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Antiracism in the Field of Neonatology: A Foundation and Concrete Approaches

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PRACTICE GAP

Concrete interventions that advance antiracism within the field of neonatology are required to address neonatal racial/ethnic health inequities and improve care and outcomes for historically marginalized patients and families.

OBJECTIVES After completing this article, readers should be able to:

1. Recognize the 4 types of racism seen as social determinants of health.
2. Characterize the unique aspects of the NICU environment that can either exacerbate or ameliorate racial inequities in health and health care.
3. Identify specific strategies neonatal clinicians can use to incorporate antiracism into every role they may play within and outside academic medicine.

ABSTRACT

Neonatal patients and families from historically marginalized and discriminated communities have long been documented to have differential access to health care, disparate health care, and as a result, inequitable health outcomes. Fundamental to these processes is an understanding of what race and ethnicity represent for patients and how different levels of racism act as social determinants of health. The NICU presents a unique opportunity to intervene with regard to the detrimental ways in which structural, institutional, interpersonal, and internalized racism affect the health of newborn infants. The aim of this article is to provide neonatal clinicians with a foundational understanding of race, racism, and antiracism within medicine, as well as concrete ways in which health care professionals in the field of neonatology can contribute to antiracism and health equity in their professional careers.

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ABBREVIATIONS

ABP American Board of Pediatrics
EF-QI equity-focused quality improvement
QI quality improvement
REaL race, ethnicity, and language data
SDOH social determinants of health
INTRODUCTION
Although the role of racism in every aspect of life in the United States has been well-researched and documented for decades, (1)(2) the murder of George Floyd on May 25, 2020, ignited a cultural movement in American society to address systemic racism in concrete ways. (3) Antiracism, the process of actively identifying and opposing racism, can be applied to all fields of medicine, including neonatology. (4) In this article, we provide a comprehensive (though not exhaustive) compendium of possible approaches neonatologists and other neonatal health care professionals may take to conduct antiracist work throughout many aspects of their careers.

BACKGROUND AND RATIONALE FOR ANTIRACIST WORK
Racism and Social Determinants of Health
According to the Centers for Disease Control and Prevention Healthy People 2030 report, “Social determinants of health (SDOH) are the conditions in the environments where people are born, live, learn, work, play, worship, and age that affect a wide range [of healthcare], health [outcomes], functioning, and quality-of-life outcomes and risks.” (5) SDOH can be grouped into 5 major domains: 1) economic stability; 2) education access and quality; 3) health care access and quality; 4) neighborhood and built environment; and 5) social and community context. Recognition of SDOH can lead to a better understanding of how social context affects biologic risks and outcomes. (5)

A focus solely on “determinants,” however, fails to recognize that the distribution of SDOH among the population is not random. (6) Instead, social, economic, and political systems distribute these “determinants” inequitably across the population. Black, indigenous, and people of color are more likely to experience reduced access to health care, receive care in lower quality hospitals, live in neighborhoods with more risks and fewer resources, have increased exposure to environmental pollution, be overcriminalized, and have diminished access to employment and wealth opportunities. (7)(8) The inequitable, racialized distribution of SDOH in the United States highlights the prominent role of racism as a key factor in SDOH. (9)

Race is a social construct and has no basis in genetics or biology. (10)(11) Race emerged as a concept when European explorers encountered individuals in the “New World,” and sought to establish a human classification system, defined by physical appearance and skin color, to construct hierarchies of power and consolidate power in the dominating group (white race). (10)(12) As noted by the evolving classifications of race in the United States census, race is not biologic, genetic, or natural, but instead evolving and responsive to sociopolitical forces that continue to reinforce and normalize whiteness as dominant over all other groups. (13)

Racism refers to the discrimination, marginalization, and/or oppression of people of color through the use of policies, ideas, and actions that differentially structure opportunity, behavior, and risk for nonwhite individuals. As defined by leaders in the field including epidemiologist and physician Dr Camara Jones, racism creates a system that restricts the lives of nonwhite individuals and communities while creating advantage for white communities. (1)(14)(15) Dr Jones defined 3 types of racism: 1) institutional, 2) interpersonal, and 3) internalized. (16) More recently, others have defined structural racism separately from institutional racism. (17) Structural racism is the “totality of ways in which societies foster racial discrimination through mutually reinforcing systems of housing, education, employment, earnings, benefits, credit, media, healthcare, and criminal justice.” (18) The inequitable distribution of police violence and killing of black men, women, and children, the disproportionate number of incarcerated black and Hispanic/Latinx individuals compared to white individuals, and the lack of representation in media, all represent forms of structural racism.

