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Pain Management in the Neonatal Intensive Care Unit Clinical Pathway

JOHNS HOPKINS
All Children's Hospital

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Rationale:

This clinical pathway was developed by a consensus group of physicians, advanced practice providers, nurses, and pharmacists at Johns Hopkins All Children's Hospital (JHACH) to standardize the management of pain in neonates and infants located in the Neonatal Intensive Care Unit (NICU). It addresses the following clinical questions or problems:

1. When to evaluate for pain
2. When to consult the Pain Team
3. When to consider non-pharmacologic and pharmacologic interventions

Background / Published Data and Levels of Evidence:

Knowledge of neonatal pain has increased dramatically over the past three decades. It is well established that newborns can detect, process, and respond to painful stimuli, and that preterm neonates are hypersensitive to pain due to immature pain-inhibiting mechanisms at birth. Gaps exist in knowledge, evidence, and clinical practice regarding neonatal pain assessment and management, which may hinder adequate pain management in this population (Gursul, 2014; Mayock, 2013; Perry, 2018; Van Dokkum, 2021).

Pain modulation and prevention are essential for optimal neurodevelopmental outcomes in infants. Caregivers expect the prevention of pain to be incorporated into their infant's healthcare plan. Nonpharmacologic interventions are essential methods for reducing pain by activating inhibitory pathways and decreasing nociceptive signaling. Incorporating non-pharmacological pain strategies into a comprehensive pain management plan is therefore critical. These strategies encompass a wide variety of interventions, including, but not limited to, positioning, skin-to-skin care, four-handed and hand-hug care, stress reduction, breastfeeding, non-nutritive sucking, and other developmentally appropriate behavioral interventions (Alinejad-Naeini, 2014; Bucsea, 2019; Liaw, 2012; Lopez, 2015; Koukou, 2022; Sadeghi Niaraki, 2022; Committee on Fetus and Newborn & Section on Anesthesiology and Pain Medicine, 2016). Refer to the NICU – Neuroprotective Care of the NICU Infant Clinical Pathway for further guidance, as well as the PAIN CARE: Non-Pharmacologic Pain Interventions appendix below.

Careful consideration must be taken when administering analgesics to neonates and infants in the NICU. This is due in part to the complexity of neonatal pain assessment and the substantial interpatient variability in metabolism, neurodevelopment, and medication clearance, all of which increase the risk for adverse effects. Pharmacological therapy should therefore be administered

using a stepwise approach, with therapy tailored to the type of pain being treated (e.g., procedural, disease-related) and used in conjunction with nonpharmacologic interventions whenever possible (Hall, 2009; McPherson, 2022; Amigoni, 2022; Committee on Fetus and Newborn & Section on Anesthesiology and Pain Medicine, 2016).

Clinical Management:

A comprehensive pain management care plan should support the infant before, during, and after pain. In all comprehensive pain management care plans, non-pharmacologic methods should be used in conjunction with pharmacologic methods.

Non-pharmacologic pain interventions:

- PAIN CARE:
    - **P**repare and coordinate care and interventions, including necessary items (clinical and comfort) for care, before starting with the caregiver(s), NICU Developmental Care Team, medical team, and NICU staff
    - **A**void and minimize painful procedures and cluster care
    - **I**nfant readiness assessed
        - Assess infant stress, sleep state if able, behavioral state, and i-Rainbow Developmental Care Tool: Modified
        - Protect dedicated sleep times
    - **N**egate noxious environmental stimulation (e.g., noise, light, scent)
    - **C**are and comfort
        - Includes positioning, skin-to-skin, four-handed, and hand-hugs care, colostrum care, and non-nutritive sucking
        - If clinically able, breastfeeding and taste stimulation
    - **A**ll hands-on deck (i.e., schedule care with caregiver(s), therapies, and other staff)
    - **R**eassess regularly for infant stress and pain
    - **E**ngage in closed-loop communication
- Refer to PAIN CARE: Non-Pharmacologic Pain Interventions appendix below

Treatment of procedural pain:

