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Neonatal abstinence syndrome

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ABSTRACT

Neonates exposed prenatally to opioids will often develop a collection of withdrawal signs known as neonatal abstinence syndrome (NAS). The incidence of NAS has substantially increased in recent years placing an increasing burden on the healthcare system. Traditional approaches to assessment and management have relied on symptom-based scoring tools and utilization of slowly decreasing doses of medication, though newer models of care focused on non-pharmacologic interventions and rooming-in have demonstrated promise in reducing length of hospital stay and medication usage. Data on long-term outcomes for both traditional and newer approaches to care of infants with NAS is limited and an important area of future research. This review will examine the history, incidence and pathophysiology of NAS. We will also review diagnostic screening approaches, scoring tools, differing management approaches and conclude with recommendations for continued work to improve the care of infants with NAS.

Introduction

Infants born to mothers using opioids often experience withdrawal. After birth, as a neonate metabolizes and clears any remaining opioid, the common signs of withdrawal such as irritability, tremors, hypertonicity, poor feeding, and loose stools may appear.[1] The term neonatal opioid withdrawal syndrome most accurately describes this syndrome, however the medical community today most commonly refers to this cluster of symptoms as Neonatal Abstinence Syndrome, or NAS.[2] We will therefore use the term NAS in this article to characterize withdrawal specifically from maternal opioid use.

NAS long predates the 21st century's opioid epidemic. The first case reports appeared in the medical literature in 1875. In that case series, nine out of twelve morphine-exposed infants died during the neonatal period.[3] The diagnosis, then known as congenital morphinism, maintained a high mortality rate throughout the first half of the 20th century.[4] In a 1959 review article, Cobrinik et al. reviewed 204 case reports dating back to 1875 and identified 37 infants who received no treatment, of which 33 died. Four of forty-one infants receiving treatment with either morphine, paregoric, or phenobarbital also reportedly died.[5] Two significant changes in the mid-20th century significantly reduced mortality associated with withdrawal - increased rates of maternal treatment for substance use disorders during pregnancy and transfer of care for infants with NAS to the neonatal intensive care unit (NICU). Both of these factors account for the continued reliance on the use of both the NICU as the preferred location of therapy for NAS and maternal opioid replacement strategies during pregnancy observed in today's clinical practice.

Until the 1950s, almost all reported cases of neonatal withdrawal involved prenatal exposure to morphine. Starting in the 1950s, neonatal withdrawal from opioids other than morphine began to appear. In 1951 researchers published the first case related to heroin.[5] After the 1964 development of

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methadone therapy for the treatment of opioid withdrawal, medical literature recorded prenatal methadone exposure with increasing frequency.[6] Now, infants may experience NAS as a result of prenatal exposure to a wide range of both prescription and non-prescription opioids, including heroin, methadone, buprenorphine, and painkillers such as oxycodone and hydromorphone.[7,8]

Over the last two decades, the use of opioids in the United States increased dramatically, including in pregnant women. From 1999 to 2014 the percent of pregnant women using opioids quadrupled.[9] Currently, if a pregnant woman is using opioids, the standard of care is to enroll her in medication assisted treatment with either methadone or buprenorphine, which was approved for use in the United States in 2002.[10,11] Thus, the incidence of opioid exposed newborns has also increased dramatically. The incidence of NAS in the United States increased from a rate of 1.3/1000 births in 2000 to 5.8/1000 births in 2012 based on data from the Kids' Inpatient Database and the Nationwide Inpatient Sample, which includes data from over 4000 hospitals.[12] More recent data from 23 hospitals in the Pediatric Health Information System (PHIS) showed a rate of 20 per 1000 live births in 2016.[13] Regional variation in the incidence of NAS reflects highest rates in areas hit hardest by the opioid epidemic, such as Kentucky, West Virginia and the New England states. Lincoln County, WV has the highest reported rate at 106.6/1000 births.[14,15]

The growing number of infants with NAS places an increasing strain on the healthcare system.[16] In 2012, infants with NAS utilized 4% of neonatal intensive care unit (NICU) beds and up to 50% in community hospital NICUs.[17] As a group, infants with NAS have one of the longest lengths of stay (LOS) of any pediatric disorder and consequently have high associated costs.[18] Aggregate hospital charges were estimated to be $1.5 billion in 2012, up from $732 million just 3 years earlier.[19] A 2017 study that included 199 hospitals in the Vermont Oxford Network reported an average length of stay of 19 days.[20] The LOS in the large database studies ranged from 17 to 23 days.[13,19] However, published reports of LOS in individual hospitals range from 5.9 days to 79 days suggesting wide variations in treatment strategies.[21,22]

The increasing severity of the opioid epidemic and the broad range of treatment strategies and outcomes across the United States warrant sustained attention by the pediatric community. This article aims to advance understanding of NAS and best practices for its effective treatment.

We will review the pathophysiology, clinical presentation, management, and long-term outcomes for opioid exposed infants, and will conclude with recommendations for NAS care and research moving forward.