Institutional racism refers to the “processes of racism that are embedded in laws ..., policies, and practices” within specific societal institutions. (19) For example, de jure housing discrimination (i.e., “redlining”) codified inequitable access to mortgages for homeownership, thereby restricting subsequent wealth attainment and upward mobility. (20)(21) Institutional and structural racism, through their normalization of a racialized world, are not actively inflicted by individual perpetrators. Similarly, complicity in the system may not be immediately apparent. (16)(18)

Interpersonal racism refers to personally mediated prejudice, assumptions, beliefs, and discrimination, as well as differential behaviors and actions, based on race. Interpersonal racism can be intentional or unintentional. Microaggressions experienced by health care professionals of color due to implicit biases, such as when a clinician of color’s presence or title is questioned, are an example of interpersonal racism. (22)

Finally, internalized racism is defined by members of minoritized groups accepting “negative messages about their own abilities and intrinsic worth.” (16)(18) These 4 pillars of racism work together to perpetuate and normalize race-based inequity, including in the inequitable distribution of SDOH.
As a result of racism in its many forms, racial and ethnic inequities, unexplained by genetic associations, exist in perinatal and neonatal health and health care. Black infants are more than twice as likely to die in the first year of age compared to their white counterparts, and the gap is widening. (23) Pregnant patients who identify as black or Hispanic/Latinx receive care in lower quality hospitals and have higher rates of preterm birth and low birthweight infants. (24) Black and Hispanic/Latinx infants admitted to NICUs have been shown to receive lower quality of care, have lower patient satisfaction scores, and have decreased rates of postdischarge high-risk infant follow-up. (25)(26)(27)(28)(29)(30)(31)(32)(33)(34)(35) Studies have begun to explore how the inequitable racialized distribution of the SDOH, as a result of racism, explains these inequities. (33)(36)(37)(38)(39)(40)(41)(42)(43)

**Conceptual Understanding of Antiracism**

Antiracism has been defined most prominently by the historian Dr. Ibram Kendi as support for and concrete actions toward the creation of policies aimed at dismantling ideas and structures that produce and normalize racial inequalities. (4) The concept of antiracism tackles the historical and present-day inertia that has allowed entrenchment of racism throughout society. (44) It recognizes that societal problems are rooted in power structures and policies rather than individuals or groups of people. Antiracism embodies an active process to redistribute and equitably share power by changing systems, organizational structures, funding, policies, practices, leadership, and culture. (45) The emphasis is on naming racist policies and actions and taking active steps for change rather than stances, statements, or generalizations. (46)

Applying antiracism in medicine is considered not only a moral imperative but also an efficient one that can help ensure that every aspect of health care, from clinical practice to public health to medical innovation, is equitable. (45) However, the application of antiracism in medicine requires a recognition of the role racism plays in the lives of individual health care professionals as well as within health care systems. (47) Ownership of the many avenues by which racism adversely affects health is fundamental to antiracist work within medicine. This article will describe how to operationalize antiracism in neonatology.

The NICU as an Optimal Setting for Antiracist Work

The field of neonatology is particularly well-suited for antiracist work for 3 main reasons. First, racial/ethnic disparities in fetal and infant health outcomes have been well-described for decades, and both have a major impact across the lifespan and contribute to lifelong health inequities. (48)(49) Many SDOH that are concentrated in black, indigenous, and people of color communities affect the risk of preterm birth and low birthweight, (50) which in turn drive disparities in infant mortality in the population. (51) Mitigating racial/ethnic disparities in perinatal and infant health outcomes requires an understanding of the downstream pathophysiology that leads to preterm labor, preeclampsia, poor fetal growth, and infant death. Neonatologists and other neonatal health care professionals have extensive clinical and academic expertise in these pathophysiologic processes as well as the care of newborns that can be leveraged to ensure the validity of research questions and interventions that aim to address infant health disparities. However, to do so, neonatal physicians and other clinicians must engage in this type of research and implementation science.