- The ideal analgesic for procedural pain must:
    - Have a rapid onset and short duration of action with minimal impact on respiratory mechanics
    - Has been documented to positively impact oxygen saturation, cerebral blood flow, tissue oxygenation, or neural activity of nociception-evoked circuits
- Oral sucrose 24% (refer to *Pain Management for Painful Procedures* policy for further guidance)
- Topical lidocaine (e.g., eutectic mixture of local anesthetics (EMLA®), lidocaine 4% cream (LMX-4®) (refer to *Pain Management for Painful Procedures* policy for further guidance)

- Intradermal (ID) lidocaine injection:
    - Lidocaine inhibits axonal transmission by blocking sodium channels
    - Typically, solutions with concentration < 2% should be used
    - Dosing:
        - Usual dose: 1 – 2 mg/kg/dose (0.1 – 0.2 mL/kg/dose of a 1% solution) ID
        - Max dose: 5 mg/kg/dose (0.5 mL/kg/dose of a 1% solution) ID
- Acetaminophen:
    - Acetaminophen acts by inhibiting cyclooxygenase enzymes in the brain and has been well studied in neonates
    - Acetaminophen may be a good option for the treatment of acute or procedural pain
    - Can be administered either enterally or rectally
    - Dosing:
        - Post-menstrual age (PMA) < 32 weeks:
            - Enteral: 12 – 15 mg/kg/dose every 12 hours
            - Rectal (PR): 12 – 18 mg/kg/dose every 12 hours
        - PMA ≥ 32 weeks:
            - Enteral: 12 – 15 mg/kg/dose every 8 hours
            - PR: 12 – 18 mg/kg/dose every 8 hours
        - Term:
            - Enteral: 12 – 15 mg/kg/dose every 6 hours
            - PR: 12 – 18 mg/kg/dose every 6 hours
    - Use caution in hepatic failure
- Opioid analgesics:
    - Medications such as morphine or fentanyl may be given to patients for procedural pain associated with invasive procedures, such as chest tube placement
    - Caution should be used when providing opioids or sedatives to any infant without a secure airway
    - In many cases, non-pharmacologic interventions and/or oral sucrose 24% will provide adequate pain relief; if opioids are needed, use the lowest effective dose
    - Dosing:
        - Morphine:
            - Intravenous (IV), intramuscular (IM), or subcutaneous (SQ): 0.05 mg/kg/dose
            - Enteral: 0.1 mg/kg/dose
        - Fentanyl:
            - IV: 0.5 mcg/kg/dose
    - To maintain minimal sedation, doses cannot be administered any sooner than every 30 minutes
        - If more frequent dosing is needed, please follow the procedure for moderate sedation
- Procedure-specific interventions

- All non-pharmacologic interventions should be done before initiation of pharmacologic interventions and continued during and after the procedure (see non-pharmacologic section)

Table 1: Procedure-specific interventions

Procedure	Interventions		
	1st Line	2nd Line	3rd Line
Circumcision*†	sucrose 24% and topical lidocaine (≥ 30 weeks' GA) or ID lidocaine	--	--
Lumbar puncture*†	sucrose 24%	topical lidocaine (≥ 30 weeks' GA) or ID lidocaine	--
Heel stick/ venipuncture/ arterial stick*†	sucrose 24%	topical lidocaine (≥ 30 weeks' GA)	--
PICC placement†	sucrose 24%	Opioid	--
PAL placement*†	sucrose 24%	topical lidocaine (≥ 30 weeks' GA)	--
Chest tube	ID lidocaine	Opioid	--
Bladder tap*†	sucrose 24%	topical lidocaine (≥ 30 weeks' GA)	Opioid
Immunizations*†	sucrose 24%	topical lidocaine (≥ 30 weeks' GA)	--
ROP exam†	sucrose 24% and tetracaine	--	--
Foley placement†	sucrose 24%	--	--
Tape removal/ dressing change†	sucrose 24%/saturation with sterile water	acetaminophen	--
Wound vac change†	sucrose 24%	acetaminophen	Opioid

