JOHNS HOPKINS ALL CHILDREN'S HOSPITAL

Iatrogenic Withdrawal Clinical Pathway

JOHNS HOPKINS
All Children's Hospital

Johns Hopkins All Children's Hospital

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Updated: 7/10/2025
Owners: ICU Pharmacists

Johns Hopkins All Children's Hospital

Iatrogenic Withdrawal Clinical Pathway

Rationale:

This clinical pathway was developed by a consensus group of physicians, advanced practice providers, and pharmacists at Johns Hopkins All Children's Hospital (JHACH) to standardize the management of iatrogenic withdrawal. It addresses the following clinical questions or problems:

1. How to evaluate patients for iatrogenic withdrawal
2. When to consider medications for the treatment of iatrogenic withdrawal
3. When to consult the Pain Team

Background:

Pain and sedation management in critically ill pediatric patients is widely variable in clinical practice. Prolonged administration of opioids, benzodiazepines, and alpha$_2$-agonists in children can lead to tolerance and withdrawal symptoms, especially if maintained for more than 3 days.[1,2] Iatrogenic withdrawal syndrome (IWS) is a clinical syndrome that manifests after a medication is either stopped, rapidly weaned, or chemically reversed after prolonged exposure.[1,3,4] Around 10 – 34% of patients admitted to the intensive care unit (ICU) are at risk of IWS.[5] Between 35 – 57% of those receiving benzodiazepines or opioids for more than 5 days and up to 77% of those receiving different classes of medications will suffer IWS.[1,2,6]

Diagnosis:

IWS symptoms are often nonspecific, frequently representing autonomic activation and/or dysfunction (e.g., tachypnea, tachycardia, hyperpyrexia, diaphoresis), gastrointestinal dysfunction (e.g., vomiting, diarrhea), and/or central nervous system (CNS) alterations (e.g., agitation, jitteriness, seizures, hallucinations, delirium).[1,7-11] The onset of symptoms may be delayed following a wean or after discontinuing medication(s) with active drug metabolites (e.g., morphine, diazepam, midazolam), or in renal and/or hepatic dysfunction.[7] IWS to alpha$_2$-agonists (e.g., dexmedetomidine) is described as a common constellation of symptoms including rebound tachycardia or hypertension, agitation/irritability, sleeplessness, tremors, hypertonicity, emesis, and diarrhea.[12-16] Although clinical symptoms alone may produce suspicion of IWS development, using validated screening tools allows for consistency and standardization of diagnosis.

The Withdrawal Assessment Tool – Version 1 (WAT-1) has been validated for the diagnosis of opioid and benzodiazepine-based IWS in pediatric ICU (PICU) populations.[2,17] The WAT-1 uses a 12-point numerical scale and is scored every 12 hours or less. In general, at JHACH, WAT-1 scores are collected every 4 hours. Scores greater than or equal to 3 are consistent with the presence of IWS but cannot differentiate between opioid and benzodiazepine withdrawal.[2,18] The WAT-1 is highly sensitive and specific for IWS from both benzodiazepines and opioids, with

good inter-rater reliability.[2] Scoring and treatment of withdrawal should be based on patient factors. There should be an understanding that patients may have elevated WAT-1 scores secondary to preexisting conditions or therapies (e.g., loose watery stools in patients with short bowel syndrome or laxative use). Consider obtaining a 'baseline' WAT-1 score before weaning medication(s).

Until a validated screening tool is developed, monitoring for IWS from alpha$_2$-agonists should be performed using a combination of associated symptoms (unexplained hypertension or tachycardia) with adjunct use of a validated benzodiazepine or opioid screening tool.[19]

Clinical Management:

As IWS is a receptor-based phenomenon, management should include the reinstitution of an agent(s) (opioid, benzodiazepine, or alpha$_2$-agonist) that has the same receptor activity.[19] Patients often receive sedation and analgesia from multiple agents during their stay, which adds complexity to identifying the cause of withdrawal. It is, therefore, important to recognize the temporal overlap in medication tapering and the clinical presentation of withdrawal, since differentiating between dexmedetomidine, opioid, or benzodiazepine withdrawal may be challenging.[20] Remember the onset of symptoms may be delayed following a wean or after discontinuing medication(s) with active drug metabolites (e.g., morphine, diazepam, midazolam), or in renal and/or hepatic dysfunction.[7]

ICU providers, Pain Team members, and pharmacists developed algorithms and recommendations for continuous infusion weaning and iatrogenic withdrawal prevention and management. These recommendations are based on the duration of the infusion. 'Early initiation' (initiation of iatrogenic withdrawal medication(s) (e.g., methadone, diazepam) on day 7 of continuous infusion) and 'peri-extubation' (initiation of iatrogenic withdrawal medication(s) within 48 – 72 hours of extubation) algorithms were created for opioid and benzodiazepine infusions as both practices are prevalent at JHACH.

