension, urinary retention, ileus, arrythmias. Side effects such as drowsiness and respiratory depression more likely in renal and hepatic impairment Morphine causes histamine release which can cause severe itching- when used for pain consider switch to oxycodone. If used for sedation and patient unsettled due to itching consider oxycodone or fentanyl Enhanced sedative effect with anxiolytics and hypnotics, antagonism of gastrointestinal effect of metoclopramide and domperidone.	Contraindications: bradycardia, acute myocardial infarction, recent heart surgery, severe hypotension, sick sinus syndrome, unstable angina Caution: cardiovascular disease, blood dyscrasias, seizures, diabetes, jaundice, myasthenia gravis, glaucoma Side effects: agitation, arrythmias, dry mouth, dizziness, hypersalivation, muscle rigidity, hyperglycaemia, insomnia, QT interval prolongation, hallucinations, hypotension, urinary retention, sudden death, agranulocytosis, embolism, neuroleptic malignant syndrome. Use with other sedating drugs adds to CNS depressant effects
Other considerations	Tolerance and dependence can occur with prolonged use - See sedation withdrawal guideline. Morphine 10-20microg/kg/hr = Fentanyl 1microg/kg/hr Consider need for laxatives, antihistamines or antiemetics Patient controlled analgesia – see trust guidance and ensure familiar with protocol	If on for >2 weeks avoid abrupt withdrawal- discuss wean with pharmacist Available as orodispersible tablets for smaller doses Limited data, especially in long-term safety. Must only be used when non-pharmacological methods have failed, most effective treatment for delirium is to minimise sedation.

Drug	Oxycodone	Paracetamol
Indications and dosing	**Analgesia** **IV infusion:** 5-30microg/kg/hr **Enteral:** Immediate release tablets or liquid Infants <6 months- 50-100microg/kg up to every 4 hours Infants >6 months and children– 100-200microg/kg up to every 4 hours, older children consider starting dose of 5mg (maximum 10mg/dose unless pain team/ pharmacist involvement)	**Pain/post operative pain** **Pyrexia with discomfort** Dosing is highly variable based on age and route. Please see the child health paracetamol guideline here. *Children under 1 yr old and/or <10kg max IV paracetamol dose is 30mg/kg/day*
Mode of action	Potent opioid analgesic. Binds to mu-opioid receptors in CNS causing inhibition of ascending pain pathways and activation of descending pain pathways and altering perception and response to pain	The precise mechanism of the analgesic and antipyretic properties of paracetamol has still to be established. It is thought to inhibit a variant of cyclooxygenase.
Pharmacokinetics (+ renal and hepatic considerations)	High oral bioavailability of around 87%. Peak onset of action: IV 20 mins Enteral 1-2hrs t ½: 3-4 hours Metabolised by liver, lower initial doses and titrate slowly Active drug and metabolites excreted in urine – start at low doses and titrate slowly, can accumulate quickly. Preferred option to morphine for analgesia in renal impairment	Peak onset of action: IV = 30-60 mins Enteral = 30-120 mins Rectal =120-180minutes Duration of action: Analgesia = 4-6 hours Antipyretic = 6 hours Oral bioavailability is 90% and IV administration offers very little benefit when compared to oral. Rectal bioavailability is highly variable and should only be considered where the IV/enteral routes are not possible. Metabolised predominantly by the liver and excreted in the urine. Paracetamol is often erroneously held for patients with deranged liver function. Paracetamol is the first-choice analgesic in deranged liver function, consider giving less frequently (e.g. QDS -> TDS). The exception to this rule is hepatoxicity secondary to paracetamol overdose – in which case paracetamol should be withheld. Patients with moderate renal impairment do not give more frequently than 6 hourly, with severe impairment may require 8 hourly dosing – discuss with pharmacy
Contraindications, side effects and interactions	Side effects, as per morphine plus pancreatitis, toxic psychosis CNS depressant effects more likely in renal and hepatic impairment and when used with other CNS depressant drugs. Enhanced sedative effect with anxiolytics and hypnotics, antagonism of gastrointestinal effect of metoclopramide and domperidone.	Side effects are uncommon and serious side effects are rare – see BNFc Always check when the patient last had a dose, also check if the patient has received paracetamol via another route. It is good practice to check the cumulative dose for the last 24 hours before giving a dose.
Other considerations	Note oxycodone is twice as potent as morphine IV oxycodone 1mg = 2mg oral oxycodone Patient controlled analgesia – see trust guidance and ensure familiar with protocols Consider need for laxatives, antihistamines or antiemetics	Regularly review when IV to PO switch is appropriate