Abbreviations: PAL, peripheral arterial line; PICC, peripherally inserted central catheter; ROP, retinopathy of prematurity
*If the patient is ≤ 30 weeks' GA, avoid topical lidocaine and move to the next line of therapy
†If the patient is < 27 weeks' GA or > 4 months of age, skip sucrose 24% and move to the next line of therapy

Table 2: Procedure-specific medication dosing

Medication	Route	Dose	Comments
Oral Sucrose 24%	Enteral	27 – 31 weeks: 0.5 mL 32 – 36 weeks: 1 mL ≥ 37 weeks: 2 mL	
Topical lidocaine	Topical	GA ≥ 30 – < 37 weeks: 0.5 g per site GA ≥ 37 weeks: ≤ 1 g per site	Apply and cover for 30 minutes before the procedure
Lidocaine injection	ID	1 – 2 mg/kg/dose (0.1 – 0.2 mL/kg/dose of a 1% solution)	Max dose: 5 mg/kg/dose (0.5 mL/kg/dose of a 1% solution)
Morphine	IV, IM, SQ	0.05 mg/kg/dose	To maintain minimal sedation, doses cannot be administered any sooner than every 30 minutes.
	Enteral	0.1 mg/kg/dose	
Fentanyl	IV	0.5 mcg/kg/dose	

Acute pain:

- Causes:
    - Fracture:
        - Usually respond well to non-pharmacologic interventions and immobilization
        - Acetaminophen can be used sparingly
    - Necrotizing enterocolitis (NEC):
        - Utilize an age-appropriate pain scoring tool that can be found in the Addendum to Pain Assessment and Management, and individualize therapy
    - Acute wound or wound breakdown:
        - Acute wounds and wound breakdown cause significant pain in neonates due to their immature skin and nervous systems
        - Neonatal skin, particularly in preterm infants, is thin and fragile with an underdeveloped barrier, making it more prone to injury and pain
        - Despite immaturity, pain pathways are functional from mid-gestation, and neonates have abundant nociceptors and heightened neuronal excitability
        - However, due to immature descending inhibitory pathways, they experience less modulation of pain signals, resulting in a more intense response
        - Tissue injury also triggers an intense inflammatory reaction, releasing chemicals like prostaglandins and cytokines that sensitize pain receptors and contribute to both acute and ongoing pain
    - Acute procedures (e.g., esophagogastroduodenoscopy (EGD), mandibular distraction)

Postoperative pain management:

- There will be a collaborative approach to post-operative pain management between Neonatology and the respective Surgical Team
- All patients will receive optimal pain management in the Operating Room, which may include local anesthesia in addition to opioids
- Neonatology and the Surgery Team should have post-operative communication regarding the specific surgical procedure, with a general categorization as a minor, moderate, or major procedure
    - If the patient is going for a surgical G-tube, please follow the post-operative care found in the *Nurse-Managed Pressure Injury Prevention and Skin/Wound Care* policy under *Appendix H: Skin Care Guidelines for the Neonatal and Neonatal Intensive Care Unit (NICU) Patients* under the section titled *Gastrostomy Tube (G-tube) Site/Skin Care Inpatient guidelines*
- Ensure the comprehensive pain management care plan is in place and the plan has been discussed with the caregiver(s)
- IV acetaminophen should be scheduled as first-line management in patients meeting the restriction criteria

    - IV acetaminophen dosing:
        - PMA < 32 weeks:
            - IV: 12 – 15 mg/kg/dose every 12 hours
        - PMA ≥ 32 weeks:
            - IV: 12 – 15 mg/kg/dose every 8 hours
        - Term:
            - IV: 12 – 15 mg/kg/dose every 6 hours
- All infants should receive scheduled acetaminophen IV, enteral, or PR for 24 hours following surgery unless a specific contraindication exists; the route of administration should be discussed with the Surgical Team before prescribing
    - If there is a major procedure:
        - Continue scheduled acetaminophen for a minimum of 72 hours and add scheduled fentanyl OR morphine
            - Fentanyl 0.5 mcg/kg/dose IV every 3 – 4 hours
            - Morphine 0.05 mg/kg/dose IV/IM/SQ every 3 – 4 hours
        - For continued pain scores ≥ 4, optimize dosing and frequency of selected opioid
        - For continued pain scores ≥ 4, transition to an opioid continuous infusion
            - Fentanyl IV continuous infusion at 0.5 mcg/kg/hour
            - Morphine IV continuous infusion at 0.1 mg/kg/hour
    - If there is a moderate procedure:
        - Continue scheduled acetaminophen for a minimum of 48 hours
        - For pain scores ≥ 4, add one of the following:
            - Fentanyl 0.5 mcg/kg/dose IV every 3 – 4 hours as needed (PRN)
            - Morphine 0.05 mg/kg/dose IV/IM/SQ every 3 – 4 hours PRN
    - If there is a minor procedure, continue scheduled acetaminophen for a minimum of 24 hours

