

Neonatal Abstinence Syndrome

History and Pathophysiology

Neonatal Abstinence Syndrome, also called NAS, is a complex of symptoms consistent with opiate withdrawal that is seen in neonates exposed to opiates before birth. Although other drugs can cause withdrawal symptoms in newborns, opiates are most often associated with abstinence syndrome requiring treatment. It has been noted for decades that women are particularly susceptible to opiate dependency. Peak age range for opiate abuse and dependency coincides with peak childbearing years. NAS is not a new disease; the first case of NAS was reported nearly 150 years ago. Subsequent resurgences in dependency on various forms of opiates have resulted in upticks in NAS reports. Research on infants with NAS during the heroin epidemic of the 1970s formed the foundation of our current approach to treating NAS.

Nationally, the incidence of NAS has increased rapidly over the past 10–15 years and now accounts for up to 20% of NICU days in some centers. On any given day at the University of Kentucky Children's Hospital, 10–20% of NICU beds are occupied by infants with a primary diagnosis of NAS. It is estimated that nearly 40,000 babies nationwide are at potential risk for NAS. A 2015 study evaluated admissions from 300 nurseries and showed an increase in NAS cases from 7/1,000 births in 2004 to 27/1,000 births in 2013. Median length of stay during that time period rose from 13 days to 19 days, and infants receiving pharmacologic treatment

for NAS rose from 74% to 87%. This has resulted in a continually increasing burden on the health care system and on costs of care. Following this trend, the number of infants born in Kentucky and reported as having NAS has climbed steadily since 2001, when 67 cases of NAS were reported statewide. In 2013, nearly 1,000 cases of NAS were reported in Kentucky, and the incidence continues to rise.

Several factors have contributed to the rapid rise in cases of NAS. Inappropriate marketing and prescribing of prescription pain medications, particularly Oxycontin, in the early 2000s led to rising rates of opiate abuse and dependency. Ten years later, limits on prescribing pain medications were followed quickly by a new influx of heroin into the state, along with steadily increasing numbers of heroin users and heroin overdoses. More recently, the broader acceptance and availability of medically assisted treatment (MAT) for opiate dependency has resulted in more women entering maintenance programs with methadone or buprenorphine. Regardless of the source of opiate, and whether it is legally prescribed, illicitly used, or used as part of a MAT program, the effects on babies exposed in utero are much the same; and all opiates are associated with a risk of NAS ranging from 50% to 90% in those exposed.

Neonatal Abstinence Syndrome is characterized by a spectrum of neurologic, autonomic, and gastrointestinal symptoms that begin when the newborn is cut

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off from the placental opiate supply. Opiates are water-soluble and easily cross the placenta to the fetus. Transmission across the placenta increases as gestational age increases. Although opioids act through opioid receptors μ , κ , and δ in adults, neonates have primarily μ receptors, with density and affinity for opioids similar to adults. These receptors are present throughout the nervous system and GI tract. With delivery of the neonate and loss of opioid at these receptor sites, aberrations in neurotransmitter production occur that cause the symptoms of NAS. Increased acetylcholine release can cause the diarrhea, vomiting, yawning, sneezing, and sweating classically seen with NAS. Noradrenaline release may result in fever, hypertension, tremors, and elevated heart rate. Decreased production of dopamine and serotonin leads to hyperirritability and disrupted sleep.

Premature infants are at lower risk of NAS than term infants, most likely due to decreased transmission of drug across the placenta and lesser density and affinity of receptors. Timing of withdrawal and duration of symptoms vary with type of opiate. Heroin and other short-acting opiates result in early withdrawal within a few hours of birth and short duration of seven to 10 days. Long-acting opiates such as methadone and buprenorphine may have onset of withdrawal delayed for several days, and withdrawal symptoms may last for a month or more. NAS that is not recognized promptly can progress to seizures and/or dehydration due to fever, sweating, and stool losses. The severity of withdrawal can be increased by use of other substances, including cigarettes, caffeine, antidepressants and benzodiazepines. Anecdotally, drugs such as Neurontin are also reported to worsen NAS symptoms and severity.

Treatment of NAS

Most centers that care for mothers with opiate dependency as well as their newborns use a variation of the original Finnegan Scoring System developed in the 1970s by Loretta Finnegan. The

scoring system is used to determine severity of NAS, need for pharmacologic treatment, and timing of weaning of the treatment drug. Morphine sulfate is the drug most commonly used to treat NAS. Methadone can also be used, and recent studies show that buprenorphine also can be used successfully in treating NAS. A small study done at the University of Kentucky showed that clonidine worked well as a primary drug for treatment of NAS in place of morphine. Secondary drugs additionally may be needed in infants with polydrug exposure or severe NAS. Most typically, phenobarbital or clonidine is added to the morphine or methadone regimen. Whichever drug is chosen for treatment, the goal is to minimize symptoms to the point where the infant can feed, sleep, interact normally, and gain weight.