ICU providers, Pain Team members, and pharmacists developed the IWS Calculator (follow the link to the calculator and download instructions), which provides conservative conversions for each infusion to an enteral medication. The calculator should NOT be used to convert infusions to intermittent dosing if the patient loses access, especially for patients on high-dose continuous infusions. The calculator provides the enteral dose of either methadone, diazepam, or clonidine. The calculator will alert the provider if the infusion dose is above the outlined threshold doses in this pathway. If this occurs, the provider should initiate the recommended mg/kg/dose every 6 hours as dictated in the algorithms, not to exceed the maximum suggested dose. For patients weighing more than 50 kg, the calculator will alert the provider that the patient-specific dose exceeds the maximum suggested doses dictated in this pathway. Contact the Pain Team for further guidance.

If the patient cannot tolerate enteral medications and intravenous (IV) formulations are required, contact the pharmacy or the Pain Team for conversions

Opioid infusions:

Iatrogenic Withdrawal Management for Patients Requiring Opioid Infusions

Duration of Infusion(s)*	Recommendations
< 5 days	Consider discontinuing opioid infusion depending on clinical status and opioid requirement
5 – 7 days	Consider weaning infusion by 25% of the CURRENT hourly rate and repeat the same dose decrease every 12 hours until off Example: fentanyl infusion at 2 mcg/kg/hour would be weaned 25% (0.5 mcg/kg/hour) to 1.5 mcg/kg/hour and would decrease by 0.5 mcg/kg/hour every 12 hours to off
> 7 days	See algorithm (*Opioid Infusions: Early Initiation of Methadone* **OR** *Opioid Infusions: Peri-Extubation Algorithm*)

**Include duration(s) of other continuous opioid infusion(s) for patients that had opioid rotation*

The majority of studies evaluating opioid replacement therapy for IWS have been performed using methadone, likely due to its high enteral bioavailability and long half-life, which allows for less frequent dosing.[21,22] Follow the methadone recommendations below once the continuous infusion has been discontinued AND the patient is not experiencing IWS, as indicated by elevated WAT-1 scores.

Methadone Recommendations for Patients Requiring Opioid Infusions for > 7 Days

Duration of Infusion(s)*	Recommendations
8 – 14 days	1. Decrease methadone by 20% of the INITIAL dose 2. Wean every 24 hours by the same amount† 3. When the dose is ~0.05 mg/kg/dose, wean frequency every 24 hours (i.e., Q6h → space to Q8h → Q12h → Q24h → OFF)
15 – 28 days	1. Decrease methadone by 20% of the INITIAL dose 2. Wean every 48 hours by the same amount† 3. When the dose is ~0.05 mg/kg/dose, wean frequency every 48 hours (i.e., Q6h → space to Q8h → Q12h → Q24h → OFF)
> 28 days	1. Decrease methadone by 10% of the INITIAL dose 2. Wean every 48 – 72 hours†† by the same amount† 3. When the dose is ~0.05 mg/kg/dose, wean frequency every 48 – 72 hours†† (i.e., Q6h → space to Q8h → Q12h → Q24h → OFF)

**Include duration(s) of other continuous opioid infusion(s) for patients that had opioid rotation*

†Wean by the same dose; do NOT continue weaning by percentages

††*Patients on opioids for prolonged periods may require less frequent weans (e.g., ≥ every 72 hours)*