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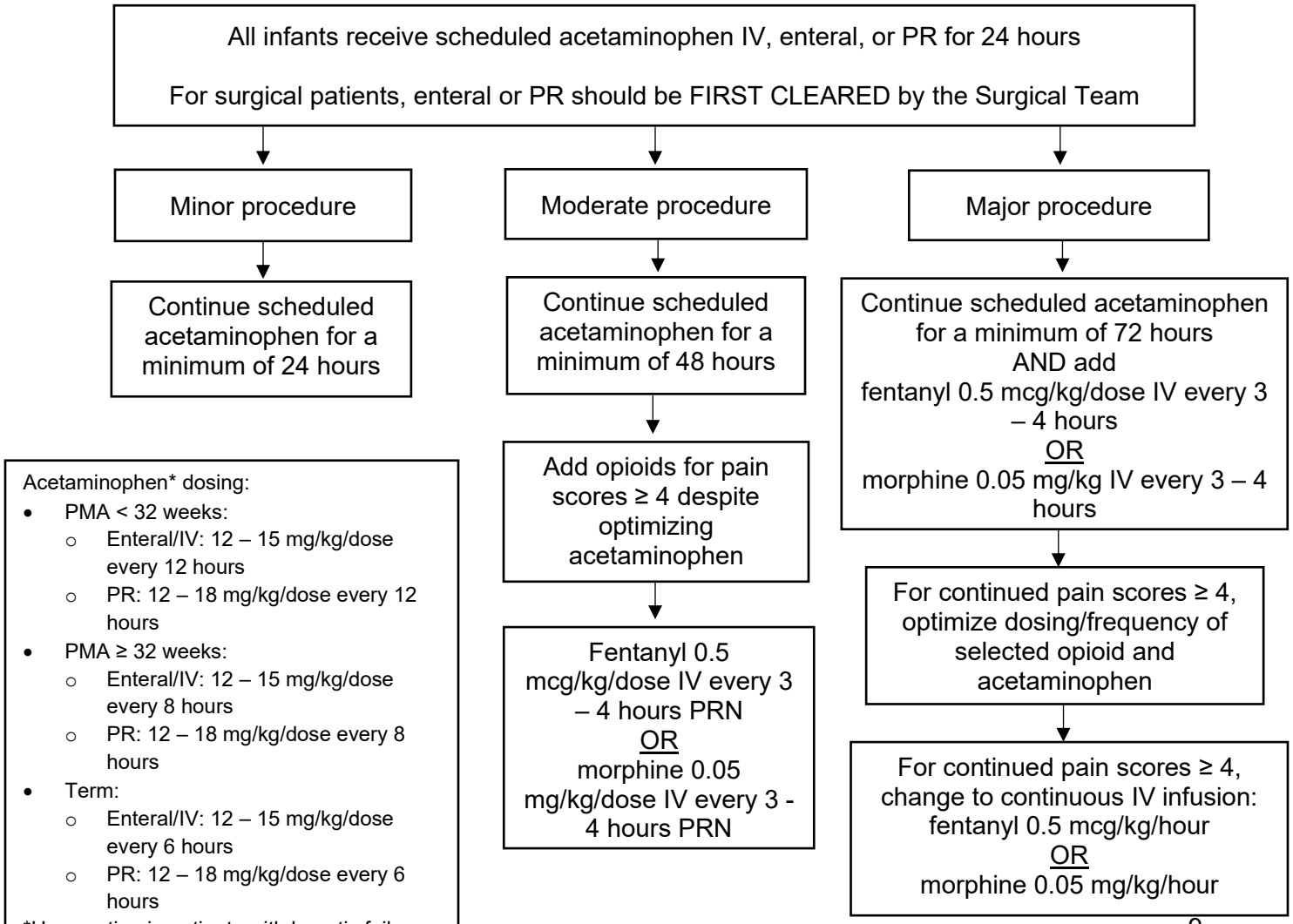
Post-operative Pain Management in the NICU Algorithm