Pathophysiology

The pathophysiologic mechanisms underlying NAS remain poorly characterized, but evidence from animal models suggests withdrawal in the newborn to likely be a distinct process from that of adults. The complex nature of immature neuronal circuits, variable levels and actions of opiate receptors (μ, κ, and δ) in the developing fetus, and contributions of differing neurotransmitters have all been cited as potential areas for divergent processes of withdrawal in the newborn.[23,24] Recent work also identified single-nucleotide polymorphisms in three genes that may correlate with variability of disease severity within the newborn population itself.[25]

Leading hypotheses for mechanisms of NAS center on increased noradrenergic output from the locus coeruleus, a nucleus in the anterior pons that acts as the central nervous system's (CNS) main norepinephrine producer.[23,24,26,27] Chronic opioid agonism of μ-opiate receptors within the locus coeruleus upregulates intracellular cyclic adenosine monophosphate (cAMP) levels over time, creating an environment for superactivation of cAMP-mediated processes once the opioid stimulus is withdrawn after birth. This superactivation of cAMP regulates ionic homeostasis of various intracellular elements ultimately resulting in increased norepinephrine release. This increased noradrenergic supply is thought to be largely responsible for the majority of signs and symptoms observed in NAS.

Many other areas of the CNS and various neuronal substrates have also been implicated as contributors to symptoms of NAS. The dopaminergic mesolimbic pathway responsible for processing responses to reward releases decreased dopamine levels from the ventral tegmental area into the nucleus accumbens during withdrawal.[23,28,29] The dorsal raphe nucleus has also been shown to release decreased levels of serotonin, which is thought to be responsible for observed sleep disturbances in neonatal withdrawal.[23,30,31] Other neurotransmitters, such as acetylcholine and glutamate have also been cited as playing a potential role in the withdrawal process through actions on gastrointestinal cannabinoid receptors and N-methyl-D-aspartate receptors, respectively.[24,32] Finally, activation of the hypothalamic-pituitary-adrenocortical axis involved in the stress response showed increased corticotrophin release in rats withdrawing from morphine.[33]

Clinical presentation & diagnosis

The Finnegan Neonatal Abstinence Scoring System (FNASS) extensively catalogues the myriad signs and symptoms of NAS and divides them into three main categories: central nervous system, metabolic/vasomotor/respiratory, and gastrointestinal (Table 1).[34] Infants with NAS typically present with signs and symptoms reflecting an increased noradrenergic state - irritability, tremors, sweating, hyperactive Moro reflexes, hypertonicity and excessive, high-pitched crying.[23,35–37] Although there is significant variation in the initial presenting signs and symptoms of NAS, the three most specific features of withdrawal include mild tremors when undisturbed, increased muscle tone and an exaggerated Moro Reflex.[38] Disturbances in sleep are also frequently observed as many infants display difficulty maintaining prolonged periods of sleep given reduced thresholds for arousal.[39–42]

The effects of withdrawal on the autonomic nervous system can lead to changes in skin perfusion, respiratory rate and temperature instability that can often be mistaken for early-onset sepsis.[35] Difficulties providing adequate nutrition are common given poor, uncoordinated feeding in a patient

Table 1 – Signs and symptoms of withdrawal as catalogued by the Finnegan Neonatal Abstinence Scoring System.

- **Central nervous system disturbances**
  - High pitched cry
  - Deficiencies in sleep after feeding
  - Tremors
  - Increased muscle tone
  - Excoriations of skin – nose, knees, or toes
  - Myoclonic jerks
  - Generalized convulsions
  - Hyperactive Moro reaction
- **Metabolic, vasomotor, respiratory disturbances**
  - Sweating
  - Fever
  - Yawning
  - Mottling of skin
  - Nasal stuffiness
  - Sneezing
  - Nasal flaring
  - Tachypnea
- **Gastrointestinal disturbances**
  - Excessive sucking
  - Poor feeding
  - Regurgitation and/or projectile vomiting
  - Loose and/or water stools

population generally requiring increased caloric demands due to the hypermetabolic state of withdrawal.[43–47] These nutritional issues are further compounded by intestinal losses from symptoms of vomiting and diarrhea associated with withdrawal. The most concerning and potentially life-threatening symptom observed in NAS is seizures, and an early report cited an incidence of approximately 8% for methadone-exposed infants.[48] The majority of these seizures were classified as myoclonic jerks with normal interictal EEG studies. Studies over the past several decades rarely report seizures related to withdrawal.[21,22,49,50]

Many factors such as the agent of exposure, dose, and polysubstance use can alter the clinical presentation of NAS.[35–37] The timing of signs and symptoms of NAS mainly depends on the specific opioid exposure. Signs and symptoms of withdrawal associated with shorter half-lives, such as heroin, will typically occur with the first 24–48 h of life, while withdrawal from opioids with longer half-lives, such as buprenorphine and methadone, will typically occur at approximately 36–60 and 48–72 h, respectively.[35–37] Agent of exposure not only affects timing of withdrawal, but may also contribute to the severity of presentation. For example, studies show that infants exposed to buprenorphine may have less severe symptoms of withdrawal, shorter lengths of stay, and receive less pharmacologic treatment than methadone exposed infants.[51–56] While maternal dose of opioid has not necessarily shown to affect severity of withdrawal, symptoms are likely to be less severe with doses $\leq$ 30 mg of methadone.[57–62]

