

Supplemental Information

OHIO CHILDREN’S HOSPITALS RESEARCH CONSORTIUM PROTOCOL FOR TREATMENT OF NAS: INTRODUCTION

The Ohio Children’s Hospitals Neonatal Research Consortium Enteral Morphine or Methadone Protocol for NAS From Maternal Exposure is a synthesis of the best available, although limited, evidence and an analysis of practice variation across the state of Ohio in a cohort of 553 term infants with maternal narcotic exposure. These are viewed as potentially better protocols that humanely and safely wean infants off narcotics over a 2- to 3-week period.

Each center should pick either morphine or methadone as their standard and use this for all infants with NAS treated in that center.

OVERVIEW OF STAGES OF TREATMENT

Scoring

All infants will be scored every 3 hours before a feeding with the modified Finnegan Scoring System. Begin scoring at every 3 hours, when the weaning phase begins; if you are not waking to feed until 4 hours, you may score every 4 hours.

1. Some experts recommend using the average of NAS scores over a 24-hour period in the stabilization and weaning phase to minimize the impact of minor variations on dosing.
2. Adjust trigger scores when >3 weeks old. Research has shown

SUPPLEMENTAL TABLE 1 Potentially Better Protocol

Nonpharmacologic	Swaddle, comfort, 22-calorie formula
Initiate	NAS score >8 q 3 h (2 times) Drug: morphine or methadone dose of 0.05 mg/kg PO
Escalate	If >12, increase by 0.02 mg/kg per dose
Stabilize	Maintain dose for 48 h
Wean	10% of stabilization dose daily discharge 48 h off drug

PO, by mouth; q, every.

that NAS scores increase over time as the infant matures, so at >21 days, all trigger thresholds should be increased by 2. (eg, we would now wean if the average of scores in 24 hours are <11).¹⁴

3. Centers should develop a plan for periodic refresher training for all nurses on the NAS modified scoring system using the D’Apolito Reliability Training system, and a training system for on-boarding new nursing staff should also be developed.

Nonpharmacologic Treatments

1. All infants with NAS will be treated with a bundle of nonpharmacologic interventions including decreased stimulation, swaddling, and continuous holding and frequent feeds.
2. Feedings: Each institution should develop a policy for the use of mother’s own milk. Consideration of supporting breastfeeding may be given if the mother is active in a treatment program and the mother’s addiction specialist supports breastfeeding. If the mother’s breast milk is not used, consider frequent feeds with an increased-caloric-density, nonlactose-containing formula at 22 kcal/oz. The higher-calorie

formula is designed to meet the exceptional caloric needs and combat the documented weight loss seen in infants with NAS. Additional calories may not be needed once the infant is a week or more into the course and weight loss is <10% of birth weight. Twenty-two-calorie formula may be discontinued when weight gain is established firmly.

3. See refs 10, 13, 14 and 26-30 for resources on nonpharmacologic interventions.

Pharmacologic Treatment, Morphine

Treatment should be initiated if an infant has 2 consecutive scores >8 or 1 score >12. Treatment is divided into the following phases: initiation, escalation, stabilization, and weaning.

Increase Dose Every 3 Hours Until Controlled (Average NAS ≤8 in 24 Hours)

Rescue dose: If infant has 1 score of >12, double the previous dose given (enteral or intravenous) × 1 and then adjust accordingly:

- If the NAS score is now <12, make the scheduled maintenance dose the same as the rescue dose that

SUPPLEMENTAL TABLE 2 Initiation Phase: Most Infants Can be Treated With Oral Medication

Morphine ^a	
PO	0.05 mg/kg per dose q 3 h
IV	0.02 mg/kg per dose q 3 h

IV, intravenous; PO, by mouth; q, every.

^a IV morphine and enteral morphine doses are not equivalent.

SUPPLEMENTAL TABLE 3 Escalation Phase

Morphine	
PO	0.03 mg/kg per dose q 3 h
IV	0.01 mg/kg per dose q 3 h

IV, intravenous; PO, by mouth; q, every.

was just administered. The first higher maintenance dose should be given at the next scheduled care and/or feed; and

- If the NAS score is still >12, increase next dose by 50% of the previous dose. Continue to do so until the score is <12.

Second Drug: Phenobarbital

Consider starting phenobarbital if

- Polysubstance exposure (benzodiazepines, barbiturates, antipsychotics, antidepressants, other sedatives/hypnotics, tobacco) is suspected or confirmed;
- and central nervous system findings (tremors, increased muscle tone, etc) rather than gastrointestinal findings predominate on the NAS subscale score;
- and the morphine dose exceeds 0.3 mg/kg per dose with the score remaining >8 or the infant is unable to wean for 2 consecutive days.