Second, racially minoritized families face disproportionate exposure to the NICU setting given the high rates of preterm birth and low birthweight in these communities. Having an infant in the NICU can cause significant parental stress and trauma. (52)(53) However, this stress is further compounded by ongoing stressors related to socioeconomic status (54) and financial insecurity, interpersonal discrimination, and other SDOH. (42)(55) The association between chronic stress and adverse health outcomes—including racial/ethnic disparities in birth outcomes—is well-documented. (56) Therefore, recognizing, acknowledging, and addressing such intersectional stressors, many of which are deeply rooted in structural, institutional, and interpersonal racism, is antiracist work.

Finally, the NICU experience occurs during a critical phase of infant development as well as the development of the parent-infant dyad relationship. Given the existing and ever-increasing knowledge about the impact of early life adversity on neural, endocrine, immune, metabolic, and epigenetic processes, (43)(53) antiracist interventions in the NICU have the potential to improve long-term health trajectories for patients and their families. This is especially true if interventions are based on an equitable “follow-through” approach that recognizes the responsibility of NICU professionals toward addressing SDOH for infants even after discharge from the NICU. (57) The NICU thus represents an opportunity to intervene on systemically racist structures, institutionally racist policies, and interpersonal instances of implicit and explicit bias that may be affecting entire families.

**APPLICATION OF ANTIRACISM TO NEONATAL HEALTH CARE**

Neonatal professionals can contribute to antiracism regardless of the roles they play in academic and health care settings.
(Fig 1). Below are concrete strategies that could be explored within each sector of neonatal medicine.

**Antiracism in Medical Education**

Contributing to antiracism through education can be accomplished in 3 main ways: through continual self-education; through the creation of new curricula for medical students, trainees, and staff; and through reform of existing structures and processes in medical education. To begin, self-education is fundamental and requires an acknowledgment that gaps in one’s personal understanding may exist either because of lack of awareness or because of implicit biases. Scholars had been writing and speaking about the historical and present-day impact of racism on health care and health outcomes long before the increased social awareness movement of 2020. (16)(58)(59) However, the past year has led to a flourishing of such literature and multimedia resources. Professional organizations, including the American Academy of Pediatrics, have created compilations of primary and secondary data, (60) published policy statements, (61) and released podcast material (62) intended to educate readers and listeners about the impact of racism on pediatric health.

Such material can be used not only to "teach the teachers" within health care and medicine, but also to develop longitudinal curricula for medical students, trainees, and staff. There remains a dearth of evidence as to best practices for how to incorporate concepts of racism, bias, and antiracism into medical curricula. (63)(64) This includes training on how to respond when micro- and macroaggressions related to discrimination and racism are witnessed in the medical workplace so that medical personnel feel empowered and knowledgeable to function as involved “upstanders” rather than passive bystanders. (65)(66) However, such curricula must be implemented broadly in medical schools, residency, and fellowship programs, as well as graduate health care programs for nurses, respiratory therapists, physical and occupational therapists, and other health care clinicians. This includes not only education of new staff in all these arenas but also in continuing education programs and maintenance of certification curricula. Much work remains to be done in this arena. A recent analysis of pediatric general and subspecialty board examination content specifications revealed that only 2 subspecialty content specifications addressed implicit bias. (67) Within the American Board of Pediatrics (ABP) preparatory information provided for the neonatal-perinatal medicine certification examination, only 2 of 875 content specifications currently address issues of race, ethnicity, and health. (67) One is worded as knowing the relationship between the ethnic origin of the parents and risk for specific genetic conditions in an infant. The second asks learners to know the range of normal serum bilirubin concentration and the effects of an infant’s age, race, and feeding circumstances on serum bilirubin. To date, no pediatric examination content specifications address racism in any form as a contributor to health outcomes.

Neonatal medicine educators can also engage in antiracism by reforming current ways in which students are taught to think about the relationship between race/ethnicity and health. The 2 ABP neonatal-perinatal medicine content specifications that currently allude to race test physiologic associations based on race; they do not test for an understanding of the root causes of race functioning as a risk factor for pathology. (67) Genetic explanations for racial disparities in disease are common in medical curricula despite the growing understanding of race as a sociocultural construct and imperfect proxy for social determinants of both health and ancestry. (68)(69) Indeed, race is commonly misrepresented in medical curricula and examination preparatory materials such as widely used question banks, as it is usually presented in imprecise uncontextualized ways that pathologize racial groups themselves. (68)(70) For instance, students may be taught that black patients have higher rates of hospital readmission without discussion of the underlying structural causes for these disparities or they may observe African patients being incorrectly described as African American. Both of these examples have the potential not only to
miseducate but also to perform microaggressions against black learners. (70) Thus, neonatal medical educators have significant opportunities to critically examine existing curricula, correct previous educational missteps, and create new content that reflects a more accurate and thus useful understanding of race and ethnicity and how it relates to neonatal and infant health outcomes. The ABP recently amended its strategic plan, adopted an antiracist action agenda that targets these previous educational shortcomings, and is working to implement new action steps aimed at antiracism within pediatrics. (71) Participation of neonatal professionals in such reforms will be crucial.