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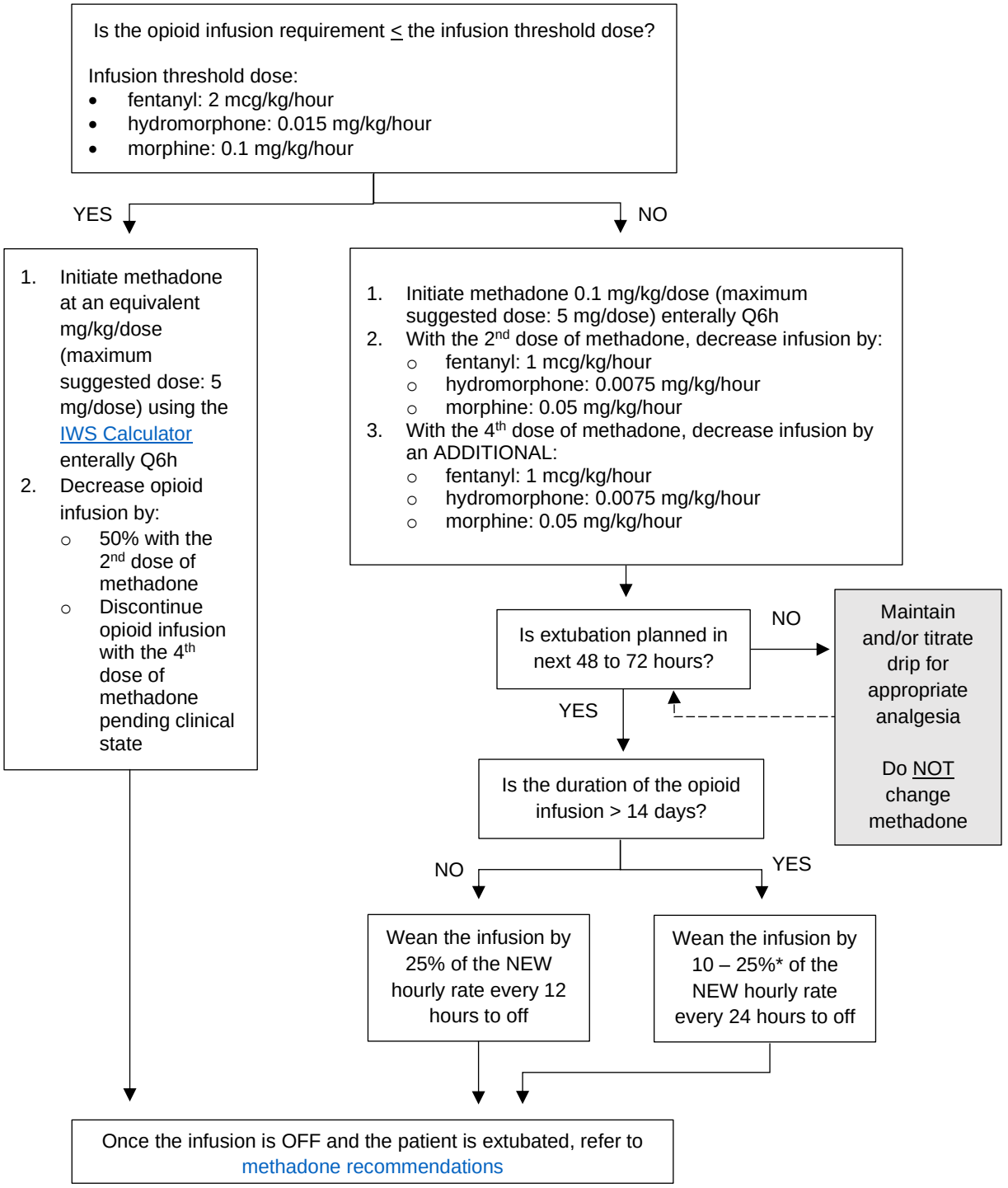
Opioid Infusions: Early Initiation of Methadone Algorithm



*Percent wean should be based on patient factors (e.g., withdrawal symptoms, duration of infusion)

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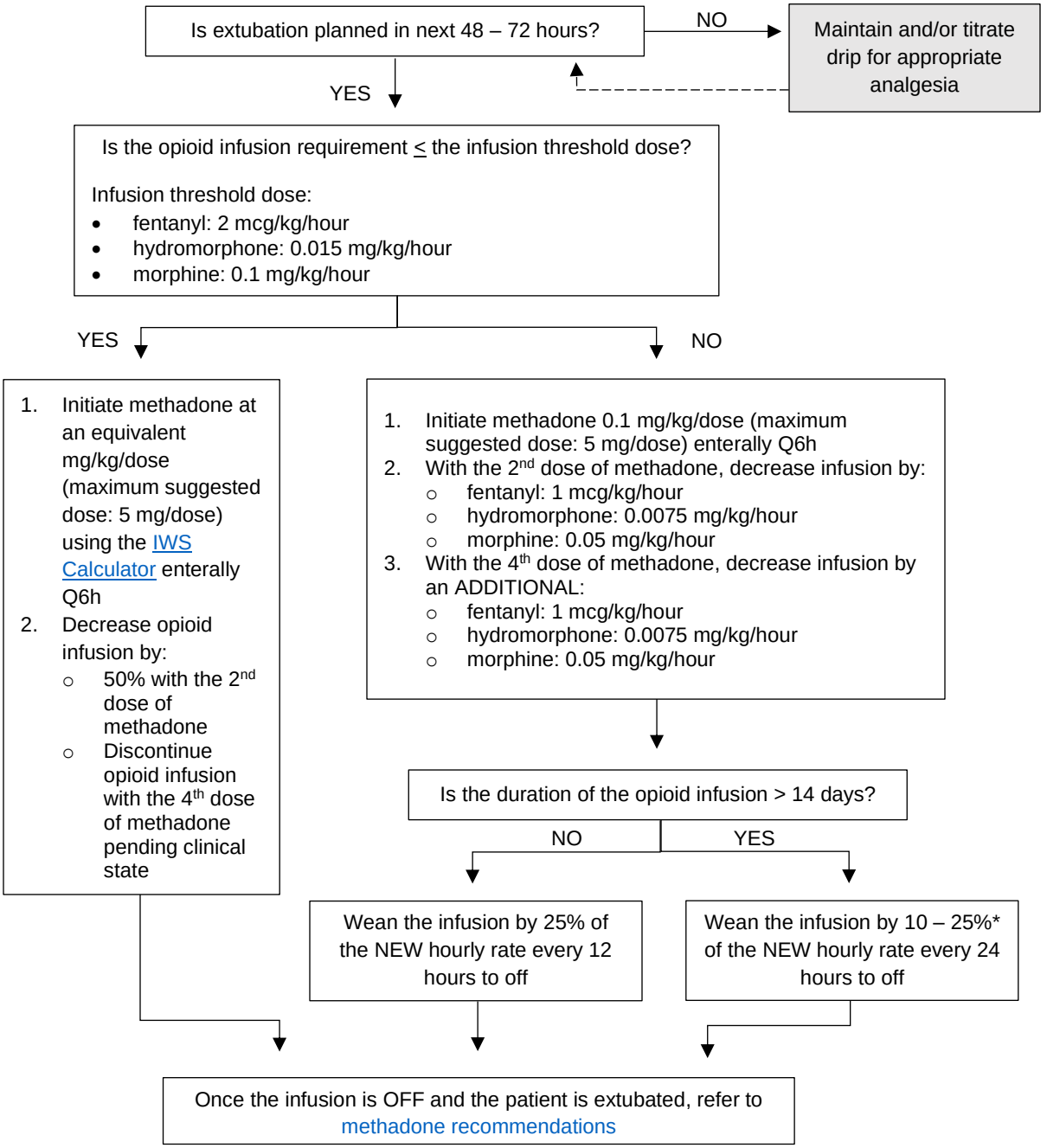
Opioid Infusions: Peri-Extubation Algorithm



