Advances in the Care of Infants With Prenatal Opioid Exposure and Neonatal Opioid Withdrawal Syndrome

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abstract

A significant number of advances have been made in the last 5 years with respect to the identification, diagnosis, assessment, and management of infants with prenatal opioid exposure and neonatal opioid withdrawal syndrome (NOWS) from birth to early childhood. The primary objective of this review is to summarize major advances that will inform the clinical management of opioid-exposed newborns and provide an overview of NOWS care to promote the implementation of best practices. First, advances with respect to standardizing the clinical diagnosis of NOWS will be reviewed. Second, the most commonly used assessment strategies are discussed, with a focus on presenting new quality improvement and clinical trial data surrounding the use of the new function-based assessment Eat, Sleep, and Console approach. Third, both nonpharmacologic and pharmacologic treatment modalities are reviewed, highlighting clinical trials that have compared the use of higher calorie and low lactose formula, vibrating crib mattresses, morphine compared with methadone, buprenorphine compared with morphine or methadone, the use of ondansetron as a medication to prevent the need for NOWS opioid pharmacologic treatment, and the introduction of symptom-triggered dosing compared with scheduled dosing. Fourth, maternal, infant, environmental, and genetic factors that have been found to be associated with NOWS severity are highlighted. Finally, emerging recommendations on postdelivery hospitalization follow-up and developmental surveillance are presented, along with highlighting ongoing and needed areas of research to promote infant and family well-being for families impacted by opioid use.

Prenatal opioid exposure (POE) increased across the United States between 2000 and 2017, with rates of maternal opioid-related diagnoses reaching 8.2 per 1000 deliveries in 2017.[1,2] The prevalence of neonatal opioid withdrawal syndrome (NOWS), a condition resulting from POE and also referred to as neonatal abstinence syndrome, has also increased the past 2 decades to 6.2 per 1000 live births in 2020.[1] Although emerging data from some states have shown a decline in the rates of NOWS between 2017 and 2021, rates vary widely across different US geographic regions, with New England and Appalachia being most heavily impacted, and rural areas seeing a faster increase (see Supplemental Table 5 and Supplemental Fig 1 for state-specific data).[2] POE disproportionately impacts lower-income and publicly-insured pregnant individuals.[1,3] Polysubstance exposure and cooccurring substance use disorders in pregnant people with opioid use disorder (OUD) are common[4,5] and occur in

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up to two-thirds of deliveries,[6] as are cooccurring mental health disorders resulting in frequent prenatal exposures to psychoactive medications.[7]

The objective of this state-of-the-art review is to highlight recent advances in the identification, diagnosis, assessment, and management of infants with POE during the delivery hospitalization and into early childhood. It aims to build upon the American Academy of Pediatrics (AAP) Clinical Report: Neonatal Opioid Withdrawal Syndrome and focus on emerging research published over the last 5 years to help guide pediatric clinical management of infants with POE.[8] Ongoing and needed research to advance the care of families impacted by POE and infants experiencing NOWS are reviewed.

IDENTIFICATION AND DIAGNOSIS

Infants who develop physiologic dependence on opioids in utero experience an abrupt discontinuation of opioid exposure after delivery. This disruption results in a decrease in binding at opioid receptors located primarily in the central nervous system and gastrointestinal tract, and an increase in noradrenaline impacting the autonomic system.[9] As a result, the clinical presentation of NOWS can include central nervous system irritability, gastrointestinal dysfunction, and autonomic hyperreactivity, resulting in alterations in sleep and wake cycles, irritability, feeding challenges, and overstimulation.[8] A list of common clinical signs and symptoms is presented in Table 1.

Because the clinical signs of NOWS have similar features to other neonatal conditions including seizures, sepsis, respiratory distress syndromes, and hyperthyroidism, for infants with a confirmed history of POE who are not responding to initial NOWS management, a full evaluation and workup for other diagnoses should be considered.

