Paediatric Intensive Care Unit

Medication Withdrawal Symptoms - Monitoring and management

Staff relevant to:	Doctors, nurses and pharmacists working in Leicester Children's Hospitals with particular emphasis on those working within the Intensive Care setting
Approval date:	February 2021
Version:	1
Revision due:	February 2024
Written by:	P Kukreja
Trust Ref:	C11/2021

Contents

1. Introduction and Who Guideline applies to

Aimed at all doctors, nurses and pharmacists working in Leicester Children's Hospitals with particular emphasis on those working within the Intensive Care setting. To be read in conjunction with existing guidelines on this topic including;

Analgesia and Sedation UHL Paediatric Intensive Care Guideline UHL C10/2009

Neonates with antenatal exposure are not included in this guideline.
Paediatric delirium assessment and management is not covered in this is guideline.

Iatrogenic withdrawal is a common side effect of prolonged sedation in critically ill pediatric patients.
The purpose of this guideline is to ensure the use of a validated withdrawal score to monitor and identify for any signs of withdrawal early. This also ensures patients who are at risk of developing withdrawal symptoms can be weaned off opioids and sedatives in a timely fashion. At the same time, it is important to remember that sedation is not a one-size-fits-all rather, it requires titration to effect.

2. Guideline Standards and Procedures

Definition and target population

Withdrawal includes the physical signs and symptoms that manifest when the administration of an opioid or benzodiazepine is withdrawn after prolonged use.
Children at risk of withdrawal include:

- Any neonate, infant or child who has been on an opioid infusion or regular dosing for 5 days or more.
- Any neonate, infant or child who has required a benzodiazepine infusion or regular dosing (minimum 2 doses/day) for 5 days or more
- Neonates, infant or child who have had previous experience of withdrawal

Other agents associated with withdrawal, albeit to varying extents, include clonidine, barbiturates, dexmedetomidine and chloral hydrate.

Signs and Symptoms of Withdrawal

It is clinically difficult to distinguish between signs of opioid and benzodiazepine withdrawal. These withdrawal signs and symptoms normally appear after 12 hours of stopping the medication with a peak of symptoms occurring at 72 hours. Withdrawal can manifest as:

CNS irritability: poor sleep pattern, tremor, convulsions, irritability, hallucinations, dilated pupils etc.

GI disturbance: vomiting, diarrhoea, abdominal pain, gagging etc.

Autonomic disturbance: Sweating, fever, yawning, hiccups, chills, increased Secretions, tachycardia, tachypnoea, hypertension

Current Guidance

Morphine, clonidine and midazolam are the most common analgesic and sedative agents used in our PICU. They are typically used in combination as they have a synergistic effect that often allows for use of lower doses of opioids. Furthermore, after 5 days of admission patients should be transferred to a long stay pathway and active weaning of these agents should be high priority.

Strategies to reduce withdrawal

Commonly used strategies to reduce the withdrawal syndrome start with efforts to reduce the total doses of benzodiazepine and opioids administered in paediatric ICU. This involves using an appropriate pain and sedation assessment scale (FLACC and COMFORT scale in our PICU), greater use of non-pharmacological intervention to reduce pharmacological sedation, adjunctive use of non-opioid analgesics (paracetamol and NSAIDS where appropriate) to reduce opioid dosing and use of sedation holidays.

Withdrawal Assessment

- The first step in withdrawal management is to conduct a withdrawal assessment using a validated tool called the **WAT 1 (see page 4)** in patients ready to commence a weaning plan **and at high risk of withdrawal**

- WAT-1 Scores should be interpreted on their trend over time. Also take into consideration other factors like course of illness, environmental factors (temperature)

- Assess all regular and PRN sedative and analgesics medications used to determine which agents will need to be weaned. This includes reviewing:
    - Opioids: Infusion and bolus doses
    - Benzodiazepines (midazolam, diazepam): infusions and bolus
    - Other sedatives: Ketamine, Alimemazine, clonidine, chloral hydrate etc.

Use of the WAT 1

- Obtain a baseline withdrawal score using the WAT 1 before any of the drugs are weaned.
- Chart a pain score as per hospital policy (e.g. 4 hourly).
- Score every 12 hours at 06:00 and 18:00 hours - based on bedside staff clinical judgement, increase to 6-8 hourly if withdrawal scores are high and intervention is required
- **Withdrawal is correlated with a score > 3 - Inform doctor if scores are high and use the withdrawal management plan as a guide to direct care.**
- Continue scoring 12hrly until 72 hours after the last PRN opioid/benzodiazepine administered.