*Percent wean should be based on patient factors (e.g., withdrawal symptoms, duration of infusion)

Benzodiazepine infusions:

Iatrogenic Withdrawal Management for Patients Requiring Midazolam Infusion

Duration of Infusion	Recommendations
< 5 days	Consider discontinuing midazolam infusion depending on clinical status and benzodiazepine requirement
5 to 7 days	Consider weaning infusion by 25% of the CURRENT hourly rate and repeat the same dose decrease every 12 hours until off For example, midazolam infusion at 0.2 mg/kg/hour would be weaned 25% (0.05 mg/kg/hour) to 0.15 mg/kg/hour and would decrease by 0.05 mg/kg/hour every 12 hours to off
> 7 days	See algorithm (*Benzodiazepine Infusion: Early Initiation of Diazepam* **OR** *Benzodiazepine Infusion: Peri-Extubation Algorithm*)

Few studies exist regarding the treatment of benzodiazepine-related IWS. Two retrospective studies reported symptom mitigation with the use of gradual taper and/or conversion from IV to longer-acting enteral benzodiazepines.[23,24] Follow the diazepam recommendations below once the continuous infusion has been discontinued AND the patient is not experiencing IWS, as indicated by elevated WAT-1 scores.

Diazepam Recommendations for Patients Requiring Midazolam Infusion for > 7 Days

Duration of Infusion	Recommendations
8 – 14 days	1. Decrease diazepam by 20% of the INITIAL dose 2. Wean every 24 hours by the same amount* 3. When the dose is ~0.05 mg/kg/dose, wean frequency every 24 hours (i.e., Q6h → space to Q8h → Q12h → Q24h → OFF)
15 – 28 days	1. Decrease diazepam by 20% of the INITIAL dose 2. Wean every 48 hours by the same amount* 3. When the dose is ~0.05 mg/kg/dose, wean frequency every 24 hours (i.e., Q6h → space to Q8h → Q12h → Q24h → OFF)
> 28 days	1. Decrease diazepam by 10% of the INITIAL dose 2. Wean every 48 – 72 hours† by the same amount* 3. When the dose is ~0.05 mg/kg/dose, wean frequency every 48 – 72 hours† (i.e., Q6h → space to Q8h → Q12h → Q24h → OFF)

*Wean by the same dose; do NOT continue weaning by percentages

†*Patients on benzodiazepines for prolonged periods may require less frequent weans (e.g., ≥ every 72 hours)*