With respect to prenatal identification, the preferred approach to identifying infants with in-utero opioid exposure at risk for NOWS is through the use of validated screening tools administered verbally or completed via written questionnaire during prenatal care and at delivery rather than toxicology testing.[8,10] For infants, toxicology testing should only be completed when it will inform clinical management; specific approaches toward perinatal toxicology testing have been reviewed in detail previously in the AAP Clinical Report.[8] It is important for clinicians to be aware of pervasive racial/ethnic disparities in perinatal toxicology testing and the unique legal consequences related to substance use screening and testing with respect to mandated child protective services reporting in their state.[11,12] Hospitals should establish clear guidelines on the actions after a positive verbal screen or aberrant test result, including that the risks and benefits of screening and testing are communicated clearly to the birth parents, and that consent is obtained before obtaining a biologic sample for toxicology testing.[13,14]

The diagnosis of NOWS is made clinically, with standardized diagnostic criteria having just been recently proposed. An expert consensus panel was convened by the US Department of Health and Human Services using a modified Delphi method that identified 2 criteria required for the clinical diagnosis of NOWS:

1) exposure to opioids during pregnancy (identified via self-report or toxicology testing); and

2) the presence of at least 2 of the most common clinical signs of withdrawal including: Excessive crying, fragmented sleep, tremors, hypertonia, and gastrointestinal dysfunction.[15]

To date, there have been no published analyses of how diagnosis codes compare with this newly proposed definition, but the US Department of Health and Human Services definition was similar to the case definition used by Kuzniewicz and colleagues in their review of POE across multiple hospitals in the Kaiser Permanente network. Kuzniewicz found a positive predictive value of 85% when compared with infant International Classification of Diseases, Ninth and 10th Revision (ICD-10), codes for NOWS[16,17]; however, the sensitivity of diagnosis codes for identifying POE was only 14% and NOWS was 32%.[17]

With respect to public health surveillance, in 2019, the Council of State and Territorial Epidemiologists' (CSTE) developed a definition that has been adopted by state

TABLE 1 Clinical Manifestations of NOWS

Easy overstimulation, Hypersensitivity, or Hyperarousal	Alterations in Tone or Movements	Autonomic Dysfunction	Sleep and Wake Cycle Disturbances
Irritability	Hyperphagia	Sweating	Fragmented sleep
Excessive crying	Tremors	Sneezing	Short sleep cycles
Hypersensitivity to normal stimuli	Hyperreflexia	Mottled skin	Difficulty maintaining alert state
Uncoordinated feeding	Jitteriness	Fever	
Hyperphagia		Nasal sruffiness	
Excessive weight loss and poor weight gain		Tachypnea	
Vomiting		Frequent yawning	
Gassiness			
Diarrhea and loose stools			

public health departments that requires prenatal exposure to opioids, benzodiazepines, or barbiturates to be confirmed by neonatal toxicology testing. Elmore and colleagues found a low positive predictive value for the CSTE definition, with only 48% of clinical cases in a Florida data set identified; the toxicology testing requirement accounted for much of the discrepancy between ICD-10 codes and the CSTE definition.[18,19]

PREPARING FOR DELIVERY HOSPITALIZATION

The delivery hospitalization can be a challenging time for birthing individuals with substance use disorders who often feel shame watching their newborn experience symptoms of withdrawal, perceive and/or experience stigma from hospital staff, and have anxiety surrounding possible child protective services involvement.[20] Prenatal consultation can help support families in preparing for the delivery hospitalization and identifying anticipated challenges after birth.[21,22] Topics that are helpful to review include promoting a healthy pregnancy leading up to delivery, the short- and long-term impacts of POE, NOWS management and treatment, human milk feeding recommendations, toxicology testing guidelines, Plans of Safe Care, and preparing for child protective services involvement if indicated. Having clear policies and procedures established for the care of opioid-exposed dyads at delivery can help with counseling patients prenatally, standardizing care, and reducing bias. A list of guidelines that multidisciplinary teams should collaborate on to standardize approaches is included in Table 2.

To create a welcoming and positive experience for families during the delivery hospitalization, providers should use person-first language when talking with and about families impacted by POE. Examples of preferred and nonpreferred language are shown in Table 3.[23] To counteract the stigma and shame parents feel, antistigma and bias training for staff working on labor and delivery, postpartum, and newborn units can be implemented.[24,25] These trainings should provide education around trauma-informed care, and reflective spaces should be made available to staff to debrief challenging and difficult experiences.[26]

TABLE 3 Examples of Person-First, Nonstigmatizing Language

Nonpreferred Terminology	Preferred Terminology
Infant terminology	Infant terminology
Addicted infant	• Infant with NOWS
Born addicted	• Substance-exposed newborn
NOWS infant	• Opioid-exposed newborn
Parental terminology	Parental terminology
Addict	• Person with OUD
Addicted mother	• Medication for OUD
Medication-assisted treatment	• Urine positive for nonprescribed substances
Dirty urine	

This is a nonexhaustive list intended to give a few examples of preferred and nonpreferred terminology.