Polysubstance, polypharmacy and cigarette exposures have all been associated with more severe presentations of withdrawal in the newborn.[35–37,63–65] Male gender may also serve as a risk factor for increased clinical severity of NAS.[66,67] Conversely, breastfeeding has been associated with less severe withdrawal likely attributable to small amounts of opioids in breastmilk and the positive effect of skin-skin contact on the withdrawing infant.[68–70] Prematurity has also been associated with milder courses of withdrawal with studies showing reduced requirement for initiation of pharmacologic therapy and shorter lengths of pharmacologic treatment.[71–73] However, the lack of a specific assessment tool for premature infants may serve as a possible confounder in interpreting these data.[74] Finally, there are studies showing variable degrees of severity of NAS based on an infant's underlying genetic makeup.[75]

Screening

Since maternal reporting of opioid exposure in utero may not be completely reliable, it is essential to maintain a high index of suspicion for a constellation of symptoms that may suggest a diagnosis of withdrawal.[76] Obstetricians should ask pregnant women about opioid use during routine obstetric visits and positive screens should be referred to medication assisted treatment (MAT) programs.[77,78] It is important that this screening is performed in a non-judgmental and supportive manner.[79] While some institutions have adopted universal toxicology testing for maternal substance use during pregnancy to improve identification of infants at risk for NAS, concerns regarding the cost of universal screening, the potential negative impact on therapeutic alliance between provider and mother, and a lack of grave outcomes associated with delayed diagnosis of NAS have all been raised in regards to policies recommending universal maternal drug toxicology screening throughout pregnancy.[76,80]

If NAS is clinically suspected in the post-natal period, further testing of either the infant's urine, cord blood, meconium, and/or hair are all viable options for attempting to identify in utero exposures.[81] Both false positive and false negative results are possible with all of these types of testing and results should therefore be interpreted in the context of the clinical scenario.[82] Collecting an infant's urine is commonly performed given access to timely results, and if pursued, should be collected as soon as possible (preferably first void) given variable metabolism and clearance of maternal agents. In general, an infant's urine testing reflects maternal use from the previous days to week prior to delivery, and may remain positive for 2–4 days depending on agent and timing of last exposure.[81,82] Cord blood testing also reflects recent exposures (hours to days), but is generally considered to be less sensitive than other specimen samples.[82]

Testing an infant's meconium is another option for toxicology evaluation and can reflect exposures from as early as 20 weeks of gestation.[83] While the sensitivity for meconium testing is superior to urine testing, slower result times and restrictions on handling the sample often make meconium testing less feasible. Care to avoid cross-contamination with urine should be taken when collecting meconium and collection should preferably occur prior to initiation of feeds to improve the accuracy of testing.[81] Testing an infant's hair is another option to reflect earlier exposures (from the third trimester) and has the added benefit of being able to be performed for up to months after birth; however, similar restrictions on sample collection may make this testing less desirable as well.[83] Nevertheless, if urine and/or cord blood testing is considered

unsatisfactory given the clinical circumstance, both meconium and/or hair testing remain viable options to pursue in attempts to garner more information regarding potential in utero exposures.[35]

Principles of management

Clinical assessment

Clinicians have used various scoring tools in the management of infants with NAS since the mid-1970s. The most influential of these tools originated in response to a heroin epidemic in Philadelphia. Dr. Loretta Finnegan and her colleagues developed the aforementioned FNASS, a tool that measures 21 different signs of withdrawal, typically requires scoring infants at intervals of every 2–6 h, and indicates initiation of pharmacologic therapy when an infant has three consecutive scores ≥ 8.[34,84] The initial implementation of the FNASS led to a 25% reduction in length of stay and a reduction in medication usage at Philadelphia General Hospital.[23] The original FNASS was modified slightly, with items moved and regrouped and excoriations of the chin, nose and knees were condensed into a single item.[85]

The pediatric community across the United States widely adopted the FNASS despite a 1998 American Academy of Pediatrics (AAP) Policy Statement recommending the Lipsitz Tool—an 11-item scale—because of its relative ease of use.[86,87] Since the development of the FNASS, several attempts have been made to find a shorter, more efficient scoring system that correlates well with the FNASS. The Neonatal Withdrawal Inventory (NWI), developed in 1998, contains only seven items, carries a high inter-rater reliability rate as well as 100% sensitivity and specificity for FNASS treatment thresholds.[88] The Neonatal Narcotic Withdrawal Index contains 7 items and offers high inter-rater reliability, though the 7th item contains 12 different symptoms.[89] The Finnegan Neonatal Abstinence Syndrome Tool – Short Form also contains 7 items and correlates well with the FNASS.[90] Though all three of these tools demonstrated good interrelater reliability and strong correlation with the FNASS, hospitals have rarely used them in practice for unclear reasons.[91] In 2009 the MOTHER NAS scale shortened the FNASS by removing overlapping items, removing items that did not appear to be responsive to medications, and added two items: irritability and failure to thrive. The MOTHER NAS contains 19 items and has been used in some published studies.[92,93] A short form of the MOTHER NAS scale that contained 5-items, distinguished between pharmacologically-treated and untreated infants similarly to the MOTHER NAS.[94] The FNASS and its offshoots are based on the assumption that tallying withdrawal signs is the best way to assess and guide treatment of infants with NAS. This assumption has never been tested.