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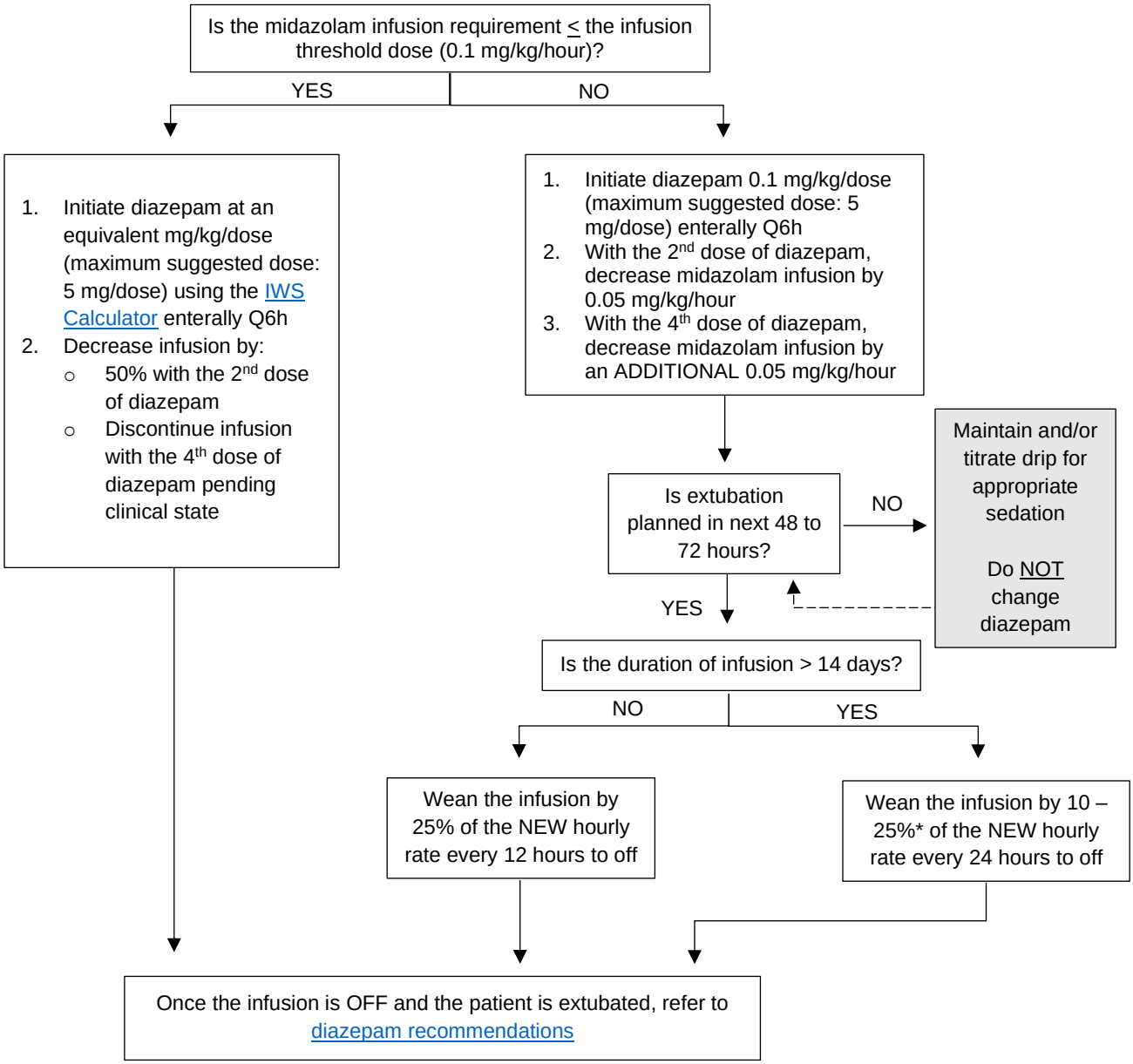
Midazolam Infusion: Early Initiation of Diazepam Algorithm



*Percent wean should be based on patient factors (e.g., withdrawal symptoms, duration of infusion)

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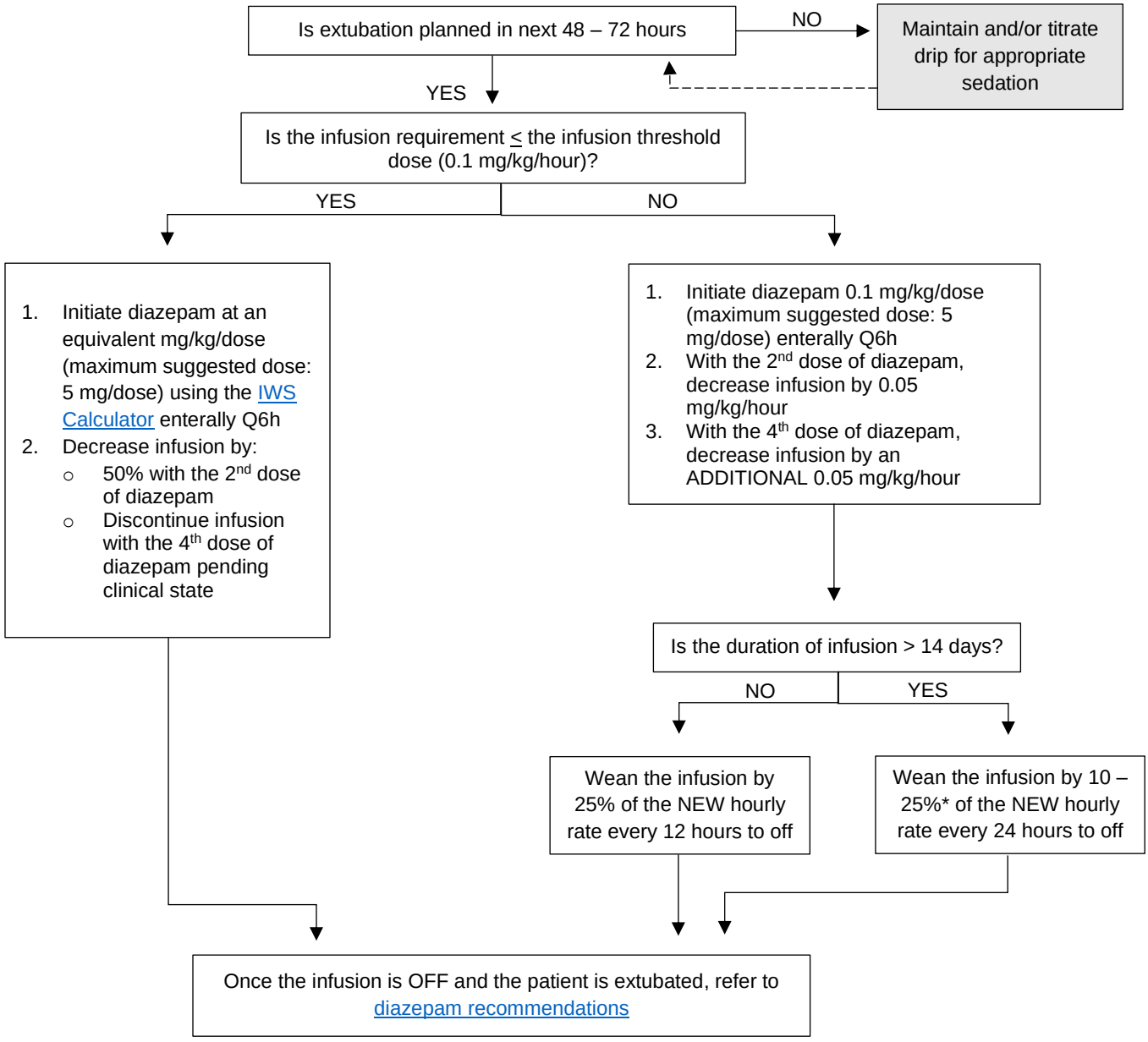
Midazolam Infusion: Peri-Extubation Algorithm