In the United States, the most frequent model of NAS care is NICU admission followed by stabilization, weaning, and eventual discharge. All infants at risk for NAS should be monitored closely and treated with behavioral methods to decrease agitation and irritability. These measures include a quiet, dark room, snug swaddling, frequent small feedings, and skin-to-skin care. Regardless of which treatment drug is selected, the use of a protocol to manage infants with NAS will result in shorter length of stay and less drug exposure during treatment than non-protocol-driven care.

Family-Driven Care

The increasing use of MAT to manage opiate dependency will continue to present the health care system with increasing numbers of newborns with NAS. With the entry of many pregnant women into MAT programs, a comprehensive, multidisciplinary treatment model that begins before delivery will allow for the best chance of success at preventing NAS. Such a treatment model can identify and address risk factors for family disruption before delivery. Women with opiate dependency have high rates of other mental health issues, including depression, anxiety disorders, and post-traumatic

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stress disorder. They frequently live in unstable environments with domestic violence and often have a history of childhood abuse and/or molestation, a history of severe physical injuries, or previous loss of children. Many will also have hepatitis C or HIV, complicating their pregnancy and their own health. Addressing all of these issues before delivery of the baby will improve MAT success and reduce maternal relapse. The role of toxic stress during pregnancy is thought to contribute to altered brain growth and chemistry in the offspring that may lead to attention deficit and cognitive delays. These effects, compounded by adverse childhood experiences that the child may be exposed to in an unsettled environment, mean that babies exposed to opiate in utero may never reach their full potential.

PATHway (Perinatal Assistance and Treatment Home) clinic, operated by the Department of Obstetrics and Gynecology at the University of Kentucky, uses a multidisciplinary approach to provide MAT to pregnant women. Before delivery, women enrolled in the program receive referral to hepatology, infectious disease, psychiatry, or other specialties needed for other medical and mental health needs. On the weekly OB/MAT check day, they meet for several hours as a group with social workers, pregnancy and childbirth educators, and peer counselors. They are taught infant massage, calming techniques, and alternative coping skills. During an additional group session held each week, social workers and counselors work more intensively on coping skills development and stress management and address issues from other stressors, such as domestic violence and legal issues. The women also meet with a neonatologist to discuss NAS and what the risks may be for their baby, as well as to review measures they can take to help ease their baby through withdrawal, including kangaroo care and breastfeeding. Typical medication treatment regimens are also discussed, as well as the general care protocols for newborns undergoing observation for NAS. Parenting issues are also addressed, including how to pick pediatricians, risks of co-

bedding, smoking cessation, and car seat safety. All activities are geared toward empowering the mother to parent her child.

Prior to the start of the PATHway program, neonates born to opiate-dependent mothers were observed for five days to determine treatment needs. After 48 hours of rooming in with their newborns, the mothers were discharged and the infants remained in the newborn nursery. Frequently, within 12 hours of the mother's discharge the neonates would be transferred to NICU for ongoing evaluation and treatment. However, compelling studies from Canada and European countries have shown that the presence of the mother with the baby during the peak time for withdrawal is vital to decrease the number of infants requiring medication-based treatment and shorten the hospital stay, as well as to improve the chances of successful breastfeeding. Thus, whenever rooms are available, PATHway program participants are now placed in a care-by-parent environment in which the mother and other family caregivers continue to provide all care for the full five days of observation. Using this approach, all of the first 16 babies fully cared for by the parents were discharged home without requiring medication for treatment of withdrawal, and 10 of the 16 (62.5%) were breastfeeding fully or partially at discharge. In contrast, only 20% of mothers continued to breastfeed or provide maternal milk if they did not do care by parent or if the baby required NICU stay and medication for treatment. During the delivery stay of all PATHway mothers, standardized orders are used that include consultation with neonatal occupational therapy to determine soothing holds and teach infant massage, and to consult with musical therapy to learn appropriate lullabies for soothing. Lactation counselors meet with the mothers daily to help with breastfeeding.

After discharge from the hospital, the mothers continue to visit PATHway clinic group sessions and see the OB physician weekly for follow-up of their delivery and MAT. Plans for transition out of the

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PATHway clinic begin at around 28 weeks' gestation and are fully implemented with transition of the mother to a private or community MAT program at the six-week postpartum visit.