ASSESSMENT AND MANAGEMENT OF NEWBORNS WITH POE

Location of Care

Rooming-in with the primary caregiver is the standard of care during the delivery hospitalization for all infants, including those with POE. Rooming-in models of care, either in the postpartum or pediatric inpatient unit, are associated with improved parental presence during the hospitalization, as well as an increase in breastfeeding initiation rates.[27] Numerous single-center studies and meta-analyses have examined the role of rooming-in on NOWS inpatient outcomes and have consistently demonstrated a reduction in the receipt of pharmacologic treatment by 20% to 60%, a decrease in the total opioid treatment days, and shortened length of hospitalization by 1 to 2 weeks when rooming-in is used compared with care in separate units, such as the NICU.[27–29]

One potential barrier to rooming-in and a current source of wide variability in clinical practice is cardiorespiratory monitoring of infants requiring treatment with opioid medications.[30] Two single-center retrospective studies of infants undergoing treatment with either morphine or methadone found no significant differences in the incidence of cardiorespiratory adverse events compared with opioid-exposed infants who did not receive pharmacotherapy.[31,32] In contrast, a randomized control trial of 117 infants receiving either

TABLE 2 Recommended Guidelines and Policies for Care of Opioid-Exposed Dyads and Multidisciplinary Teams

Recommended clinical guidelines	Recommended hospital policies
Screening of birthing person for substance use	Indications for social work assessment and reporting to child protective services
Clinical rationales for toxicology testing for birthing person and newborn, including if and how consent will be obtained	Rooming-in and care location policies
NOWS assessment protocol	Parental engagement and visitation
NOWS nonpharmacologic and pharmacologic treatment algorithm	Jitteriness
Duration of observation for NOWS	
Breastfeeding recommendations in the setting of recent substance use	
Discharge criteria	

morphine or methadone who underwent cardiac monitoring reported a total of 13 adverse events including shallow breathing, bradycardia, oxygen desaturation, and lethargy, and 1 episode of apnea.[33]

The coronavirus disease 2019 (COVID-19) pandemic also impacted rooming-in approaches. During the initial phase of the pandemic, a single-center study described how a policy requiring that parental caregivers stay on the postpartum unit decreased the number of transfers to the NICU, but did not decrease the overall length of hospitalization for NOWS.[34] Another statewide quality improvement (QI) collaborative showed that COVID-19 protocols hindered parental rooming-in and that infants had longer lengths of hospitalizations compared with a preCOVID-19 group.[35]

NOWS Assessment Tools

Infants with POE should be monitored for signs of withdrawal every 3 to 4 hours during the delivery hospitalization, with assessments timed around when the infant is awake and/or nursing assessment times.[8] These assessments should begin shortly after birth and for 4 to 7 days if no pharmacologic treatment is required, or continue for 24 to 48 hours after stopping medications if pharmacotherapy is indicated.

Several different NOWS assessment tools are currently available. Standardization of the approach selected and the following conditions should be prioritized.[8] First, the infant should be kept in the room with the caregiver for assessments and the caregiver should be included in the assessment process to engender trust and engagement.[8] Second, the assessment should occur after a feeding and consider the entire period since the last evaluation.