In addition, research has never validated the FNASS to improve management of infants with NAS.[95] A FNASS score of 8 is higher than normally seen in non-opioid exposed infants and may be a valid cutoff for the diagnosis of NAS, but there is no research indicating that this cutoff is appropriate for starting pharmacologic therapy.[96,97]

Beyond the lack of validation as a treatment tool, the FNASS (and other related tools), falls short in several additional ways. First, it requires clinicians to disturb the infant in order to obtain an accurate score. To evaluate a Moro reflex or determine if an infant has tremors when disturbed, the scorer must unwrap an infant's swaddling and stimulate the infant in an attempt to elicit or exacerbate signs of withdrawal. Second, infants managed with a treatment protocol based on the FNASS record an average length of stay approaching three weeks.[19] This length of stay stands among the longest lengths of stay of any pediatric disorder outside of prematurity.[18] Third, in as much as the FNASS often leads to high rates of pharmacologic treatment for infants with NAS, the FNASS also impedes timely response to an infant experiencing significant withdrawal. With periodic scoring at 2–6 h intervals, between 4 and 12 h might pass before an infant will obtain 3 scores ≥ 8 to initiate or escalate treatment. Fourth, though the FNASS gives more weight to severe symptoms such as tremors or convulsions, it still values symptoms such as yawning and sneezing that likely have little to no clinical significance.[23]

Pediatricians long considered the FNASS as the "gold standard" for assessing opioid exposed infants. However, the lack of rigorous testing and multiple flaws in the tool suggest that this may not be warranted and has led to the development of other approaches. A new assessment method called the eat, sleep, console (ESC) approach was recently developed and evaluates infants on their ability to function in the setting of withdrawal.[21] In a study comparing the effect on management of the functional ESC approach versus the FNASS-based protocol, investigators continued to obtain FNASS scores on 50 infants with NAS but managed them using the ESC approach. Of the 50 infants in the study only 6 (12%) were treated with morphine. Had the FNASS been used to guide management, 31 (62%) would have been treated with morphine. There were no readmissions or adverse events reported.[98] Other institutions have adopted the ESC approach and also demonstrated substantial reductions in length of stay.[99] The ESC approach is relatively new and the few studies that have employed it have demonstrated a substantial reduction in pharmacologic treatment.[98,99] However, it is unclear what the implications of the decrease in medication usage is on long-term outcomes.

Alternative assessment approaches

There have been recent attempts to develop clinical prediction tools as well as more objective, physiologic measures of withdrawal. One tool was developed to predict whether an infant would receive pharmacotherapy based on a Finnegan based treatment protocol. Infants were evaluated at 36 h for skin excoriations, muscle tone and tremors (score of 0–5). Those with scores ≤ 1 were unlikely to receive pharmacologic treatment and those with scores of ≥ 4 were likely to receive pharmacologic treatment.[100] Physiologic markers such as pupillary size and brain derived neurotrophic factor (BDNF) levels are not likely to be clinically relevant because of the difficulty in measuring pupillary size and the necessity for blood draws to obtain BDNF values.[101,102] However, higher levels of skin conductance have been found in infants with NAS

compared to controls and have been linked to an increased likelihood of pharmacologic treatment.[103–105] Measuring indicators of physiologic stress may be practically difficult for day-to-day management but may be a useful tool to evaluate assessment and treatment strategies.

Non-pharmacologic interventions

The 2012 AAP Clinical Report on NAS recommends non-pharmacologic interventions as the first-line of therapy for infants showing initial signs of withdrawal (Table 2).[35] These treatments focus on providing both low stimulation environments with dark lighting and quiet surroundings, as well as soothing techniques such as swaddling, swaying, sucking, shushing, skin-to-skin contact and sideways/stomach position for the infant while awake to prevent auto-stimulation and reduce irritability.[36,37] Feeding on demand with frequent, small volume feedings should be offered to minimize the contribution of hunger and hyperphagia to irritability as well. Cluster feeding can be a common feature of both normal newborn physiology as well as for infants with NAS, and infants with NAS will undoubtedly have difficulty adhering to a regimented 3-hour feeding schedule.[106,107]

Early supplementation with high-calorie formula or breastmilk fortifier should be considered, especially if concerns for weight loss develop.[108,109] While there is no specific calorie per kilogram amount that these infants will need to gain weight, nutritional needs will likely be increased in the setting of withdrawal. In general, maternal HIV infection and polysubstance abuse are common contraindications to breastfeeding, but most institutions will have their own policy statements on determining safety recommendations for breastfeeding.[110] Given the potential benefit of breastfeeding on the severity of NAS, lactation consults should be offered (if available) to aid in establishing a healthy latch for patients who display a degree of dyscoordination in oral motor function. Patients may also require intermittent nasogastric tube feeds to support nutrition if feeding is disturbed by dyscoordination and/or sleepiness.[108,109]

Table 2 – Non-pharmacologic interventions to soothe infants and strengthen parental-infant bonding.