Feeding Infants with NAS and Follow-up after Discharge

As with most newborns, the optimal feeding for babies with NAS is maternal breast milk. Mothers who are HIV positive or using illicit drugs should be discouraged from breastfeeding, as should mothers who are not yet stable on a program or who are continuing to have frequent relapses. Academy of Breastfeeding Medicine guidelines recommend encouraging breastfeeding for mothers enrolled in MAT for at least 90 days and with no evidence of relapse in the past 30 days prior to delivery. Because many newborns going through withdrawal will have ineffective feeding, frequent consultation with lactation nurses will help establish milk supply as well as help with latching and developing alternative milk-feeding methods such as syringe, cup, or finger-feeding with pumped milk until adequate breastfeeding can be established. Evaluation by a neonatal speech therapist may also be beneficial to rule out any significant tongue-tie, weakness, or swallowing issues that may interfere with feeding. Mothers are frequently told that the methadone or buprenorphine in the breast milk will help ease the baby through withdrawal. Although some methadone or buprenorphine does cross to the breast milk, the actual amount is quite small and not likely to be therapeutic. Presence of the mother and frequent skin-to-skin contact are more likely the reason that breast-fed infants require less treatment for NAS than formula-fed infants.

In the absence of breastfeeding, the evidence for one brand of formula over another is lacking. Based on the presence of loose stools and perceived gassiness in babies with NAS, a low- or no-lactose formula is often selected to decrease these symptoms. Good Start Soothe, a WIC formulary product that has reduced lactose and added probiotic, is the

formula used in the NAS treatment protocol at the University of Kentucky. Very few babies undergoing treatment for NAS have persistent diarrhea with Good Start Soothe, and we saw no increase in diarrhea noted when changing to the low-lactose formula from a lactose-free formula. Babies who have frequent loose, watery stools despite treatment should also be considered for milk protein allergies and may respond quickly to a more elemental formula such as Nutramigen, Pregestimil, or Alimentum. Recent observational data from the NICU Graduate Clinic has raised concerns that babies recovering from NAS progress to high BMI later in infancy. After a period of ineffective feeding, hyperphagia may be persistent and result in over-eating after the initial stages of withdrawal. Monitoring for early excess body mass should also be done, and consultation with a dietician with expertise in infant nutrition should be obtained if rapidly increasing weight is seen.

Whether neonates born to opiate-dependent mothers require treatment or not, they have follow-up needs that cannot be ignored. Mild symptoms of withdrawal may persist for several weeks, so frequent weight and feeding checks should be done during the first month or two of life to make sure the transition to home has gone smoothly and that breastfeeding is successful, weight gain is appropriate, and the home environment is stable. Many infants will need testing for hepatitis C at 18 months due to maternal infection. Finally, all infants exposed to opiates in utero should receive developmental evaluation every few months for the first few years of life. There is some evidence that intrauterine opiate exposure, as well as morphine use after delivery, is associated with decreased brain growth. Infants with NAS are at increased risk for neurocognitive developmental delays from drug exposure, adverse childhood traumas, and toxic stress from an unsettled home environment. Early referral to First Steps should be considered for all infants with a history of NAS or opiate exposure in utero.

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The Future of NAS Treatment

The goal of caring for infants with opiate exposure is to have minimal withdrawal without need of pharmacologic treatment. Current trends across the United States indicate a higher percentage of newborns exposed to opiates are receiving pharmacologic treatment than ever before. Protocol-driven medication management of newborns will decrease length of stay only so much. Ongoing studies looking at differences in genetic markers may lead to individualized risk assessment and pharmacologic treatment for babies at risk for NAS in the near future.

Additional reductions in need for treatment and in length of stay will come from more programs, bed spaces, and facilities dedicated to maintaining the mother–infant pair together throughout the withdrawal and treatment phase. Development of home-based treatment programs with home health services will decrease length of stay and length of treatment needed.

Complementary medicine holds the promise of reducing the need for pharmacologic intervention for NAS. Infant massage is a technique easily learned by parents. They routinely report massage to be a successful calming tool both in and outside of the hospital. Aromatherapy has been shown to decrease production of the stress hormone cortisol in infants in small studies and is currently being studied, with FDA permission, in babies with NAS at the University of Kentucky. Additional forms of touch therapy and energy-flow techniques such as acupuncture and acupressure have shown some promise in treating withdrawal in adults and in some small infant studies. Jin Shin Jyutsu (JSJ), a soft-touch acupressure form of energy-flow therapy, is being incorporated into NAS care of some infants at the University of Kentucky as well. Most infants receiving JSJ show decreased respiratory rate and heart rate as well as improved sleep in the 24 hours after they receive JSJ treatment, and a controlled trial is in development. Family members can easily

be taught to do JSJ on their baby and on themselves at home, giving families another tool in their toolbox for caring for their NAS baby and for decreasing maternal stress.

Most important, identifying and assembling a group of nonjudgmental counselors, therapists, doctors, nurses, lactation specialists, and home health aides with a real interest in improving care of NAS infants and their families are key to the successful recovery of these mothers and the best possible outcomes for their infants.

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We would like to sincerely thank Lori Shook, MD for contributing to this edition of the Nutrition Branch Newsletter. Dr. Shook is a Professor of Pediatrics at the University of Kentucky and was named one of the Best Doctors in America for 2015-2016 in Neonatology.

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