Minor (Anticipated duration of pain ~24 - 48 hours)	**Moderate** (Anticipated duration of pain ~72 hours)	**Major** (Anticipated duration of pain ~96 hours)
Bronchoscopy	G-tube placement	Combined open procedures in multiple parts of the body
Central line placement	Laparoscopic procedures (including Nissen fundoplication)	Esophageal atresia repair
Chest tube placement	Myelomeningocele repair	Exploratory laparotomy (with bowel resection, creation of stomas, and extensive adhesiolysis)
Circumcision	Open inguinal hernia repair	Median sternotomy
Laparoscopic inguinal hernia repair	Peritoneal dialysis catheter insertion	Open Nissen fundoplication
Reservoir	Thoracoscopic procedures with chest tube placement	Thoracotomy
Thoracoscopic procedures without chest tube placement	Ventriculoperitoneal shunt	Tracheostomy
Ventriculosubgaleal shunt		



Acetaminophen* dosing:

- PMA < 32 weeks:
  - Enteral/IV: 12 – 15 mg/kg/dose every 12 hours
  - PR: 12 – 18 mg/kg/dose every 12 hours
- PMA ≥ 32 weeks:
  - Enteral/IV: 12 – 15 mg/kg/dose every 8 hours
  - PR: 12 – 18 mg/kg/dose every 8 hours
- Term:
  - Enteral/IV: 12 – 15 mg/kg/dose every 6 hours
  - PR: 12 – 18 mg/kg/dose every 6 hours

*Use caution in patients with hepatic failure

Authorized prescribers to assess the patient at a minimum every 24 hours for pain control and ability to wean medications

Acute on chronic pain:

- Causes:
  - Mechanical ventilation
  - Significant hydrocephalus/increased intracranial pressure (ICP)
  - Fractures due to osteopenia
  - Severe muscle spasticity
- Treatment:
  - See the Treatment of Acute on Chronic Pain in the NICU Algorithm below
- Continuous IV infusion:
  - Continuous infusions are sometimes appropriate when PRN medications must be given frequently, as multiple IV-line breaks can increase the risk of infection
  - Medications should be initiated as PRN doses to prevent overuse and over-sedation

Medications:

- General information:
  - Long-term use of opioids and benzodiazepines in infants can lead to prolonged mechanical ventilation, delay in the passage of meconium, and carries an inherent risk for tolerance and withdrawal, necessitating prolonged dose taper regimens
  - There is recent evidence of an increase in severe neurological morbidity with these medications
- Opioids
  - Treatment with opioids does not have a significant effect with respect to neonatal mortality, duration of ventilation, short-term or long-term neurodevelopmental outcomes, incidence of severe intraventricular hemorrhage (IVH), any IVH, or periventricular leukomalacia
  - Opioid exposure is associated with:
    - Longer courses of mechanical ventilation, hypotension, pharmacologic withdrawal, urinary retention, decreased intestinal motility, NEC, severe bronchopulmonary dysplasia (BPD), longer length of stay, lower cognition, and lower motor and language development scores at 2 years of age
  - Opioid tolerance can develop after 7 – 10 days of exposure, requiring dose escalation during pain treatment followed by gradual dose tapering to avoid physiologic withdrawal
    - If a patient is on opioids for ≥ 7 days, the patient should be monitored for withdrawal
  - Fentanyl:
    - Is 50 – 100 times more potent than morphine
    - A single dose of fentanyl given to ventilated preterm infants significantly reduces pain behaviors and changes in heart rate; it also increases growth hormone levels (Hall, 2009; Mayock, 2013)