- **5 S's to sooth an infant by mimicking the womb environment**
  - Swaddle
  - Sway
  - Sideways position
  - Shush
  - Suck
- **Feeding on demand and/or cluster feeding**
- **Creating a low stimulation environment**
  - Dark lighting
  - Quiet surroundings
- **Rooming-in with parents at infant's bedside promotes:**
  - Continuous & immediate assessment of the infant by the parents
  - Provision of feeding on demand and/or cluster feeding
  - Breastfeeding (if allowed)
  - Lactation consultation (if available)
  - Skin-skin contact
  - Strengthening of maternal-infant bonding
  - Clinician anticipatory guidance, education, & empowerment to optimize parental care
- **Delivering an empowering message to parents that highlights their role in care**
- **Prenatal counseling with families to describe & highlight importance of their role in care**

Recent quality improvement work in the care of infants with NAS has focused on the powerful effects of parental rooming-in, with parents providing immediate assessments of their infant's status and non-pharmacologic interventions such as swaddling and on-demand feeds when they are at the bedside.[111–115] Rooming-in allows for increased skin-skin time and may improve success in establishing breastfeeding. The reports also identify the importance of delivering an empowering message to the parents so they understand the magnitude of their involvement in the care of their infants, with certain centers developing prenatal counseling visits to set expectations for parental roles in the postnatal care of their infant.[116] To date, these studies have shown some of the greatest reductions in length of stay with reported length of stay as low as 6 days for infants with NAS. These studies have also conferred significant cost savings and reductions in pharmacologic usage.[21]

Many institutions share significant barriers in both clinician and parental biases to overcome in order to optimize this power of the parental-infant dyad in the management of NAS.[117] Parents express feelings of guilt, mistrust and judgement from staff involved in the care of their infants.[118] Similarly, provider biases need to be addressed in order to instill a committed program of non-pharmacologic interventions with the parents providing the majority of the care at the bedside. In these models of care, clinicians have shifted roles from primarily providing direct care to the infants to stepping back and providing support and coaching to parents on how to optimize non-pharmacologic care for their own infants.[21] When parents are not available, many hospitals have utilized volunteer "baby cuddlers" to assist in helping optimize the delivery of non-pharmacologic care.[114]

Currently most research defines infants treated for NAS as only those who receive pharmacologic treatment. However, the improvements in LOS and reduced exposure to pharmacologic therapy related to the implementation of non-pharmacologic care and rooming-in models suggests that these interventions should be considered as treatment. Future work should attempt to account for potential dose response effects of non-pharmacologic care by attempting to directly measure both quantity and quality of parental rooming-in.

Alternative treatments

Many alternative treatment strategies have also been used in the management of NAS. Studies evaluating the use of Reiki, massage, acupressure and auditory stimulation have shown positive effects on infant vital signs and behaviors.[119–122] A study on the use of laser acupuncture showed a reduction in length of stay and duration of pharmacologic therapy, although the reported reduced length of stay of 35 days was significantly longer than previous reports.[123] Finally, there are studies underway evaluating the effect of aromatherapy, particularly the use of lavender and chamomile oils, on length of stay and salivary cortisol levels.[124]

Pharmacologic interventions

Though non-pharmacologic care is the first-line treatment, pharmacologic treatment has been essential to the care of infants with NAS.[35] However, the agents used and how they are used vary greatly across institutions.[91,125] The published rates of infants treated pharmacologically ranges from as low as 12% to as high as 91%.[23] The goal of medication therapy has generally been to achieve short-term improvement in withdrawal signs as measured by a reduction in FNASS scores or scores of another symptom-based tool. Pharmacotherapy can provide short-term improvement in withdrawal signs, but this short-term improvement is likely at a cost of worsening intermediate-term outcomes such as increased length of stay. The effect of pharmacotherapy on long-term outcomes is unknown. The 2012 AAP policy statement recommends using pharmacotherapy when indicated but points out that the unnecessary use of medications may prolong the overall duration of withdrawal to the detriment of maternal-infant bonding.[35]

There is a robust body of literature, including several randomized control trials, comparing length of stay or length of pharmacologic treatment between different pharmacologic agents. Despite these studies, there is no consensus as to what the best medication or combination of medications is to treat infants with NAS and the length of stay varies widely between institutions even when using the same medications. Opioids are the most commonly used agents either alone or in combination with other classes of medication.[91,125] Paregoric and tincture of opium, though popular choices in the past, are no longer routinely used because of their high alcohol content.[23] Based on survey data, morphine is used as the first line agent in the majority of institutions. A study using the PHIS database, reported that 90% of infants treated pharmacologically received morphine.[13] Morphine has a short half-life and is usually dosed every 3 or 4 h, often coinciding with feeds.[126] The frequent dosing of morphine may require the infant to be disturbed more frequently but also allows for more frequent dose adjustments. Methadone has been used with increasing frequency and a recent multi-centered study reported shorter length of stay for infants treated with methadone compared to those treated with morphine.[127] Methadone has a longer half-life and is usually given twice daily.[128] Buprenorphine, given sublingually has also been the subject of recent research and has demonstrated a shorter length of stay than morphine in some studies.[93,129]

Phenobarbital and clonidine are frequently used as second-line pharmacologic therapy either as a rescue medication given when a pre-determined maximum dose of the first-line medication has been reached, or in combination with an opioid at the start of treatment.[13,91,125] Twenty percent of the infants in the PHIS hospitals received both morphine and phenobarbital.[13] The safety of these medications is uncertain in infants with NAS. Clonidine can cause bradycardia and hypotension and the long-term developmental effects of exposure to phenobarbital or opioids is uncertain.[130]