The 2 most commonly used approaches for assessing NOWS are the Finnegan Neonatal Abstinence Scoring Tool (FNAST) and the Eat, Sleep, and Console (ESC) assessment approach. The FNAST is a 21-item tool that characterizes all clinical signs possibly associated with neonatal withdrawal, with certain signs weighted on the basis of perceived severity. The original tool has since undergone several modifications and abbreviations.[36–38] The ESC assessment approach was established by Grossman and colleagues to prioritize the functional needs of a newborn, focusing on 3 domains: The ability to eat the expected amount based on gestational and postnatal age, sleep undisturbed after a feeding for at least 1 hour, and being consoled within 10 minutes of soothing attempt.[39] Over the past 5 years, the ESC approach has been implemented across the country, particularly through statewide NOWS QI collaboratives in association with implementation of nonpharmacologic care bundles.[40,41] The ESC approach with use of a standardized ESC care tool has been recently evaluated in a multicenter clinical trial using a stepped-wedged randomized design across 26 hospitals that found that the ESC approach reduced time to infant discharge readiness by 6 days compared with the FNAST approach, without a significant increase in in-hospital safety events, unscheduled health care utilization, or nonaccidental trauma through 3 months postdischarge. Unlike QI efforts that coupled ESC implementation with pharmacotherapy changes, pharmacologic treatment protocols used by sites in the ESC–NOW trial were unchanged and still led to decrease in need for pharmacological treatment.[42] Follow-up to assess long-term neurodevelopmental outcomes, growth, and family well-being through 24 months of age is ongoing.[43]

NONPHARMACOLOGIC INTERVENTIONS

Environmental Modifications

First-line treatment of NOWS should prioritize nonpharmacologic interventions that are individually tailored to the infant's specific needs. The caregiver's functioning and ability to appropriately respond to their newborn's cues is critical to promote bonding and minimize further infant dysregulation while promoting optimal nonpharmacologic care.[44] Environmental modifications that have been used to decrease overstimulation include reducing noise and bright lights in the infant's room, swaddling and skin-to-skin time to reduce hyperarousal, and clustering of care times to limit disruptions to infant sleep. Recently, a randomized controlled trial using a vibrating crib mattress found a significant reduction in cumulative dose and length of pharmacotherapy in the subgroup of newborns that received <3 weeks of pharmacotherapy, but no reduction in overall need for pharmacotherapy or length of hospitalization.[45] A recent Cochrane review examined the efficacy of several novel nonpharmacological treatments of infants with POE. It included randomized control trials evaluating a vibrating mattress, prone positioning, waterbed, and a low stimulation nursery setting. They found that studies ranged from no evidence to very low certainty evidence of reducing length of hospitalization or need for pharmacologic therapy.[46]

Feeding Interventions

Breastfeeding in the setting of NOWS has been associated with decreased severity and duration of symptoms,[47] and birthing parents motivated to breastfeed should be supported in their efforts, assuming they have no ongoing use at delivery, are engaged in prenatal care, and have no other contraindications to breastfeeding.[48,49] In the case of formula feeding, there remains no consensus as to the first-line formula. Recent studies examining low lactose or partially hydrolyzed formulas compared with standard infant formulas have not demonstrated any differences in NOWS hospitalization outcomes.[50–54] With respect to higher caloric density formula, although a recent randomized controlled trial found no significant differences

in NOWS outcomes in the high calorie versus usual care group, a multicenter QI initiative found that higher calorie formula did lead to reduction in length of stay, weight loss, and need for secondary pharmacologic agents.[53,55] Hyperphagia, excessive weight loss, and poor weight gain in the setting of NOWS is common because of increased metabolic demand.[56,57] For infants unable to meet minimal goal volumes, or with excessive weight loss despite adequate feeding, nasogastric supplementation should be considered until oral volume intake improves.

PHARMACOLOGIC INTERVENTIONS

When infants with POE continue to show signs of NOWS after maximizing nonpharmacologic options, the AAP supports the use of an opioid as the first-line pharmacologic agent.[8] Table 4 highlights common dosing amounts and frequencies for the most studied medications when administered with standard doing, as needed dosing, and weaning protocols.