Loading dose: 10 mg/kg per dose by mouth every 12 h × 2 doses by mouth or 20 mg/kg per dose intravenously × 1. (The enteral formulation contains 10% alcohol. Dividing dose by mouth may decrease risk of emesis and/or sedation.)

Maintenance dose: 5 mg/kg per dose by mouth once daily (do not weight adjust).

Phenobarbital weaning: Two approaches may be used. (Neither has been directly studied.) Each center should pick 1 method:

1. Discontinue when on second to last step of morphine weaning to assess for tolerance of discontinuation. Given the long half-life of phenobarbital, this will wear off gradually over 4 days; and
2. Discharging infant from the hospital on phenobarbital with subsequent weaning to be done either in Neo Clinic or by infant's primary care provider.

(Given the high alcohol concentration limiting exposure may be the best practice. Hypnotic or nicotine withdrawal occurs rapidly and generally is completed by day 5- thus longer phenobarbital exposure may not be needed.)

Stabilization

All scores remain ≤8 for a minimum 48 hours. Seventy-two hours of stabilization may be used if the dosage has had to be increased by >0.4 mg/kg or if phenobarbital was added.

Morphine Weaning Phase

Once stabilized on same dose for 48 hours, use this dose as the starting point of the weaning process. Begin weaning the dose by 10% (of the original dose when the first weaning was started) every 24 hours. Drug may be discontinued when a single dose is <0.02 mg/kg per dose. Please see below for example.

Ad lib infants: Given the shorter duration of action of enteral morphine, it is best suited to be dosed on an every-3-hours schedule. Infants should be allowed

to ad lib feed but should be kept on an every-3-hours drug schedule.

Backslide: If an infant has 2 consecutive NAS scores >8 during the weaning process, ensure that nonpharmacologic measures are optimized (ie, swaddling, holding, decreased stimuli, etc) before going back to previous dose at which patient was stable. If the infant's scores continue to be elevated (even after physical examination to ensure nothing else is wrong and/or bothering the infant), either weight adjust the medication and/or continue to back up in a stepwise fashion until the patient's scores are ≤8. Once the infant is stabilized on the new dose for minimum 48 hours, resume 10% weaning but consider weaning at less frequent intervals.

Discharge

Observe the infant in-house for 48 hours off of morphine before discharge.

Example

Infant X (weight: 3.2 kg) required 2 dose increases of his morphine to get his NAS scores consistently ≤8. He has now been on the dose of 0.32 mg (0.1 mg/kg per dose) by mouth every 3 hours for 72 hours. The team would like to begin weaning. As long as his scores remain consistently ≤8, please decrease by 10% every 24 hours.

Day 1: 0.29 mg every 3 hours (0.09 mg/kg)

Day 2: 0.26 mg every 3 hours (0.08 mg/kg)

SUPPLEMENTAL TABLE 4 Initiation Phase: All Treatments are With Oral Medication

Methadone	
PO	0.05 mg/kg per dose q 6 h

PO, by mouth; q, every.

Day 3: 0.22 mg every 3 hours (0.07 mg/kg)
 Day 4: 0.19 mg every 3 hours (0.06 mg/kg)
 Day 5: 0.16 mg every 3 hours (0.05 mg/kg)
 Day 6: 0.13 mg every 3 hours (0.04 mg/kg)
 Day 7: 0.1 mg every 3 hours (0.03 mg/kg)
 Day 8: 0.06 mg every 3 hours (0.02 mg/kg) for 24 hours and then stop
 Monitor in-house for minimum of 48 hours before discharge.

Pharmacologic Treatment With Methadone

Treatment should be initiated if an infant has 2 consecutive scores >8 or 1 score >12 Treatment is divided into the following phases: initiation, escalation, stabilization, and weaning.

1. Increase dose if NAS still >8 after 3 doses of methadone;
2. If NAS still >8 3 doses later, increase to 0.15 mg/kg per dose every 6 hours; and
3. Initiate the second drug, phenobarbital.

Consider starting phenobarbital if

- Polysubstance exposure (benzodiazepines, barbiturates, antipsychotics, antidepressants, other sedatives and/or hypnotics, or tobacco) is suspected or confirmed;
- and central nervous system findings (tremors, increased muscle tone, etc) rather than

gastrointestinal findings predominate on the NAS subscale score;

- and the methadone dose exceeds 0.2 mg/kg per dose with score remaining >8 or if the infant is unable to wean for 2 consecutive days.

Loading dose: 10 mg/kg per dose by mouth every 12 hours × 2 doses by mouth or 20 mg/kg per dose intravenously × 1. (The enteral formulation contains 10% alcohol. Dividing dose by mouth may decrease risk of emesis and/or sedation.)

Maintenance dose: 5 mg/kg per dose by mouth once daily (do not weight adjust).