        - Continuous IV infusions decrease the neuroendocrine stress response, but boluses increase the duration of mechanical ventilation and a trend toward a longer time to full enteral feeds
        - Studies show that exposure to a continuous IV infusion for 1 week was associated with neurodevelopmental impairment at 24 months CGA (Amigoni, 2022; McPherson, 2022; Perry, 2018; Van Dokkum, 2021)
        - Given the above information, fentanyl should always be initiated PRN, then moved to scheduled doses if needed, and continuous IV infusions should be limited to < 1 week
        - Dosing:
            - Intermittent dosing: 0.5 - 3 mcg/kg/dose IV every 2 – 4 hours
            - Continuous IV infusion: 0.5 – 3 mcg/kg/hour
    - Morphine:
        - Mean onset of action is 5 minutes, and the peak effect is at 15 minutes
        - Routine use of a morphine continuous IV infusion in preterm infants who received ventilatory support neither improved pain relief nor protected against poor neurologic outcome (Hall, 2009; Mayock, 2013; McPherson, 2022)
        - Neonates are at greater risk for opioid-associated respiratory depression because of their immature respiratory center responses to hypoxia and hypercarbia
        - 2021 update to the Cochrane review concluded that there is uncertainty whether opioids have any effect on reducing pain in mechanically ventilated infants (McPherson, 2022)
        - Dosing:
            - Intermittent dosing: 0.05 - 0.2 mg/kg/dose IV, IM, or SQ every 3 – 4 hours
            - Continuous IV infusion: 0.01 - 0.2 mg/kg/hour
- Alpha-2 agonists:
    - Dexmedetomidine:
        - Highly selective, centrally acting alpha-2 adrenergic agonist
        - Mechanism of action:
            - Activation of alpha-2 adrenergic receptors in the medullary vasomotor center leads to a reduction in norepinephrine turnover and sympathetic nervous system signaling from the locus coeruleus, leading to increased endogenous gamma-aminobutyric acid (GABA)-ergic activity, which causes sedation
            - Stimulates the release of substance P from the dorsal horn of the spinal cord, leading to analgesia, and can potentiate the effects of opioids
        - Stimulates the natural sleep pathways and induces activity similar to non-rapid eye movement in adults and children
        - The effects in the airway and respiratory system also mimic natural sleep and therefore maintain spontaneous breathing and upper airway tone

- It is postulated that its use should enable quicker weaning off mechanical ventilation and support extubation
    - Due to the early extubation, fewer infants received dexamethasone
- Main concerns with its use are bradycardia and hypotension
- Feeds are well tolerated during dexmedetomidine infusion because it does not cause GI dysmotility
- Intranasal (IN) dexmedetomidine:
    - IN dexmedetomidine (IV formulation via the IN route) at JHACH is restricted to one dose per procedure, administered by providers appropriately credentialed in moderate sedation.
        - Patients must meet all the following criteria:
            - Age ≥ 6 months – ≤ 18 years old
            - No IV placed or without a working IV
            - Require moderate sedation for a procedure or pre-operatively
    - Can be used for magnetic resonance imaging (MRI)
        - 3 mcg/kg/dose as a single dose
        - MUST be administered by a provider credentialed in moderate sedation
        - The median time to achieve sedation using it as a single agent is 10 minutes
- Continuous IV infusion dosing:
    - CGA 28 – 36 weeks:
        - Initiate at 0.1 mcg/kg/hour
        - Titrate up by 0.1 mcg/kg/hour every 12 hours as needed
        - Max infusion rate: 1.5 mcg/kg/hour
    - CGA > 36 weeks:
        - Initiate at 0.3 mcg/kg/hour
        - Titrate up by 0.1 mcg/kg/hour every 6 hours as needed
        - Max infusion rate: 2.5 mcg/kg/hour