Although a larger number of centers currently use morphine as their primary agent, several randomized controlled trials and a meta-analysis of methadone versus morphine have found improved short-term NOWS outcomes including length of stay attributable to NOWS and length of treatment of methadone-treated infants.[33,58] More recently, buprenorphine has been evaluated as a first-line agent with a reduction in length of stay attributable to NOWS compared with morphine and methadone in single-site studies.[59,60] With respect to secondary agents, phenobarbital and clonidine are the most commonly used medications, with phenobarbital associated with a shorter length of hospitalization compared with clonidine, but longer total time on medication because of prolonged outpatient weans.[61] A recent multi-site randomized trial evaluating the effect of maternal ondansetron administration during delivery and infant ondansetron after birth showed a nonstatistically significant reduction in infant opioid pharmacologic therapy in the ondansetron group compared with placebo.[62] Regardless of choice of primary or secondary agent, a standardized protocol for dosing administration and weaning protocols has been associated with improved outcomes.[63] A multicenter study is ongoing to assess the impact of standard versus accelerated weaning on total opioid treatment days.[64]

In the past 5 years, the most widely changing practice has been around the use of symptom-triggered, as needed dosing as opposed to standing, scheduled dosing. Both morphine and methadone have been examined in QI

TABLE 4 Pharmacologic Agents for Treatment of NOWS

Medication Name	Morphine	Methadone	Buprenorphine	Clonidine	Phenobarbital
Preferred use as primary or secondary agent	Primary	Primary	Primary	Secondary	Secondary
Standing dosing	0.3–1.0 mg/kg per d PO divided every 3–4 h	0.2–0.9 mg/kg per d PO divided every 6–12 h	13–40 mcg/kg per d SL divided in 3 doses	1 mcg/kg PO q4 h	Loading: 10–20 mg/kg per dose PO. Standing dosing: 5–8mg/kg per d PO in 1–2 divided doses
PRN dosing	0.03–0.05 mg/kg per dose PO every 3–4 h	0.07 mg/kg per dose PO q6–8 h	N/A	N/A	N/A
Weaning	10% per d down to 10%–20% of max dose	10% per d down to 10%–20% of max dose, or space interval	10% per d until at 10% of the max dose	Increase from q4 to q8 to q12 to off	20% every 3–7 d starting 2–3 d after primary opioid treatment has been weaned off
Monitoring levels	N/A	N/A	N/A	N/A	Therapeutic range: 15–30 mcg/mL
Advantages	Shorter half-life; more frequent dosing tailored to symptoms	Longer half-life, which may be better for more severe withdrawal	May be more advantageous for buprenorphine-exposed infants	No known risk for neurodevelopmental delays; no risk for infant sedation	May be better for polysubstance exposure; outpatient weaning is possible
Disadvantages	Longer length of treatment compared with methadone in several randomized controlled trials	Longer half-life makes it more difficult to tailor toward symptomatic dosing	Sublingual administration with high ethanol (30%) content	Blood pressure and heart rate monitoring during clonidine treatment because of risk of hypertension and arrythmias	Risk of neurodevelopmental delays with prolonged exposure; high ethanol content in some preparations

N/A, not applicable; PO, by mouth; PRN, pro re nata - as needed; SL, sublingual.

projects, usually as part of nonpharmacologic care bundles and implementation of ESC protocols, with infants requiring on average 2 doses of medication.[32,40,41,65,66] A multicentered retrospective analysis compared the use of as-needed morphine to as-needed methadone and did not find any differences in short-term hospitalization outcomes.[67] A randomized controlled trial to assess symptom-based dosing compared with scheduled dosing has been proposed and is currently in development.[68]

CONTRIBUTORS TO SEVERITY OF NOWS PRESENTATION

Several important studies have furthered our understanding of contributors to NOWS severity, which has been heterogeneously defined in studies to date.[69,70] Coexposures to other substances and medications, maternal and neonatal characteristics, genetic factors, and postnatal environmental factors have all been found to be associated with NOWS severity, and key associations with recently published data are summarized below:

Medications to Treat OUD

One recent study utilizing sophisticated matching techniques to compare prenatal buprenorphine versus methadone use among a national cohort of pregnant people with OUD found a significantly reduced percentage of infants receiving a diagnosis of NOWS among buprenorphine-exposed neonates.[69] Despite these findings, the use of medications to treat OUD during pregnancy should be individualized; furthermore, most of these studies were performed before the rise of nonprescribed fentanyl in the drug supply, for which methadone is often preferred to stabilize patients.[70]

Prescribed Opioid Medications

For prescribed opioid medications, Straub and colleagues created 6 different opioid-prescribing trajectories and found that NOWS risk increased from exposure to higher doses of opioids, as well as cumulative exposure, one of the first large-scale studies to examine the risk of NOWS from chronic prescription opioid use.[71]