Antiracism in Clinical Care
Incorporating antiracism in clinical care fundamentally requires an understanding of the causal pathways by which racism, segregation, and inequality affect both the care we offer infants and the health outcomes they experience. In a seminal piece discussing interventions to reduce racial/ethnic inequities in preterm birth, Beck and colleagues propose concrete strategies to address the 3 main causal pathways they identified. One strategy to address the disproportionate preterm birth risk among black patients is equitable access to high-quality prenatal care for high-risk patients with maternal-fetal medicine physicians who can provide therapies, such as cerclage, when indicated. (42) To address the socioeconomic disadvantage NICU families disproportionately experience, neonatal programs could work on bolstering discharge planning and early intervention programs. Finally, NICUs might begin to address the lower quality of care minoritized infants have been shown to receive (30)(32) by instituting disparity dashboards to track care delivery and outcomes by the race, ethnicity, and preferred language of an infants’ family (often referred to as REaL data). (72)

Clinical dashboards that display REaL data can assist NICUs in ensuring that existing and new algorithms do not inadvertently perpetuate or widen disparities in quality of care or outcomes. Such “intervention-generated inequalities” have been found among adult inpatients and after certain major public health campaigns but are poorly studied in neonatology. (73) Clinical algorithms used for diagnostic or management purposes that adjust or correct for race may be even more problematic, as there is evidence that these may contribute to new disparities and inequities in access to care and outcomes. (74) Racial/ethnic standards for fetal growth are 1 example in the field of perinatology where race-based corrections exist. (75) It has been posited that racial/ethnic corrections for fetal growth rate patterns may be masking underlying socioeconomic and sociopolitical factors that affect fetal growth, which may contribute to birthweight disparities. (76) Such questions are critical for neonatal clinicians to consider, study, and address.

Antiracism in Quality Improvement
As with diagnostic algorithms or practice guidelines, quality improvement (QI) initiatives have the potential to leave disparities unchanged or widen them, especially if stratified data are not monitored. (77) QI offers a compelling approach to improve disparities with targeted antiracist, inclusive interventions, aiming to reduce a disparity. Specifically, equity-focused quality improvement (EF-QI) (73) offers an action-oriented framework whereby equity is integrated throughout a QI initiative at every stage to address a disparity, from the development of a smart aim to identifying drivers to designing and testing change ideas.

After identifying a disparity, intentionality in mapping key stakeholders to include patients, families, and relevant community partners, with a focus on the group(s) experiencing the disparity, is critical to EF-QI. Stakeholders collaboratively brainstorm root causes focusing on systems, processes, and policies, specifically identifying sources of structural racism. (78) These reflective and in-depth discussions among stakeholders can help QI teams design and prioritize targeted antiracist interventions centered around the patient and family voice. EF-QI initiatives are essential to further a culture of equity and antiracism and place the value of equity similar to that assigned to patient safety.

For example, black-white disparities in breastfeeding rates have been widely documented in the literature and locally in individual units, prompting several QI initiatives aimed to improve breastfeeding rates, especially among black patients who are experiencing this disparity. (31)(79) A multidisciplinary stakeholder group is assembled, including patients who identify as black or African American and community partners who are dedicated to empowering and serving black patients. Qualitative work and interdisciplinary discussions on root causes, specifically drivers of racism and bias within the health care system, inform potential interventions that are subsequently prioritized with stakeholder input. This process centered around the lived experience of black patients and community partners helps teams develop targeted, antiracist interventions that can be tested and refined through plan-do-study-act cycles and potentially implemented in the future.
Antiracism in Research