*Percent wean should be based on patient factors (e.g., withdrawal symptoms, duration of infusion)

Dexmedetomidine infusion:

Iatrogenic Withdrawal Management for Patients Requiring Dexmedetomidine Infusion

Duration of Infusion	Recommendations
≤ 5 days	Consider weaning infusion by 25% of the CURRENT hourly rate and repeat the same dose decrease every 12 hours until off For example, dexmedetomidine infusion at 2 mcg/kg/hour would be weaned 25% (0.5 mcg/kg/hour) to 1.5 mcg/kg/hour and would decrease by 0.5 mcg/kg/hour every 12 hours to off
> 5 days	See *Dexmedetomidine Infusion Algorithm*

To date, unlike the withdrawal syndromes from opioids or benzodiazepines, there has not been a comprehensive summary of the clinical presentation, risk factors, preferred weaning protocols, or clinical management of dexmedetomidine withdrawal.[25] A meta-analysis of published literature from 2000 – 2022 found that exposure to dexmedetomidine for greater than or equal to 24 hours may be associated with dexmedetomidine withdrawal, characterized by hypertension, tachycardia, and agitation.[25] Furthermore, management of dexmedetomidine withdrawal commonly included a dexmedetomidine taper with or without clonidine.[25] Follow the clonidine recommendations below once the continuous infusion has been discontinued AND the patient is not experiencing IWS, as indicated by clinical signs of withdrawal (e.g., hypertension, tachycardia, agitation) with/without elevated WAT-1 scores.

Clonidine Recommendations for Patients Requiring Dexmedetomidine Infusion for > 7 Days

Duration of Infusion	Recommendations
6 – 14 days	1. Decrease clonidine by 20% of the INITIAL dose 2. Wean every 24 hours by the same amount* 3. When the dose is ~0.05 mcg/kg/dose, wean frequency every 24 hours (i.e., Q6h → space to Q8h → Q12h → Q24h → OFF)
15 – 28 days	1. Decrease clonidine by 20% of the INITIAL dose 2. Wean every 48 hours by the same amount* 3. When the dose is ~0.05 mcg/kg/dose, wean frequency every 48 hours (i.e., Q6h → space to Q8h → Q12h → Q24h → OFF)
> 28 days	1. Decrease clonidine by 10% of the INITIAL dose 2. Wean every 48 – 72 hours† by the same amount* 3. When the dose is ~0.05 mcg/kg/dose, wean frequency every 48 – 72 hours† (i.e., Q6h → space to Q8h → Q12h → Q24h → OFF)

*Wean by the same dose; do NOT continue weaning by percentages

†*Patients on dexmedetomidine for prolonged periods may require less frequent weans (e.g., ≥ every 72 hours)*