- Clonidine:
    - Mechanism of action:
        - A centrally acting alpha-2 selective adrenergic agonist
        - Stimulates the pre-synaptic alpha-2 adrenoceptors of the locus coeruleus, decreasing norepinephrine release
    - It has also shown action in cholinergic, purinergic, and serotonergic pathways, resulting in analgesia
    - May exert neuroprotective effects by preventing apoptosis induced by anesthesia
    - Reduces such noradrenergic activity, thus reversing the cause of opioid withdrawal
    - It can cause hypotension and bradycardia, but the doses that were used in clinical trials were not associated with significant differences in the

incidence of these adverse effects in the treatment group compared with the control group (McPherson, 2022; Romantsik, 2017)
        - Dosing
            - Dosing: 0.5 – 2 mcg/kg/dose enterally every 3 – 6 hours
- Gabapentin:
    - A gamma-aminobutyric acid analog, which is thought to inhibit pain via voltage-dependent calcium ion channels in the central nervous system
    - It has been used to treat neuropathic pain related to visceral hyperalgesia in the neonatal population
    - It has a mild reported side effect profile and apparent lack of drug-drug interactions due to its renal route of excretion
    - Symptom relief for chronic irritability and feeding intolerance occurred in both populations, as was a reduction in the use of opioids and benzodiazepines (Burnsed, 2020; Edwards, 2016; Sacha, 2017)
    - Option for the management of refractory pain and agitation in pediatrics, as it is highly lipophilic, hence, penetrates well through the blood-brain barrier
    - Decreases the mean number of other neuro-sedative medications from 2.5 per day at the start of therapy to 1.7 per day after 14 days of gabapentin (Sacha, 2017)
    - The use of gabapentin in medically complex neonates and infants was associated with a reduction in pain scores and the need for multiple neuro-sedative medications (Burnsed, 2020; Edwards, 2016; Sacha, 2017).
        - It might be a good option for patients with chronic BPD or patients with severe IVH
    - Dosing:
        - 2.5 – 10 mg/kg/DAY in divided doses enterally every 8 hours
        - Increase dose every 2 – 3 days to reach the desired effect
        - Maximum daily dose is 35 mg/kg/DAY

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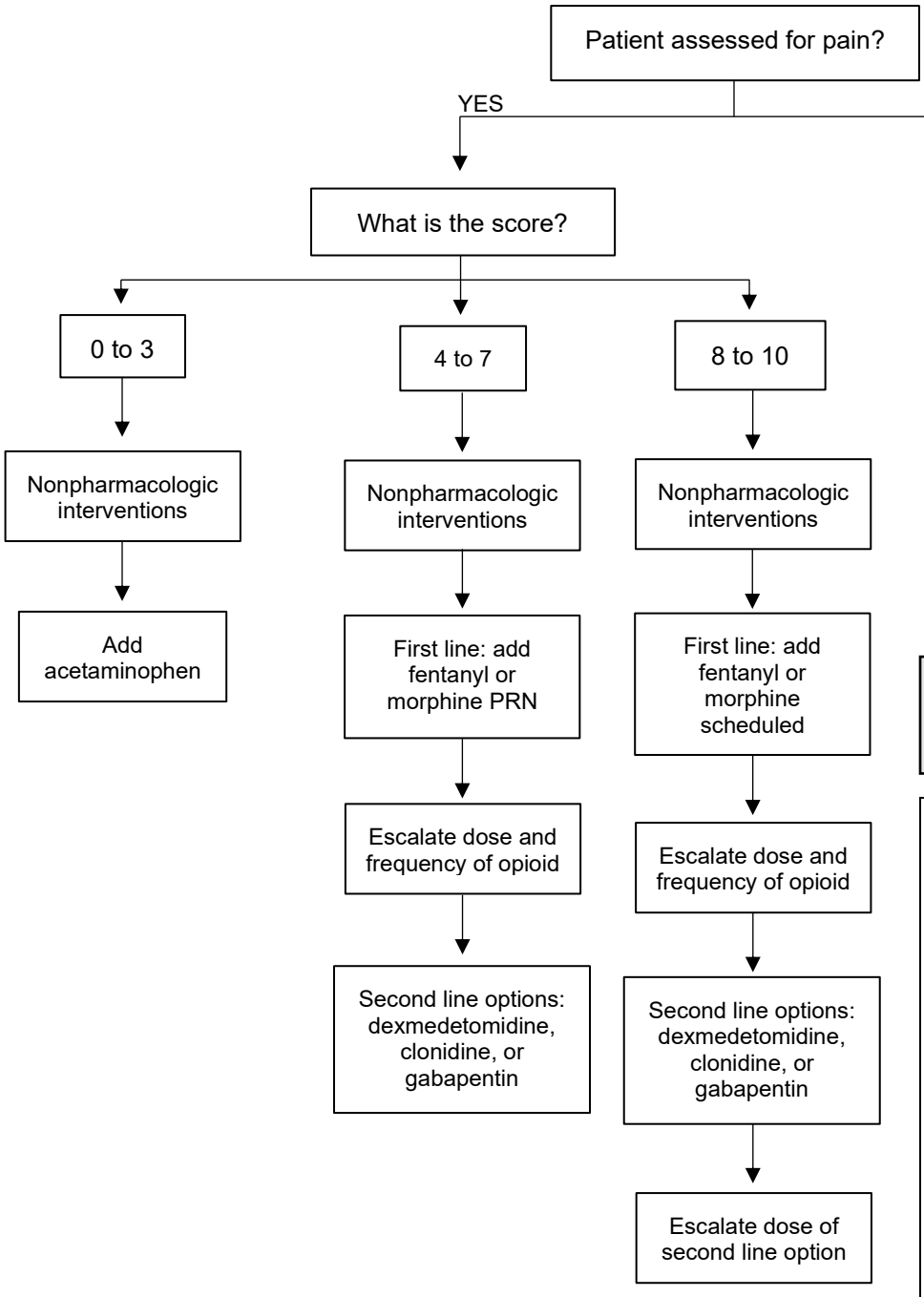
Treatment of Acute on Chronic Pain in the NICU Algorithm