Phenobarbital weaning: Two approaches may be used. (Neither has been directly studied.)

1. Discontinue when on second to last step of methadone weaning to assess for tolerance of discontinuation. Given the long half-life of phenobarbital, this will wear off gradually over 4 days; and
2. Discharge the infant from the hospital on phenobarbital for 30 days with subsequent weaning to be done either in Neo Clinic or by infant’s primary care provider.

(Given the high alcohol concentration, limiting exposure may be the best practice. Hypnotic or nicotine withdrawal occurs rapidly and generally is completed by day 5; thus, longer phenobarbital exposure may not be needed.)

SUPPLEMENTAL TABLE 5 Escalation Phase

Methadone	
PO	0.1 mg/kg per dose q 6 h

PO, by mouth; q, every.

Stabilization

All scores remain <8 for minimum 48 hours. Seventy-two hours of stabilization may be used if the dosage has had to be increased by >0.4 mg/kg or if phenobarbital was added.

Weaning Phase

Once stabilized on same dose for 48 hours, use this dose as the starting point of the weaning process. Begin weaning the dose by 10% (of the original dose when the first weaning was started) every 24 hours. Drug may be discontinued when a single dose is <0.02 mg/kg per dose. Please see below for example.

Ad lib infants: Infants should be allowed to ad lib feed but should be kept on an every-6-hours drug schedule.

Backslide: If the infant has 2 consecutive NAS scores >8 during the weaning process, ensure that nonpharmacologic measures are optimized (ie, swaddling, holding, decreased stimuli, etc) before going back to previous dose at which the patient was stable. If the infant’s scores continue to be elevated (even after physical examination to ensure nothing else is wrong and/or bothering the infant), either weight adjust medication and/or continue to back up in a stepwise fashion until the patient’s scores are <8. Once the infant is stabilized on new dose for a minimum of 48 hours, resume 10% weaning but consider weaning at less frequent intervals.

SUPPLEMENTAL TABLE 6 Example

Step	Dose per kg	Interval
1	0.05 mg/kg	q 6 h × 4
1a: Escalate to obtain NAS score <8. Once the infant is stable for 24 h, begin weaning back to 0.05 mg/kg by weaning daily by 0.025 mg/kg per dose.		
2	0.04 mg/kg	q 6 h × 4
3	0.03 mg/kg	q 6 h × 4
4	0.02 mg/kg	q 6 h × 4
5	0.02 mg/kg	q 8 h × 4
6	0.02 mg/kg	q 12 h × 4
7	0.01 mg/kg	q 12 h × 4
8	0.01 mg/kg	q 24 h × 4

Observe the infant for 72 hours off methadone before discharge. q, every.

Discharge

Observe the infant in-house for 72 hours off of methadone before discharge.

PARTICIPATING OPQC NAS SITES

- Akron Children’s Hospital
- Akron Children’s St Elizabeth/ Mahoning Valley Hospital
- Akron Children’s Hospital at Summa Health System
- Akron General
- Aultman Hospital
- Bethesda North Hospital
- Cincinnati Children’s Hospital Medical Center
- Cleveland Clinic
- Dayton Children’s Hospital Medical Center

- Fairview Hospital
- Good Samaritan Hospital
- Hillcrest Hospital
- Mercy Children’s Hospital
- Mercy Anderson Hospital
- MetroHealth Medical Center
- Miami Valley Hospital
- Mount Carmel East Hospital
- Mount Carmel West Hospital
- ProMedica Toledo Children’s Hospital
- Nationwide Children’s Hospital
- Nationwide Children’s Hospital NICU at Mount Carmel St Ann’s
- Nationwide Doctors Hospital
- Nationwide Dublin Methodist Hospital
- Nationwide Grant Hospital
- Nationwide Riverside Methodist Hospital
- The Ohio State University

- University of Cincinnati Medical Center University Hospital
- University Hospitals Cleveland Medical Center, Rainbow Babies and Children’s Hospital
- Adena Regional Medical Center
- Atrium Medical Center
- University Hospitals Elyria Medical Center
- Fort Hamilton Hospital
- Genesis Healthcare System
- Good Samaritan Hospital Dayton
- Kettering Medical Center
- Licking Memorial Hospital
- Lima Memorial Health System
- Marion General
- OhioHealth MedCentral Mansfield
- Mercy Health West
- Mercy Hospital Fairfield
- Mercy Medical Center - Canton
- Mercy Regional Medical Center (Lorain)
- ProMedica Bay Park Hospital
- Soin Medical Center
- Southern Ohio Medical Center
- Southview Medical Center
- Springfield Regional Medical Center
- St Rita’s Medical Center
- The Christ Hospital
- Trumbull Memorial Hospital
- Upper Valley Medical Center

SUPPLEMENTAL REFERENCES

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