WITHDRAWAL ASSESSMENT TOOL VERSION 1 (WAT – 1)

Patient Identifier														
	Date:													
	Time:													
Information from patient record, previous 12 hours														
Any loose /watery stools	No = 0 Yes = 1													
Any vomiting/wretching/gagging	No = 0 Yes = 1													
Temperature > 37.8°C	No = 0 Yes = 1													
2 minute pre-stimulus observation														
State	SBS[1] ≤ 0 or asleep/awake/calm = 0 SBS[1] ≥ +1 or awake/distressed = 1													
Tremor	None/mild = 0 Moderate/severe = 1													
Any sweating	No = 0 Yes = 1													
Uncoordinated/repetitive movement	None/mild = 0 Moderate/severe = 1													
Yawning or sneezing	None or 1 = 0 ≥2 = 1													
1 minute stimulus observation														
Startle to touch	None/mild = 0 Moderate/severe = 1													
Muscle tone	Normal = 0 Increased = 1													
Post-stimulus recovery														
Time to gain calm state (SBS[1] ≤ 0)	< 2min = 0 2 - 5min = 1 > 5 min = 2													
Total Score (0-12)														

Withdrawal Assessment Tool (WAT-1) Instructions

Start WAT-1 scoring from the first day of weaning in patients who have received opioids +/or benzodiazepines by infusion or regular dosing for prolonged periods (e.g. >5 days). Continue twice daily scoring until 72hours after the last dose.
The Withdrawal Assessment Tool should be completed at least once per 12h shift (06:00 and 18:00). The progressive stimuli assessment provides a standard stimulus for observing signs of withdrawal.

3 indicators obtained from the nursing documentation in the previous 12 hours are scored with one point:

- **Loose/watery stools,** which are not consistent with the patient's age, medical condition or baseline pattern.
- **Vomiting/retching/gagging** that cannot be attributed to other causes or interventions.
- **Temperature elevation** that remains >37.8 more frequently than not during the previous 12 hours and is not associated with infection.

5 indicators assessed during a 2 minute observation of the patient at rest are scored with one point:

- State behavior based on observation (asleep/awake/calm =0 or awake/distressed = 1)
- Tremors that are moderate to severe and cannot be attributed to another clinical cause.
- Sweating that is observed and not related to an appropriate temperature regulation response
- Uncoordinated/repetitive movements that are moderate to severe including head turning, leg or arm flailing or torso arching.
- Yawning/sneezing that is observed more than once in the 2 minute observation period.

2 indicators assessed during a progressive arousal stimulus scored with one point:

- Startle to touch that is severe
- Muscle tone that is increased

1 indicator assessed during an observation period following the stimulus scored with up to two points:

- Time to return to calm state that is greater than 5 minutes will receive 2 points.
- If the time to return to calm state is 2-5 minutes, it will receive 1 point.

Higher scores indicate more withdrawal symptoms; lower scores indicate fewer withdrawal symptoms. Interpretation is based on their trend over time. **A score greater than 3 indicates withdrawal. Scoring should be done 12hrly or more frequently if warranted**

(Adapted from: Curley et al. State behavioral scale: A sedation assessment instrument for infants and young children supported on mechanical ventilation. Pediatr Crit Care Med 2008; 7(2): 107-1)

Withdrawal prevention guidelines

Please follow the weaning algorithm on **page 9** to help guide the weaning process with the aim of prevention of withdrawal symptoms. Those requiring opioids /benzodiazepines for <5 days should not require withdrawal scoring and the medications can be stopped without weaning, unless on very high doses or showing signs of withdrawal while reducing/stopping medicines.

Order of drugs to wean:
The suggested order of weaning for patients is;
ketamine,
benzodiazepines,
opioids,
chloral hydrate or alimemazine(trimeprazine)
clonidine.
Although ketamine is not associated with producing an abstinence syndrome, there are reports of patients developing tolerance to the drug and requiring increasing dosage to achieve the same effect. Hence, stop ketamine by reducing it quickly over a few hours. It is usually the first drug to be stopped.

Consider analgesic needs of the patient and continue paracetamol and/or NSAIDS if pain is an ongoing issue.