Although there has been an explosion of health disparities literature in the last decade, research has predominantly focused on identifying or understanding disparities. (80) Conversely, research aimed at achieving health equity, especially in the field of pediatrics, has significantly lagged. (80) Antiracism in research requires an understanding that conducting studies focused on exploring health disparities is not necessarily synonymous with antiracist health equity–driven research. That is because health equity requires the creation and application of concrete goals and processes to move society toward the elimination of health disparities. (80) This requires prioritizing “third- and fourth-generation” research that seeks to solve existing disparities and evaluate the effectiveness of interventions, respectively. (81)

Antiracist research requires thoughtful use of race as a variable in human studies. Clear standards for how to use race in research studies are lacking and as such, it has been frequently interrogated in ways that are conflicting, ineffective, and even misleading. (82) Race and the related, though distinct, concept of ethnicity, are important variables that must be understood as proxies for socioenvironmental systems, processes, interactions, opportunities, or ancestral heritages that are more challenging or impossible to measure. (69)(82) Until recently, there has been no expectation that scientists and authors state the reasons for exploring racial/ethnic differences in their study outcomes, or name what upstream driver of health might be represented as a proxy by race. (82) Given the increasing realization of the dangers of such uncontextualized research questions in upholding racial health inequities or even bolstering implicit bias, some journals have begun to update guidelines with respect to reporting on race and ethnicity. (83)(84)(85)

Neonatal researchers should ensure that conceptual frameworks are grounded by an understanding not only of what race may be serving as a proxy for but also that they are informed by the academic experience of scholars of color and the lived experiences of people of color. (82)(86) Work framed in this way is critically needed in the perinatal space; there are many unanswered questions regarding the impact of racism on neonatal health care delivery and neonatal outcomes. Few articles specifically examine racism in the NICU, (36)(73)(87) and none evaluate best practices or interventions for how to dismantle structural, institutional, interpersonal, or internalized racism that affect NICU patients and their families. Finally, antiracist research also necessitates that findings be connected back to the communities and people whose lives the study aimed to describe or improve. (80) Science dissemination efforts are critically important to antiracist research, both for the purposes of feedback and also to increase the likelihood that scientific findings translate into measurable changes in people’s lives.

Antiracism in Academic and Health Care Administration

One of the most important ways to engage in antiracist work in a health care setting or academic institution is by diversifying every level of the workforce. The benefits of diversifying the medical workforce are well-documented: it increases group performance; (88) promotes cultural awareness and humility; increases access to racially and culturally concordant care; increases overall health care coverage of marginalized patient populations; mitigates provider bias issues; and improves patient experiences and satisfaction in health care systems. (89)(90)(91) In short, creating a diverse workforce is foundational to repairing the hard-earned mistrust of medicine and institutional health care that exists among many minoritized communities. (89)(91) It is important to remember that there are various mechanisms that interrelate to create a nondiverse workforce; in particular, administrative committees should examine whether they are experiencing low applicant diversity, appointment biases, departure biases, or a combination of all 3. (88) Addressing retention issues and departure biases in particular will require critical evaluation of the workplace culture that exists within divisions and an acknowledgment that micro- and macroaggressions are a common experience for people of color in health care. (92) Each of these factors will require its own distinct set of strategies along with leadership buy-in to enact such strategies, including protected, recognized time to do so, especially given how often underrepresented minoritized health care professionals and academicians get called to do such work at the expense of time for their own individual career goals and promotion metrics. (93) It will also require a distinct look at the diversity of people in subsectors of a division or department, such as the diversity of those who hold leadership positions, receive lecture invitations, or are invited to sit on expert panels.

Documenting both historical and ongoing trends in workforce diversity is an important first step. A survey conducted in 2018 of over 500 neonatologists across the country found that only 10% self-identified as belonging to a racial/ethnic group that is underrepresented in medicine. (94) According to the most recent data released by
the Accreditation Council for Graduate Medical Education, the percentage of neonatal-perinatal medicine fellows in the 2019–2020 academic year who self-identify as a race or ethnicity underrepresented in medicine was 14%; disaggregated data show an especially severe lack of representation from American Indian/Alaska Native and Native Hawaiian/Pacific Islander communities (Fig 2). However, these cross-sectional data belie the fact that the proportion of underrepresented minoritized neonatal-perinatal medicine fellows may be diminishing over time, as was shown by Montez et al in a recent examination of racial/ethnic trends among pediatric trainees from 2007 to 2019. (96)

Finally, workplace diversity does not exclusively apply to physicians in neonatology but also to all health care personnel (or staff) within our field. Given the critical roles that all members of large neonatal multidisciplinary teams play, workforce diversification should also be prioritized among advanced practice professionals, nurses, pharmacists, respiratory therapists, occupational/physical/speech therapists, social workers, lactation consultants, dieticians, and all other allied health professionals. Administrative committees should thus endeavor to collect and continuously track more comprehensive data on the diversity of all personnel who work in NICUs.