Based on differing outcomes of head-to-head studies on medications or combination of medications, it is difficult to determine which pharmacologic treatment approach will lead to the shortest hospital stays.[131–134] It is equally difficult to explain the wide variation in outcomes between studies using the same medication to treat infants with NAS (Fig. 1).[135–137] The length of stay for infants treated with morphine ranges from 5.9 days to 42 days.[21,138] Infants treated with methadone have reported length of stay ranges from 16 days to 44 days and those treated with buprenorphine have reported length of stay ranges from 12.4 days to 32 days.[127,132,139,137] One study listed the length of stay for infants treated with tincture of opium as 79 days.[22] This tremendous variation is highly unusual, difficult to explain, and makes drawing conclusions about the utility of a particular medication difficult to determine. For instance, in a 2002 study by Coyle et al., the authors demonstrated a greater than 50% decrease in length of stay when treating infants with tincture of opium and phenobarbital versus tincture of opium and a placebo. Though the results were highly significant, the length of stay for the two groups were 38 and 79 days respectively.[22] While 38 days is significantly shorter than 79 days, it is also weeks longer than the length of stay for infants in many other studies. Of note, non-pharmacologic interventions are not controlled for in these studies which may explain some of the variation in length of stay. Moving forward, studies evaluating the impact of pharmacologic therapies should account for non-pharmacologic exposures in the randomization process given the significant impact these practices can have on patient outcomes.

One of the reasons that length of stay is so long in infants with NAS is that once pharmacologic treatment is started, medications are weaned off slowly.[35] Weaning protocols are not consistent between institutions but are usually between 10–20% of the peak dose every day that clinical scores remain below the treatment cutoff.[23] Though standardization of weaning protocols has shown to be beneficial in comparison to a non-standardized approach, there are no studies addressing the overall necessity or effectiveness of long medication weans and their use leads to days to weeks of pharmacotherapy.[140,141] The long-term impact of the additional exposure to these medications is unknown. However, the intermediate effect of these weaning protocols is that once a decision has been made to give a single dose of morphine, the infant may be fated to receive scores of doses before the morphine is discontinued. To date, two quality improvement projects have reported the use of 'as needed' dosing in lieu of a lengthy weaning protocol. This approach, in conjunction with optimization of non-pharmacologic therapies, substantially reduced the number of doses and overall amount of medication given to infants receiving pharmacotherapy without reported adverse events.[21,142]

Location of treatment

Studies comparing inpatient versus outpatient management of NAS have reported reduced length of stay and costs associated with outpatient management, although the majority of these length of stay are longer than the aforementioned reports focusing on optimization of non-pharmacologic care and rooming-in models.[143–147] Furthermore, outpatient management has been associated with increased overall pharmacologic exposures and there remain concerns surrounding