Polysubstance Exposure

Coexposure to nonprescribed substances, including cocaine and cannabis, is strongly associated with more severe NOWS.[72–74]

Psychiatric Medication Exposure

Many different classes of psychiatric medications have been found to be associated with more severe NOWS, including selective serotonin reuptake inhibitors,[75,76] benzodiazepines,[77] and gabapentin.[74] Exposure to 2 or more psychiatric medication types is also associated with more severe NOWS.[6]

Prenatal Care

Engagement in prenatal care was found to mediate the relationship between medication for opioid use disorder and NOWS severity in a sample from 30 hospitals across the United States.[73]

Genetic and Epigenetic Factors

In addition to clinical and environmental factors, both genetic variation and epigenetic modifications are being studied to better understand their contribution to NOWS severity. In a recent, genomewide association study, a locus on chromosome 7 downstream of sorting nexin 13 was associated with receipt of pharmacologic treatment.[78] Additional studies have looked at epigenetic modification and the association with NOWS severity and found differences in DNA methylation levels in infants who received more pharmacotherapy for NOWS and differences in methylation levels within placental tissue associated with infant receipt of pharmacologic treatment.[79–81]

DISCHARGE PLANNING

A clinical readiness checklist can be used to assess whether an infant experiencing NOWS is ready to be safely discharged. Common elements include resolution of withdrawal symptoms, a period of 24 to 48 hours of observation after stopping pharmacological treatment, adequate feeding and weight gain, safety assessment of the caregivers, completing a plan of safe care, and placing referrals for outpatient follow-up.[8] A discharge bundle implemented at a single site in Tennessee found significant improvements in referrals to recommended developmental surveillance programs, home visiting, and specialist referrals.[82]

OUTPATIENT MANAGEMENT

Once the immediate withdrawal signs of NOWS have passed, there is a clear drop in evidence-based practice and recommendations. Yet, recent studies looking at the first year after birth have identified concern for increased risks of infant morbidity and mortality including: A lower rate of attendance at well-child visits[83] and at recommended developmental follow-up services,[84] higher rate of emergency department visits[85,86] and hospital admissions,[85–87] and increased risk of mortality for infants with POE or NOWS.[88,89]

The evidence around long-term outcomes is not only scarcer, but also has more limitations, which make the interpretation of the findings more difficult.[90,91] Over the past 5 years, a handful of meta-analysis and prospective studies have aimed to evaluate the impact of POE. First, two meta-analyses compared POE with non-exposed controls (1 included 26 studies going back to 1979, the other with 16 studies starting in 1993) and found motor and cognitive delays for infants and preschool-aged children.[92,93]

For both of these studies, limitations include failure to differentiate exposure to methadone or buprenorphine from heroin, not all studies adjusted for socioeconomic status, and adjusting for other prenatal exposures such as nicotine, alcohol, or polydrug exposures was not discussed. Schwartz and colleagues performed a meta-analysis assessing POE and attention-deficit/hyperactivity disorder symptoms and identified a positive association in preschool- and school-aged children compared with non-exposed controls.[94] Although the studies included in Schwartz's analyses accounted for polysubstance exposures, only half accounted for socioeconomic or postnatal environmental factors, including out-of-home placement. Czynski and colleagues published the results of neurodevelopmental assessments on infants requiring pharmacologic treatment of NOWS who received either morphine or methadone as part of a randomized clinical trial and found no differences across 3 neurodevelopmental scales used between discharge and 18 months by NOWS treatment type.[95] There are currently several rigorously designed, large-scale, clinical trials and longitudinal studies focusing on long-term outcomes for infants with POE and its management on different child outcomes, including development, growth, and morbidity, that aim to address the limitations of previously published studies.[43,90,91,96]

Developmental Surveillance

Because of the increased risk of developmental delays, it is recommended that infants with POE are formally assessed for developmental concerns.[97] Newborn developmental follow-up clinics are available at some centers to provide episodic developmental screening and testing with multidisciplinary team supports.[8] Similarly, infants with POE can benefit from early intervention services, which are available across the country for infants and toddlers at risk for developmental delays.[98] In some states, a diagnosis of NOWS is considered a qualifying condition to receive services for a full year,[99] but rates of engagement among eligible infants remain low.[84]