Another critical venue for antiracist work is academic reform, specifically the paths to promotion, tenure patterns, and existing success metrics. Racial/ethnic disparities in scientific publications, teaching evaluations, and extramural funding have contributed to the lack of diversity in senior positions in academic medicine and health care institutions. (97)(98) This may be due in part to the “minority tax” experienced by many underrepresented faculty, which refers to the time spent assisting with institutional diversity, equity, and inclusion work at the expense of time invested in other activities traditionally prioritized by promotion and tenure committees. (93) Relatedly, underprioritization and underfunding of the advocacy, service, mentorship, community outreach, and media/dissemination efforts that underrepresented minoritized individuals are more likely to conduct can also affect their long-term academic success to the detriment of diversity goals in academic medicine. (97) The ongoing COVID-19 global pandemic has highlighted the need for clear public health messaging, strong community engagement, and trust-building efforts between the medical community and the lay public. (99) As such, these types of activities merit comparable consideration and weighting by promotion
and tenure committees. (97) Neonatal divisions can evaluate metrics of success and search for evidence of disproportionate penalization of their underrepresented team members with respect to service, promotion, or compensation. However, this will require departmental/unit-wide buy-in. Prioritizing the antiracist work that neonatologists and other neonatal health care professionals are doing through academic policy reform is antiracist work itself.

Antiracism via Community Engagement

Central to antiracist work is the lived experiences of the groups experiencing racism. The voices of racialized families and community stakeholders are thus essential to making antiracist projects authentic and effective. (100) Projects can (and often do) miss the mark when such perspectives are not incorporated at every step, beginning with project conception. Furthermore, NICU parents may be particularly motivated to participate in research as a way to cope with their own experiences and contribute to positive change. (101) However, meaningfully integrating families and community partners into scholarly projects requires 2 main components. The first is to take concrete steps to create an inclusive environment to ensure that stakeholders feel valued, respected, and welcome. This may require eliciting feedback about ways in which academic or health care environments have not felt inclusive in the past. Secondly, antiracist integration of community partners also means that all stakeholders benefit from the work in tangible and intangible ways. For instance, family and community partners could be included as coauthors on abstracts, talks, and scientific papers. Most importantly, they should be compensated for their time, expertise, and perspectives. This will entail building in funding for such compensation into departmental budgets and grant proposals. For example, funders can formalize an expectation of including family and community stakeholders by requiring applicants to describe how they will collaborate with and compensate diverse community members as research partners. (86)

Importantly, family and community alliances can help bridge the differences between health care sectors and the communities experiencing racism in ways that build trust and ensure academic projects and institutional initiatives are responding to community needs in safe and respectful ways. Community collaborations have been most widely used by the primary care sector. (102) However, neonatologists and other neonatal care professionals engaged in research, policy, and QI work can and must begin to conceptualize ways in which diverse family and community voices can be included to improve upon the perinatal work undertaken in hospitals, newborn nurseries, and NICUs. For instance, the perspectives of minoritized outpatient doulas, lactation consultants, birthing support people, and birth parents can be invaluable to EF-QI initiatives aimed at improving inpatient postpartum breastfeeding support. (79) Ultimately, collaboration with family and community stakeholders can bolster every aspect of antiracist work discussed in previous sections if concrete steps are taken to ensure that it is done in an equitable, inclusive, and just manner.

CONCLUSIONS

Racism affects health and health care in various ways, from macrostructural forces related to governmental policies down to the ways in which interpersonal discrimination and bias become internalized in individuals and communities of color. The field of neonatology and the care provided to infants in newborn nurseries and NICUs are not immune to these processes; rather, a comprehensive view of racism helps explain the pervasive and recalcitrant perinatal and neonatal health disparities that exist