Using clonidine as part of a sedation program, and continuing it into the withdrawal period will help to reduce the incidence of abstinence in the majority of patients

Note: Above is a guideline and will need to be tailored to the patient's clinical situation. For example, in some situations it may be more important to wean the sedative first if there is an ongoing requirement for analgesia.

Converting to Enteral dosing of analgesics and sedative and how to wean:

An early goal in weaning should be to convert all medications to enteral formulation as early as possible.
Please see Appendix 2 for oral conversion
Once enteral formulation has been established, you can continue the same % wean that was being weaned while in IV form. Once you get to low doses, the weaning involves increasing the interval between the doses rather than reducing the dose further.
Established weaning plan should be clearly documented in notes, discharge plan (weaning dose and frequency), and handover. Example: the original dose of Clonidine was 2micrograms/kg/h, weaning plan is 25% every 24h = wean by 0.5microgram/kg/h every 24h.

Recommended Morphine weaning:

Wean as per appendix 1
Can be converted to enteral route from around 10micrograms/kg/hour infusion.
Give oral morphine 4-6hrly according to need/calculated dose (try to avoid going above BNF-C max dose of 200micrograms/kg/dose but there are exceptions to this if patient very tolerant to opioids/need to convert to enteral from much higher iv dose)
If on 4hrly dosing can wean doses or consider keeping the same dose and increase the dosing interval to 6hrly.
Wean every 24-48 hours as tolerated by the patient.
Wean until reach a low dose per kg for that patient or minimum of 200microgram 4-6hrly. It is difficult to measure doses of oral morphine below 200micrograms so avoid prescribing.
You would then continue to increase the interval between the doses to 8hrly then to 12hrly and possibly 24 hourly before ceasing. Depending on the patient some may go to PRN or stop at 8hrly.

Recommended Diazepam weaning:

Until at a dose of 0.05mg/kg 6hrly
Once at 0.05mg/kg 6hrly, then increase the interval between the doses to 8hrly for 24 hours, then 12 hrly and then to 24hrly before stopping (or same period of time you were weaning previously i.e. if was weaning every 48hours then would do this for 48hours).
Note: it is often at these smaller doses that it is difficult to wean off the drug without symptoms of withdrawal. If this is the case, you may need to slow the wean further.

Recommended Clonidine weaning:

Dose should remain the same until opioid and/or benzodiazepine is completely weaned off or increased if withdrawal signs are present

Once opioid and/or benzodiazepine have been successfully discontinued, then the clonidine should be weaned over 3-5 days to avoid rebound hypertension.

Length of administration:

<5 days – no weaning is necessary
5 – 10 days - reduce dose by 50 % (of original dose) every 24 hours closely observing for withdrawal (should be able to stop in 48hrs)
>10 days – reduce dose by 25% (of original dose) every 24 hours (should be able to stop in 4 days on this regime)

Conversion from IV to oral clonidine: (100% bio-availability)

Once on IV infusion of 0.5 micrograms/kg/hr can be converted to oral.
Commence on enteral clonidine 3micrograms/kg/dose 6 hrly (usual max 5 microgram/kg/dose)
Can increase frequency if unable to tolerate high clonidine doses, so split total daily dose over more administrations (e.g. 3-4hrly)
Wean down to 1mcg/kg per dose every 6 hours and then increase the interval between doses to 8hrly, 12hrly and then cease. Each step would be for 24 hours. Depending on patient may be able to stop at 8hrly dosing.

Monitor Blood Pressure 6 hourly while weaning Clonidine. If blood pressure increases by 50% from the previous 24 hours consider slowing the rate of weaning and increase dose to previous higher dose before symptoms of withdrawal appeared for 24-48 hours and then start weaning again

3. Education and Training

Education and training are ongoing processes, promoted through induction and continuous bedside teaching. Nursing education is supported by Nursing educators and practice development teams. Training for medical staff is provided during lunch time teaching (on Wednesdays)

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Treatment algorithm followed and documented	Audit	ICU Consultant		Clinical practice group
Withdrawal assessment completed and documented	Audit	ICU Consultant		Clinical practice group