Hepatitis C

For children whose birth parent had a detectable hepatitis C viral load during pregnancy, guidelines recommend testing with hepatitis C virus (HCV) antibody test to be first completed at 18 months of age. The timing of this test avoids potential false positives from circulating maternal antibodies.[100] New recommendations by the Centers for Disease Control and Prevention have proposed that testing for HCV infection be conducted between 2 and 6 months of age with nucleic acid testing for HCV RNA to allow for proper referral and follow-up with providers experienced in pediatric hepatitis C management.[101] Regardless of the time of testing, currently, treatment of hepatitis C is only approved after 3 years of age.[100,101]

Vision Screening

Infants with POE may have an increased risk of ocular abnormalities, with the most common being strabismus, nystagmus, and reduced visual acuity. There is also evidence that changes in the amplitude, latency, and response in visual evoked potentials testing can be detected as early as the neonatal period and persist later in childhood.[102] Early detection of vision disorders is essential to provide prompt ophthalmologic treatment and to improve developmental outcomes.

AREAS FOR FUTURE RESEARCH TO ADVANCE CLINICAL PRACTICE

The present research and practice improvement landscape with respect to POE is an exciting one, with many clinical advances made in the past decade. Large studies are being conducted across the country assessing novel NOWS treatment modalities and the impacts of POE on children and families.[68,90,91,96]

As the medical community comes to consensus around the best clinical diagnosis for NOWS, there remains a need to further align it with surveillance metrics used by state public health departments and determine the appropriate diagnostic codes for infants with POE who do not necessarily experience signs of withdrawal to inform studies assessing long-term outcomes of in-utero exposures. Incorporating type of POE, including prescribed or administered opioids compared with nonprescribed use (eg, polysubstance use and newer exposures including fentanyl and xylazine), is crucial to accurately describe and quantify the impact of prenatal exposures. Additionally, efforts should be made to remove stigmatizing or inaccurate language from ICD-10 codes; for example, the 2 recommended codes P96.1 (neonatal withdrawal symptoms from maternal use of drugs of addiction) and P04.49 (newborn affected by maternal use of other drugs of addiction) do not offer a nonstigmatizing option when POE results from maternal use of medications to treat OUD, not a "drug of addiction."[103]

With respect to assessment, with adequate feeding becoming a criterion for adequately managed withdrawal in the increasingly used ESC approach, optimal feeding support bundles are needed, including supporting parents who desire to provide breast milk in addition to formula options. Additionally, with the current shift to function-based assessments, studies incorporating the ability of the caregiver to respond to an infant's needs will be beneficial to expanding individualized nonpharmacologic options. Reducing subjectivity in applying assessment tools and further development of objective measures of withdrawal can further help with ongoing assessment standardization.

With respect to pharmacologic treatment, the growing popularity and success of as-needed dosing for NOWS

treatment in reducing prolonged iatrogenic opioid exposures warrants an evaluation of its short-term and long-term effects, isolated from the implementation of other QI bundles. Studies should incorporate the recommended core set of NOWS outcomes (need for pharmacologic treatment, total dose and duration of opioid treatment, need for adjuvant therapy, and length of hospitalization) to standardize measures of NOWS severity reported.[104,105]

Finally, with respect to long-term outcomes, ongoing studies aim to fill our gap in understanding around the potential neurodevelopmental impacts of POE and different NOWS management approaches. Although there is potential for major breakthroughs in understanding the effects of opioids on the developing brain, ensuring the scope of focus is expanded to include the interpersonal, intrapersonal, and environmental factors that contribute to child development and well-being, is critical to identifying the supports needed to improve outcomes for opioid-exposed dyads, including improving engagement in the recommended developmental surveillance and treatments.

ABBREVIATIONS

AAP: American Academy of Pediatrics
COVID-19: coronavirus disease 2019
CSTE: Council of State and Territorial Epidemiologists
ESC: Eat, Sleep, and Console
FNAST: Finnegan Neonatal Abstinence Scoring Tool
HCV: hepatitis C virus
ICD-10: International Classification of Diseases, 10th Revision
NOWS: neonatal opioid withdrawal syndrome
OUD: opioid use disorder
POE: prenatal opioid exposure
QI: quality improvement

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