Figure 3. Strategies neonatal clinicians can undertake to tackle each level of racism within neonatology.
among minoritized communities. As such, it is incumbent upon neonatologists and other neonatal professionals to acknowledge, understand, and intervene on the various pathways by which racism affects health. Actions and interventions that tackle racism at all 4 levels (structural, institutional, interpersonal, and internalized) can be incorporated into all aspects of work undertaken by all neonatal health care professionals in practical and measurable ways (Fig 3). (3) When such work is approached with an attitude of cultural humility that prioritizes lifelong self-evaluation and critique, rather than an expectation of learned cultural competency, (103) the impact is magnified. In short, choosing to integrate antiracism into the work we do for infants is synergistic to our field’s mission to provide high-quality, equitable, family-centered care to optimize outcomes.
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Partial Enteral Discharge Programs for High-risk Infants

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PRACTICE GAPS

In recent years, an increasing number of NICUs in the United States have supported earlier discharge with partial enteral feedings for infants who are otherwise medically ready for discharge. While this earlier discharge approach has led to successful outcomes for infants and families who have appropriate follow-up support, there are still some gaps and controversies in the current medical literature that need to be addressed by future studies. Neonatal and pediatric clinicians need to be aware of this approach and recognize the importance of supporting this medically complex population.

OBJECTIVES After completing this article, readers should be able to:

1. Identify and distinguish clinical readiness for infants who may qualify for discharge with home enteral feedings.
2. Review the clinical associations that may affect infants’ postdischarge feeding success.
3. Describe the need for involvement of multidisciplinary clinicians both before and after NICU discharge.

ABSTRACT

Premature infants or infants born with complex medical problems are at increased risk of having delayed or dysfunctional oral feeding ability. These patients typically require assisted enteral nutrition in the form of a nasogastric tube (NGT) during their NICU hospitalization. Historically, once these infants overcame their initial reason(s) for admission, they were discharged from the NICU only after achieving full oral feedings or placement of a gastrostomy tube. Recent programs show that these infants can be successfully discharged from the hospital with partial NGT or gastrostomy tube feedings with the assistance of targeted predischarge education and outpatient support. Caregiver opinions have also been reported as satisfactory or higher with this approach. In this review, we discuss the current literature and outcomes in infants who are discharged with an NGT and provide evidence for safe practices, both during the NICU hospitalization, as well as in the outpatient setting.

AUTHOR DISCLOSURE Drs Ermarth and Ling have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

BPD  bronchopulmonary dysplasia
ED  emergency department
GT  gastrostomy tube
NGT  nasogastric tube
PMA  postmenstrual age
PO  oral intake
SGA  small for gestational age
VLBW  very low birthweight
INTRODUCTION

Discharge readiness of infants in the NICU is sometimes prolonged and complicated, and the timing of discharge often relies on the subjective opinion of the neonatology team. (1)(2)(3)(4) Three physiologic competencies are generally recognized as essential before hospital discharge of the preterm infant: oral feeding sufficient to support appropriate growth, the ability to maintain normal body temperature without an isolette/warmer, and respiratory control that is sufficiently mature. (4) Historically, preterm infants and medically complex infants were not typically discharged from the hospital until they reached oral intake (PO) independence. If progress toward enteral tube independence stalled, a surgical gastrostomy tube (GT) was often placed before discharge. However, prolonging the hospital stay also has risks, including, but not limited to, bloodstream infections, respiratory or other opportunistic infections, and medical errors, as well as parental stress from travel and infant separation. (4)(5)

In the last decade, advancements in NICU feeding practices have included earlier recognition of infants with delayed or dysfunctional oral feeding, as well as targeted interventions to decrease length of stay and allow earlier discharge from the hospital. Most NICUs now have specialized feeding therapists who work with infants and families and focus on steps to achieve PO independence as soon as possible. (6)(7) In 2003, a large, high-powered, multicenter, randomized, controlled trial demonstrated that individualized developmental care of very low birthweight (VLBW) preterm infants led to several improved outcomes compared with controls, including fewer days of parenteral feedings; shorter transition periods to full enteral feeding; better average daily weight gain; younger ages at discharge; fewer days in intensive care and in the hospital; lower total hospital cost; fewer cases of necrotizing enterocolitis; and better growth (weight, height, and head circumference) at 2 weeks after intervention. (8)

Despite these developmental interventions, many infants remain hospitalized in the NICU days to weeks beyond 40 weeks’ postmenstrual age (PMA) because they continue to require enteral tube feedings.