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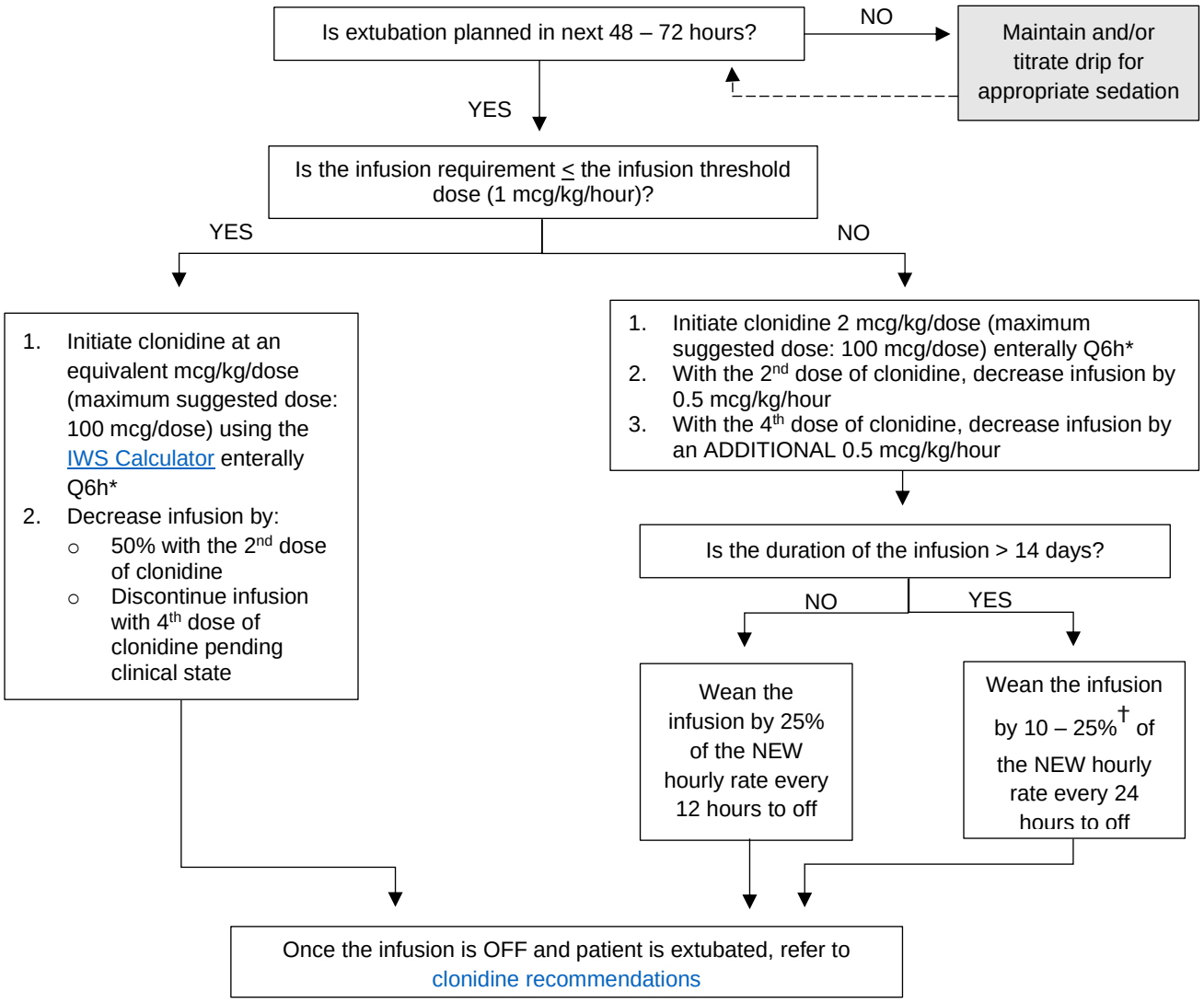
Dexmedetomidine Infusion Algorithm



*Clonidine patches may be utilized at a relatively equivalent total daily dose recommended in the IWS Calculator; see below for further guidance.

†Percent wean should be based on patient factors (e.g., withdrawal symptoms, duration of infusion)

Clonidine patches:

This clinical pathway was developed to assist with enteral clonidine dosing and weaning; however, clonidine patches may be utilized at a relatively equivalent total daily dose recommended in the calculator. Available patch sizes include (0.05 mg/24-hour (0.1 mg/24-hour half-patch using adhesive covering), 0.1 mg/24-hour patch, 0.15 mg/24-hour (0.3 mg/24-hour half-patch using adhesive covering), 0.2 mg/24-hour patch, and 0.3 mg/24-hour patch). Refer to the (CLNPOL049) *Medication Administration* policy, *Appendix L: Transdermal (Medicated Patch) Administration Chart* for further guidance on partial patches. If starting transdermal therapy or transitioning from enteral to transdermal therapy, consider an overlap enteral regimen for 1 to 3 days, as the transdermal route takes 2 to 3 days to achieve therapeutic effect.[26]

> Example: A patient (12 kg) requires dexmedetomidine 1 mcg/kg/hr. The Dosing Calculator recommends 2 mcg/kg/dose (24 mcg/dose) every 6 hours. The patient's total daily dose is 8 mcg/kg/DAY (96 mcg/DAY). The nearest patch size would be 0.1 mg/24-hour patch.