Note, if the patient is ≥ 6 months or has difficult pain control, consider consulting the Pain Team

Medication Dosing

Fentanyl:
- Intermittent dosing: 0.5 – 3 mcg/kg/dose IV every 2 – 4 hours
- Continuous IV infusion: 0.5 – 3 mcg/kg/hour

Morphine:
- Intermittent dosing: 0.05 - 0.2 mg/kg/dose IV/IM/SQ every 3 – 4 hours
- Continuous IV infusion: 0.01 - 0.2 mg/kg/hour

Dexmedetomidine continuous IV infusion:
- CGA 28 – 36 weeks: Initiate at 0.1 mcg/kg/hour
- CGA > 36 weeks: Initiate at 0.3 mcg/kg/hour

Clonidine:
- Enteral: 0.5 - 2 mcg/kg/dose every 3 – 6 hours

Gabapentin:
- Enteral: 2.5 - 10 mg/kg/DAY in divided doses every 8 hours
- Increase dose every 2 – 3 days to reach the desired effect
- Maximum daily dose is 35 mg/kg/DAY

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Outcome Measures:

1. Pain score improvement:
    a. What it measures: Whether an infant's pain level improves after treatment
    b. Percentage assessed: Use a validated pain scale (such as Neonatal Pain, Agitation, and Sedation Scale (N-PASS) or Face, Legs, Activity, Cry, Consolability (FLACC)) before and after the procedure
    c. Goal: Pain scores should decrease by at least 2 points after treatment

2. Use of comfort measures:
    a. What it measures: How often do staff use non-pharmacologic methods to help improve infants' pain and stress cues
    b. Percentage assessed: Recorded use of interventions like swaddling, sucrose 24%, or breastfeeding during painful procedures
    c. Goal: At least 80% of infants should receive these comfort measures

3. Caregiver satisfaction:
    a. What it measures: How satisfied caregivers are with how their infant's pain was managed
    b. Percentage assessed: Give a short survey to caregivers
    c. Goal: 85% or more of caregivers report being satisfied

Clinical Pathway Team

Pain Management in the Neonatal Intensive Care Unit Clinical Pathway

Johns Hopkins All Children's Hospital

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Disclaimer:

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

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Appendix 1: PAIN CARE: Non-Pharmacological Pain Interventions