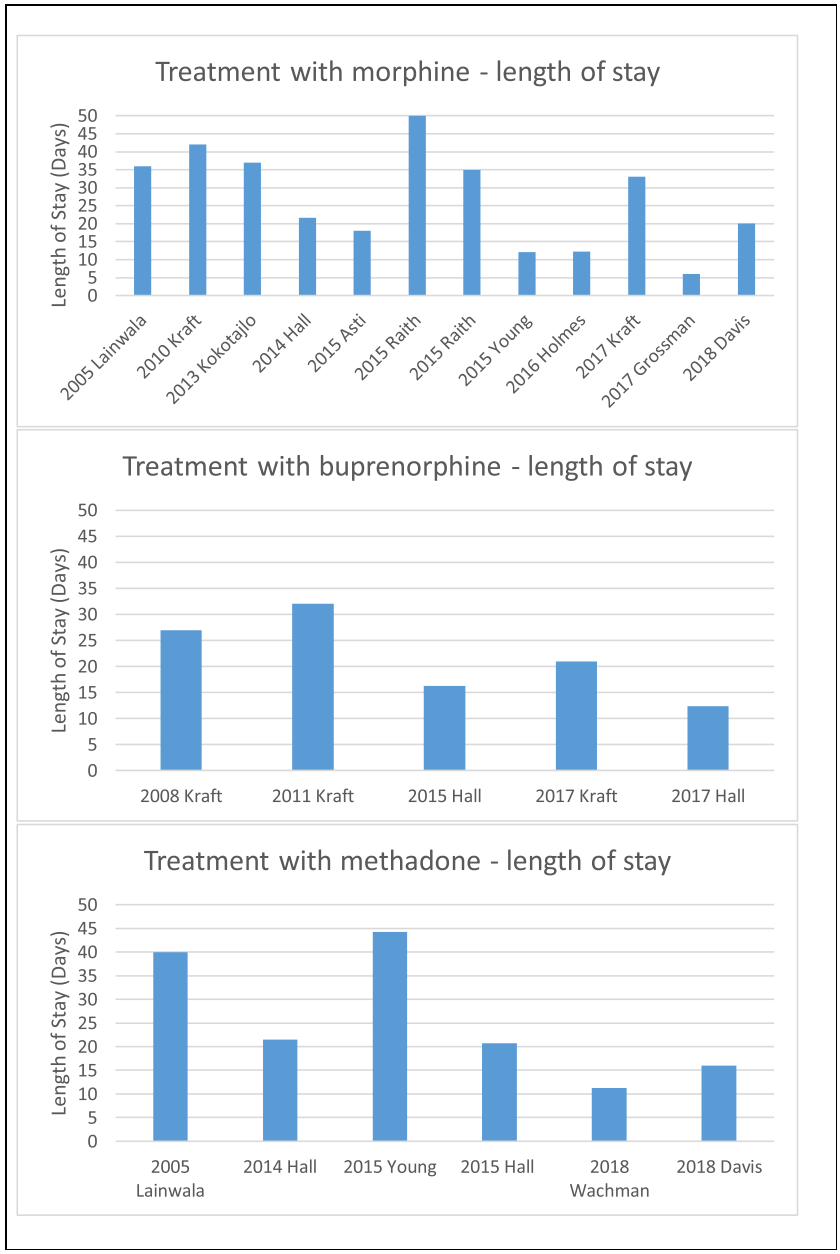

Fig. 1 – Variation in length of stay data presented by treatment medication*

*Data from Lainwala[131], Kraft[138], Kokotajlo[135], Hall[137], Asti[136], Raith[123], Young[132], Holmes[114], Kraft[93], Grossman[21], Davis[127], Wachman[99], Kraft[133], Hall[139].

discharging families with histories of opioid addiction with prescriptions for opioid therapy.[146,147]

Within the inpatient setting itself, there are few studies examining the impact of location of treatment on care outcomes. Recent administrative data from the PHIS national database showed that 87% of infants with NAS were admitted to the NICU.[13] Similarly, results from a telephone survey done in Canada showed that approximately 90% of infants requiring pharmacologic therapy for NAS were admitted to the NICU.[148] To date, there is only one study comparing care for infants transferred to the NICU versus continuing care on a postnatal ward that showed decreased morphine use and length of stay for infants remaining on the postnatal ward. The authors hypothesized that the quieter environment and increased bonding with the mother on the postnatal ward associated with an ability to room-in likely contributed to the observed outcomes.[149]

There is no clear indication for admission to the NICU for management of NAS and this continued practice likely reflects tradition over evidence-based practice. Recent quality improvement work has achieved decreased length of stay and exposure to pharmacologic treatment by transferring patients directly to the general inpatient pediatric unit instead of the NICU. This change in practice was undertaken given the difficulty of a NICU without single rooms to support rooming-in to provide an intensive, committed, first-line non-pharmacologic treatment program.[21] Concerns for seizures and the perceived need for cardiopulmonary monitoring

during pharmacologic therapy have historically been the main reasons for managing infants with NAS in the NICU; however, as noted previously, recent reports indicate that seizures are a rare occurrence in association with NAS.[23] Inpatient pediatric units are generally equipped to assess and manage infants with seizures. Furthermore, there is no current evidence-based recommendation regarding the need for routine, continuous cardiopulmonary monitoring in the management of infants with NAS.

Hospital discharge

Recommendations on the timing of hospital discharge have generally been based on both clinical factors, as well as considerations for agent of exposure and expected onset of symptoms. For agents with extended half-lives, the AAP Policy statement recommends monitoring patients for anywhere between 4–7 days prior to considering discharge.[35] Delayed onset of NAS beyond 7 days has been reported, but is generally considered a rare presentation.[150] For infants born to mothers taking short half-life opioids who display minimal symptoms of NAS that parents are able to manage without further pharmacologic therapy, hospital discharge at 3 days of age may be reasonable.[35]

Given the lack of evidence-based recommendations surrounding timing of discharge, clinicians should assure that infants show proper intake of formula or breastmilk, are appropriately consolable, are able to sleep, do not require pharmacologic therapy based on the used assessment tool strategy for approximately a 24-hour period (assuming not utilizing an outpatient weaning program), and that caregivers are established and feel comfortable providing routine, non-pharmacologic care for their infant prior to considering a patient suitable for discharge.[21] The Child Abuse Prevention and Treatment Act (CAPTA), reauthorized by Congress in 2010, calls for a notification of child protective services for any substance exposed infant. CAPTA also calls for a plan of safe care at discharge which includes assurances of appropriate outpatient services.[151]

Establishing early hospital discharge follow-up is recommended to both reinforce caregiver education, monitor for continued and/or delayed signs and symptoms of NAS, and follow growth and weight in patients with known increased energy expenditures. It may be beneficial to arrange follow-up appointments with developmental specialty clinics and home-based nursing assessments to monitor weight, development and to provide continued support/coaching for parents caring for infants with NAS.[23]

Long-term outcomes

Much of the focus on the management of infants with NAS has been during the initial hospitalization. Over the past few years there has begun to be more emphasis, from researchers as well as funding agencies, to understand the long-term outcomes or consequences of NAS.[152]