Drug	Promethazine	Propofol
Indications and dosing	**Adjunct for sedation** **Enteral or slow IV:** 1 month- 11 yrs 0.5-1mg/kg QDS (max 25mg) 12 years and above 25-50mg QDS Available as tablets and liquid - consider crushing tablets for larger doses (i.e. ≥25mg)	**Short procedural sedation – discuss with consultant** Please refer to SORT Procedural Sedation guideline **Short term sedation in intensive care** Please refer to SORT Procedural GA guideline **Anaesthesia/sedation** *Use of propofol >8 hours should be avoided where possible due to risk of propofol infusion syndrome (PRIS) in children, discuss with consultant*
Mode of action	Phenothiazine derivate which provides sedation by blocking histamine-1 and alpha-adrenergic receptors to provide sedation. Also acts on central dopamine receptors to produce antiemetic effects and has anti-cholinergic properties.	Not fully understood but thought to induce sedation and anaesthesia through positive modulation of the inhibitory effect of the neurotransmitter GABA by binding with GABAA receptors
Pharmacokinetics (+ renal and hepatic considerations)	Onset of action: Oral 20 mins IV 3-5 mins Peak onset between 2-3hrs and effects last around 4-6 hrs Long-acting antihistamine - t½ 10-15 hrs Extensive first pass metabolism by the liver to main active metabolite promethazine sulfoxide and primarily eliminated in urine. Use with caution in renal and hepatic impairment, avoid in severe impairment as risk of accumulation. Start at lower end of dose range and give less frequently.	Highly lipophilic drug which is up to 98% bound to plasma protein. Large distribution volume and metabolised via liver to inactive metabolites which are mainly excreted in urine- caution in both hepatic and renal impairment – increased risk of haemodynamic instability and accumulation, prolonged waking time. Onset of action: 30 seconds Duration of action: 3-10 minutes depending on dose and duration of infusion t ½: three compartment model- Alpha- 2-8 mins, Beta (2nd distribution) – 40 mins, terminal- 300-700 mins, up to 1-3 days after prolonged infusion. With prolonged administration propofol distributes into tissues and on discontinuation can redistribute into plasma which may increase time to wakening
Contraindications, side effects and interactions	Neonates – significant antimuscarinic activity – discuss with consultant before prescribing Contraindicated if <6 years-old due to potential for fatal respiratory depression, psychiatric and CNS events. However still used in patients <6 years-old on PIC due to availability of close monitoring. Caution in epilepsy (lowers seizure threshold) Can cause QT prolongation and hypotension Side effects (frequency not known): Arrythmias, confusion, dry mouth, movement disorder, jaundice, anticholinergic syndrome, insomnia, thrombocytopenia, restlessness	<16 years old there is a higher risk of PRIS which can be fatal - metabolic acidosis, arrythmias, cardiac failure, rhabdomyolysis, hyperlipidaemia, hyperkalaemia, hepatomegaly and renal failure. Caution in shock, cardiovascular disease, epilepsy, hypotension, hypovolemia, raised intracranial pressure and respiratory impairment. Caution with other HR and BP lowering drugs especially at high doses – vasopressors may be required. Caution with haemodynamic instability in cardiac patients in particular. Use with other sedating drugs adds to CNS depressant effects Side effects: apnoea's, arrythmias, hypotension, thrombosis, seizures, pancreatitis, pulmonary oedema, green urine, rash, pain on injection
Other considerations	Generally, does not require weaning, may consider for very prolonged use Enteral clonidine or sedating antihistamines should be used in preference to chloral hydrate	Propofol provides 0.1g/ml of fat (lipid) – if using for >3 days or high risk for lipid overload (e.g. hepatic impairment, long-term TPN) check plasma triglyceride levels regularly

12 Implementation

The PICU nursing education team alongside pharmacists will ensure the training and implementation of this document onto PICU. This guideline will be included in all PICU resident Doctor inductions and will be sent out to all PICU Consultants and current resident Doctors.

13 Roles and responsibilities

It is the responsibility of all staff working on PICU looking after a patient on sedation to understand and familiarise themselves with this document.

14 Document review

All Trust policies will be subject to a specific minimum review period of one year; we do not expect policies to be reviewed more frequently than annually unless changes in legislation occur or new evidence becomes available. The maximum review period for policies is every three years. The author of the policy will decide an appropriate frequency of review between these boundaries.

Where a policy becomes subject to a partial review due to legislative or national guidance, but the majority of the content remains unchanged, the whole document will still need to be taken through the agreed process as described in this policy with highlighted changes.

This PICU sedation guideline will be reviewed in one year or with any change in practice/ evidence

15 Process for monitoring compliance

The purpose of monitoring is to provide assurance that the agreed approach is being followed. This ensures that we get things right for patients, use resources well and protect our reputation. Our monitoring will therefore be proportionate, achievable and deal with specifics that can be assessed or measured.

Key aspects of this policy will be monitored:
(Copy this table and insert below if further tables are required)

Element to be monitored	Effectiveness and uptake of recommendations
Lead (name/job title)	
Tool	Audit
Frequency	Yearly
Reporting arrangements	

Where monitoring identifies deficiencies actions plans will be developed to address them.

16 References

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