The Clonidine Recommendations for Patients Requiring Dexmedetomidine Infusion for > 7 Days table above does not describe the weaning of a clonidine patch. Contact the Pain Team for recommendations.

Weaning multiple medications:

There is no guidance on best practices for weaning multiple medications. In general, patient factors dictate when and how to wean. A common practice at JHACH is alternating wean days (i.e., weaning methadone today by 10 – 20% and then diazepam tomorrow by 10 – 20%). In most cases, methadone and diazepam are weaned off before the clonidine wean is initiated. Consider consulting the Pain Team if unable to wean successfully after 3 consecutive attempts or for patients with a complex analgesia/sedation history.

Managing withdrawal symptoms:

As IWS is a receptor-based phenomenon, management should include the reinstitution of an agent (opioid, benzodiazepine, or alpha$_2$-agonist) that has the same receptor activity.[19] Scoring should be based on patient factors. Patients may have elevated WAT-1 scores secondary to preexisting conditions. Consider obtaining a 'baseline' WAT-1 score before weaning medication and treating a WAT-1 score if > 2 above baseline.[27]

If the patient requires 4 or more doses of a PRN medication for elevated WAT-1 scores in 24 hours, the maintenance dose may be increased or changed back to the previously tolerated dose.

Medication	Dose	Frequency	Indication
clonidine	0.5 – 1 mcg/kg/dose	Every 4 hours as needed (Q4h PRN)	WAT-1 ≥ 3*
diazepam	0.05 – 0.1 mg/kg/dose		
morphine	0.05 – 0.1 mg/kg/dose		

*Consider obtaining a 'baseline' WAT-1 score before weaning medication and treating a WAT-1 score if > 2 above baseline

Discharge:

Home weaning criteria:

Home weaning may be considered for patients who demonstrate stable tolerance to the weaning process, as evidenced by:

- No requirement for PRN medications post-wean
- WAT-1 scores consistently below 4
- Medication dosing intervals not exceeding every 8 hours

The decision to initiate home weaning should account for case-specific factors, including:

- Complexity of the weaning regimen (e.g., number of medications involved)
- Availability of home nursing support
- Considerations for out-of-state discharge

For weaning regimens involving methadone, consultation with the Acute Pain Service is strongly recommended to ensure safe and effective management.

A comprehensive, printed weaning schedule must be provided to the patient's caregivers, with clear instructions and confirmation of their understanding. The Acute Pain Service can provide this if needed.

Follow-up for extended weaning:

Patients undergoing extended weaning protocols (exceeding 10 days) should have a referral to the Acute Pain Service at least 48 hours before presumed discharge, with follow-up scheduled in the Chronic Pain Clinic for ongoing wean management.

Methadone prescribing guidelines:

JHACH does not restrict methadone prescribing by providers; however, involvement of the Pain Team or Chronic Pain Clinic is strongly encouraged to optimize patient outcomes. If the Pain Team is not utilized, a single outpatient provider or practice should be designated to oversee methadone management and prescription refills, ensuring continuity of care.

Considerations for out-of-state patients:

For patients residing outside of Florida, the Pain Team does not provide telemedicine services beyond state lines. This may pose challenges for out-of-state patients requiring extended weaning and necessitates coordination with local providers.

Consultation:

Consider consulting the Pain Team if:

- Unable to wean successfully after 3 consecutive attempts
- Complex analgesia/sedation history
- Patients > 50 kg
- Transfers out of the ICU

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Outcome Measures:

- Pathway utilization and adherence
- Pathway deviations
- Duration of continuous infusions
- Duration of weans

Clinical Pathway Team
Iatrogenic Withdrawal Clinical Pathway
Johns Hopkins All Children's Hospital

Owner(s): ICU Pharmacists

Adapted from: *Analgesia-Sedation WEANING Heart Institute Guidance*

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Disclaimer:

Clinical Pathways are intended to assist physicians, physician assistants, nurse practitioners, and other healthcare providers in clinical decision-making by describing a range of generally acceptable approaches for diagnosing, managing, or preventing specific diseases or conditions. The ultimate judgment regarding the care of a particular patient must be made by the physician in light of the individual circumstances presented by the patient.

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Appendix A: Withdrawal Assessment Tool – Version 1 (WAT-1)[2]

Information from patient records, previous 12 hours		
Any loose**/**watery stools	No = 0 Yes = 1	
Any vomiting**/**retching**/**gagging	No = 0 Yes = 1	
Temperature > 37.8°C	No = 0 Yes = 1	
2-minute pre-stimulus observation		
State	SBS^{28} ≤ 0 or asleep/awake/calm = 0 SBS^{28} ≥ +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^{28} ≤ 0)	< 2 minutes = 0 2 – 5 minutes = 1 > 5 minutes = 2	
Total Score (0 – 12)		

Abbreviations: SBS, State Behavioral Scale