5. Supporting References

1. Drug Withdrawal Plan and Form: Sedation Weaning Plan – Starship Hospital Auckland Guidelines
2.Playfor, S., Jenkins, I., Boyles, C. et al. Consensus guidelines on sedation and analgesia in critically ill children Intensive Care Med (2006) 32: 1125 https://doi.org/10.1007/s00134-006-0190-x
3. Cunliffe M, McArthur L, Dooley F Managing sedation withdrawal in children who undergo prolonged PICU admission after discharge to the ward. *Paediatr Anaesth 2004;**14**:293–8. doi:10.1046/j.1460- 9592.2003.01219.x*
4. Diagnostic and statistical manual of mental disorders, DSM-IV-TR. Washington, DC: American Psychiatric Association; 2000. p. 208.
5. YasterM,PunjabiNM.Sedation, sleep promotion, and delirium screening practices in the care of mechanically ventilated children: a wake-up call for the pediatric critical care community. *Crit Care Med*. 2014;42(7):1592-1600.
6. Franck LS, HarrisS K, Soetenga DJ, Amling JK, Curley MA. The Withdrawal Assessment Tool-1 (WAT-1): an assessment instrument for monitoring opioid and benzodiazepine withdrawal symptoms in pediatric patients. *Pediatr Crit Care Med*. 2008;9 (6):573-580.

6. Key Words

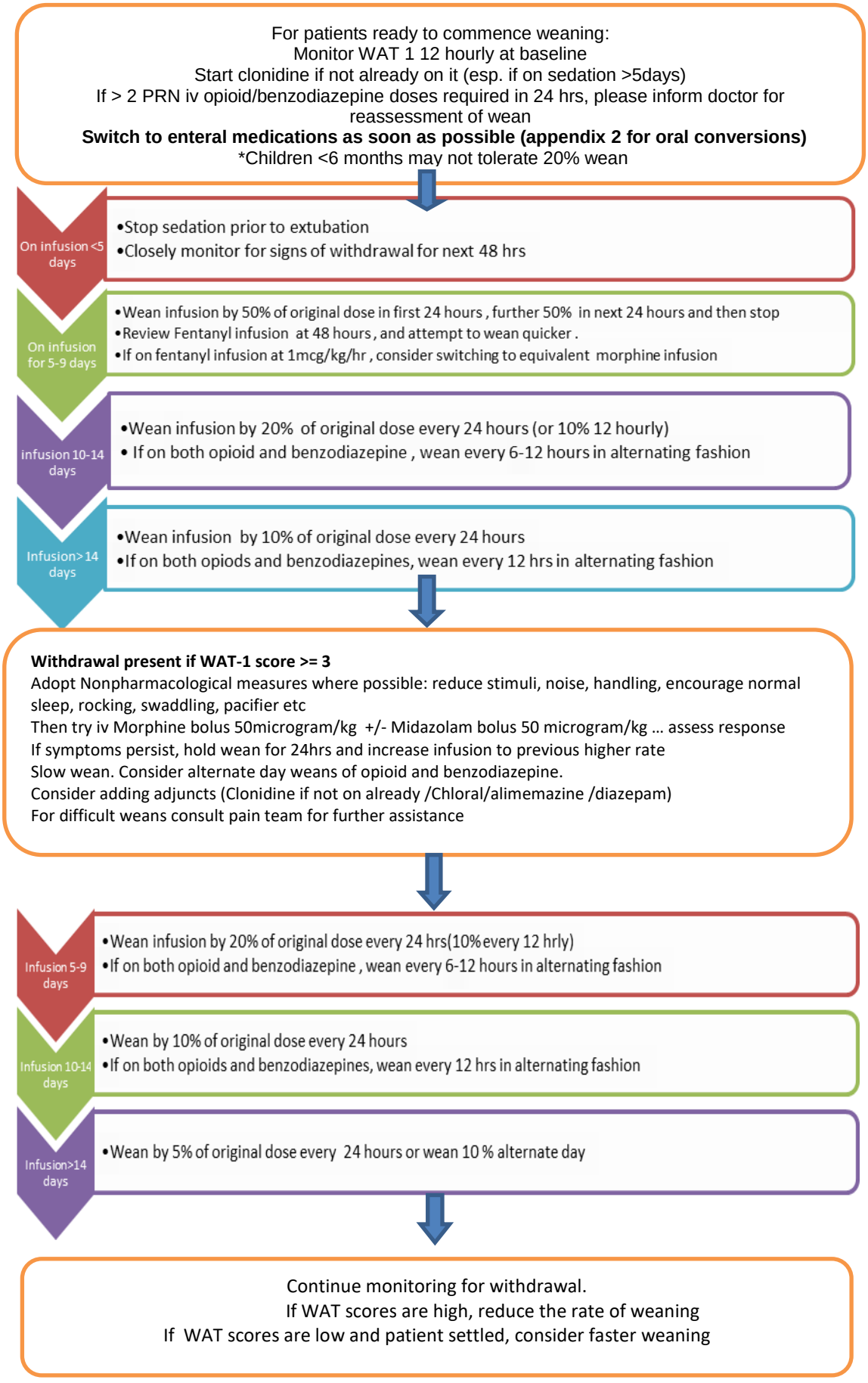
Alimemazine, Benzodiazepines, Chloral hydrate, Clonidine, Ketamine, Morphine, Opiods, WAT 1, Wean, Weaning, Withdrawal/ Withdrawal symptoms