Though the data are limited, there are several studies addressing longer-term outcomes in children with NAS in areas including, vision, behavior, cognitive development, motor development, school performance and mortality. However, there remains a lack of clarity on the long-term consequences of NAS and most of these studies have faced major challenges as children with NAS are frequently lost to follow-up and many live in relatively unstable environments. It is also difficult to find adequate controls for these subjects because even controlling for socio-economic factors does not control for the added stresses of families dealing with substance use disorders.[153] In addition, the standard approach to management of NAS in the hospital has resulted in the separation of the infant from the mother.[17] There are data in both animal and human studies that suggest that this type of separation can have long-term consequences.[154–158] The majority of the current long-term data suggest that infants with NAS, treated with a traditional model with parents who are not receiving specific parenting support, will have generally poorer long-term outcomes than their peers.[153]

Infants with NAS have demonstrated increased rates of strabismus, reduced visual acuity, nystagmus and other visual motor problems.[153,159,160] Significantly poorer psychomotor outcomes have also been demonstrated starting at 12 months of age through early adulthood based on the Bayley Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI). Most studies showed no significant differences for infants less than 12 months of age.[153,161–163] Cognitive deficits compared to peers have also been described in several studies.[164,165] Investigators have reported impaired verbal and perceptual abilities and have demonstrated significantly poorer scores on the Columbia Mental Maturity Scale compared to matched controls.[166,167] In one study, Israeli children born to mothers using heroin were either adopted or raised by their parents. Both groups had lower performance IQ scores compared to controls. However, the adopted children had normal verbal IQ scores and math and reading abilities, while the children raised by their parents scored significantly lower in all three categories.[168] Other studies have demonstrated that infants exposed to opioids prenatally had attention problems and high rates of hyperactivity as young children.[159,163]

Deficiencies in school performance were reported in a 2017 study. In New South Wales, Australia 2234 children diagnosed with NAS were compared to a control group in grades 3,5 and 7. Children with NAS performed progressively worse compared to peers. Composite test scores for children with NAS were lower in grade 7 than the control group scores in grade 5.[169]

Increased mortality for opioid exposed children have been demonstrated in studies over the past 40 years from New York, Finland, Norway, England and Australia.[170–174] A 10-year study in New York City demonstrated a mortality rate that was four times greater for opioid exposed children and six times greater over eight years in Australia.[172,173] In an eight-year study from Sheffield, England, 32 unexplained deaths were reported for children under 28 days of age. In twelve of those deaths, the mothers were either in methadone programs or had misused opioids during pregnancy.[174]

Though it is not clear how much of the poor outcomes reported in the above long-term outcome studies are related to prenatal exposure to opioids, there is clearly some concern that some combination of opioid exposure, prolonged

hospitalizations at birth, and vulnerable, high-stress home environments have led to a host of concerning outcomes. However, of note, the first major randomized controlled trial of infants exposed to methadone or buprenorphine, known as the MOTHER study, published a follow-up study evaluating these infants at 3 years of life. Each infant received a battery of developmental tests starting at 3 months of age and continuing at regular intervals until 36 months. The investigators reported no difference between infants exposed to methadone or buprenorphine and also showed no negative effects on physical, mental or behavioral development.[175] It is not clear why previous studies have shown developmental deficiencies in children treated for NAS while children in this study followed a path of normal development. It is notable that the infants in this study had frequent follow-up with study personnel and surveys of the mothers, suggesting that the children had a consistently more enriched home environment. This MOTHER study does suggest that regardless of what long-term effects in utero exposure may have on an infant, a positive home environment may be sufficient to allow for normal development.[175] There is a large body of literature describing the importance of infant-mother bonding during early infancy and the positive impact of parenting support.[155,156,176] In caring for infants with NAS, much of the focus has been on the short and intermediate-term outcomes and though the evidence on effective approaches to good long-term outcomes is itself in its infancy, there appears to be ample data to suggest that encouraging maternal infant bonding in the hospital setting and providing parenting support as an outpatient are likely to have a positive impact. To successfully allow for adequate bonding, providers must facilitate rooming-in whenever possible in managing infants with NAS and more focus must be placed on identifying or developing supports for families during the hospital stay and at the time of hospital discharge.

Conclusions and future directions

The current opioid epidemic has dramatically increased the incidence of NAS which has caused an increasing burden on families and the health care system. This epidemic has also provided an opportunity to rethink our traditional approaches to care. The traditional, FNASS approach to care centered in a NICU environment has focused almost exclusively on improving the short-term outcome of reducing measurable signs of withdrawal, potentially at the detriment of maternal-infant bonding. The goals of post-natal treatment should extend to a focus on intermediate outcomes such as length of stay, and most importantly, long-term outcomes. Newer management strategies that optimize non-pharmacologic interventions and focus on the bonding of the infant and parents with rooming-in models have demonstrated substantially lower length of stay than the national average as well as reductions in hospital costs and use of pharmacologic therapy.[21,114,142] Early bonding between babies and mothers, coupled with parenting supports during infancy and childhood may hold some promise in improving long-term outcomes. Maintaining and strengthening the parental-infant bond should serve as a main tenet of therapy, and many institutions will need to develop creative responses to overcoming barriers that interfere with this essential tenet of therapy.

There are few randomized controlled trials to help guide management approaches and more such studies are clearly necessary. The traditional FNASS based approaches to management are not built on foundational, high-quality evidence and their standing as the status quo should not be misconstrued as a gold standard. There is an opportunity to find better ways to manage and support these infants and families to create strong long-term outcomes.

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