---

The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

CONTACT AND REVIEW DETAILS	
Guideline Lead (Name and Title) Pompa Kukreja - Consultant	**Executive Lead** **Chief Medical Officer**
Details of Changes made during review: **New guideline** **Archive** Morphine and Clonidine - Oral UHL Childrens Intensive Care Guideline C22/2010	

Appendix 1 WEANING ALGORITHM



Appendix 2: CONVERSION CALCULATIONS

Opioid Conversions:

Conversion of IV morphine to enteral morphine:

Oral to parenteral potency of morphine varies between 2:1 and 3:1. Therefore, when converting morphine IV to enteral multiply the IV dose by 2-3.

1) Can be converted from around 10microgram/kg/hr if tolerating enteral
1) Calculate the total daily dose of morphine IV in 24 hours
2) Multiply daily dose by 2-3 to give total daily dose of enteral morphine in 24 hours
3) Divide into 4 or 6hrly dosing

Conversion of IV fentanyl infusion to IV morphine infusion

Fentanyl is more potent then morphine. In acute pain, the relative potency of fentanyl to morphine is 1:100. In the chronic situation (i.e. those patients who requiring weaning) the potency is thought to be 1: 25-50. When changing between opioids the tolerance between opioids is not thought to be the same so the dosage of the new opioid should be reduced by 25-50%.

E.g. 1microgram/kg/hr of fentanyl= 25-50 microgram/kg/hr of morphine

Conversion of IV fentanyl to enteral morphine

Convert to IV morphine first then to enteral morphine following the steps above.

__mcg/24hr of fentanyl IV divide 1000 x 25 x 3 = ___mg/24hr of enteral morphine (divide into 4 or 6 hrly dosing)

Benzodiazepine conversions

Conversion of IV Midazolam to Diazepam:

1) Calculate the total daily IV midazolam
2) Divide total daily dose by 3 to give total daily dose of IV or enteral diazepam
3) Divide total daily dose of diazepam by 4 to get 6hrly dosing

__mg/24 hr of iv midazolam divide 3= ____mg/24hr of diazepam (divided by 4 to get 6hrly dosing)

4) Start diazepam and decrease IV midazolam by 50% with 1st dose of diazepam. Cease IV midazolam infusion with 2nd dose IV or enteral diazepam.
5) IV Diazepam can be used if enteral route not feasible

Conversion of IV diazepam to enteral diazepam

Use a 1: 1 conversion of IV diazepam to enteral diazepam
Maximum Doses: IV/Enteral Diazepam = 10mg

Appendix 3: WEANING OF CHLORAL HYDRATE

Pharmacology
Mechanism of action is similar to benzodiazepines.

Pharmacokinetics
Chloral hydrate is rapidly absorbed and peak efforts occur within 30-60minutes.
It is metabolized by alcohol dehydrogenase to trichloroethanol (TCE), which is the active metabolite.

Adverse Effects
Hypotension
Bradycardia
Arrhythmias
Hepatotoxicity
Hyperbilirubinemia
Withdrawal and paradoxical reactions

Long term use:
Long term use of chloral hydrate has not been well studied. It is thought that dependence and hence withdrawal can occur with long term use of chloral hydrate however it is not known if a weaning regimen is required for chloral hydrate

Weaning
- In patients who require an opioid and benzodiazepine wean, it is likely that they would have also been using regular chloral hydrate

- If the patient is being established on a formal benzodiazepine wean that includes diazepam it is unlikely you will need to formally wean the chloral hydrate as mechanism of action would be similar.

- Chloral hydrate should be kept PRN in the initial few days while appropriate doses of opioids and benzodiazepines are being titrated for the patient.

Dosing during weaning
- Suggested dose should be 15-30mg/kg 6hrly PRN po/ng
- As weaning of sedatives occur chloral hydrate prn interval should be increased (12hrly or 24hrly)