In the last decade, to address this persistent dependence of patients on enteral tube feedings, many NICUs have implemented earlier discharge programs with partial home enteral nutrition via either NGT or GT feedings for infants who have oral feeding dysfunction as the only remaining inpatient medical issue. Although the 2008 and 2018 American Academy of Pediatrics (AAP) statements on hospital discharge for high-risk infants emphasized individualized discharge plans and promoted close follow-up for nutrition and growth, there is no formal guidance about home enteral nutrition due to the lack of studies. (4) To date, the Cochrane Neonatal review group has only evaluated 1 randomized early home enteral nutrition program compared with a standard care program; the group with early discharge with home enteral nutrition showed reduced mean hospital stay of 9.3 days and reduced clinical infections compared with controls. Yet, no formal recommendations have been made for early discharge feeding programs, given the evidence was limited to 1 experimental group. (9) Since this review in 2015, there has been a growth of early discharge programs for infants with home enteral nutrition, given the possibilities of health advantages and family dynamic advantages for infants in the home setting. This review provides updated information about improved feeding practices and outcomes of individualized earlier discharge programs for NICU infants with continued oral feeding dysfunction.

ORAL READINESS AND FEEDING INTERVENTIONS DURING NICU HOSPITALIZATION

The incidence of outpatient oral feeding difficulty of medically complex and premature infants can be as high as 80%, and oral feeding dysfunction remains a main reason for continued NICU hospitalization of this population. (4)(6)(7) Recently, Edwards et al. analyzed the Moderate Preterm Registry of the National Institute of Child Health and Human Development Neonatal Research Network and found that for infants born between 29 and 34 weeks’ PMA, oral feeding dysfunction was either the primary reason or a concomitant reason for continued hospitalization, and 69% of this population still required NICU hospitalization at 36 weeks’ PMA. (10)

To address the goal of establishing PO independence sooner in the preterm population, more NICUs are including therapist-led decision making focused on individualized, more intensive oral therapy to the infant’s neurodevelopmental therapy plan. (11)(12)(13) Developmentally, many premature infants are unable to achieve partial to full PO ability safely until closer to 34 weeks’ PMA, which means historically many NICUs did not introduce feeding therapy until after this gestational age marker. Recent studies support premature infants practicing using an immature suck as a form of non-nutritive therapy to build oral feeding skills. (12)(13) In supporting an infant’s oral progress, Amaizu et al. found that 1 to 2 sessions of PO practice per day was just as successful as 6 to 8 sessions per day when introduced as early as 26 to 29
weeks’ PMA, however, this single-center study had a small sample size and low power to detect true differences. (14) A recent pilot study of 40 premature infants used the premature infant oral motor intervention method to encourage early PO skills. (15) Infants were randomized to have a speech therapist or parent administer daily 5-minute sessions of stimulation and non-nutritive feeding practice starting around 31 to 32 weeks’ PMA. Between the parent versus therapist group, mean PMA to first PO was 33 weeks in both groups, with similar mean time to full PO of 7.7 days in the parent group and 6.3 days with therapists. Qualitative measures of parental satisfaction in this study were high and supported individual and family-centered hospital care to reduce infant toxic stress, as described by the AAP. (16)

Compared to controls without intervention, preterm infants receiving both oral and nonoral tactile sensorimotor therapies showed earlier suck-swallow strength compared with controls starting at 29 weeks’ PMA. (17) Similarly, a previous cue-based feeding pathway showed reduced time to PO in another study for infants of more than 32 weeks’ PMA. (11) Once these study infants demonstrated suck-swallow coordination with a pacifier for 3 minutes, they were then allowed to practice twice daily per feeding therapist and nurse evaluation and advance PO feeding based on individual cues. By using this algorithm, this study showed an earlier time to full PO by 6 days and improved weight gain in the cue-based group compared with controls. (11) Using this cue-based therapy method, premature infants develop PO skills earlier, which potentially allows for earlier discharge. (11)(12)(15)(18)(19) With individualized therapy and analysis of sucking patterns (eg, consistent pattern of 1 suck per second), practitioners may be able to identify infants who can progress toward successful partial PO sooner. (7)(11)(17) In addition, targeted education for all NICU caregivers such as bedside nurses and therapists on cue-based feeding practices, rather than using a volume-driven feeding approach, has been shown to lead to earlier discharge and improved parental involvement. (19)(20) A recent quality improvement initiative at a quaternary NICU center showed that standardization of the feeding approach and training of feeding therapists in the cue-based scoring method resulted in a younger PMA for a preterm infant’s first PO intake and a mean decrease in length of stay by 10 days compared with controls. (20)

**DISCHARGE READINESS FOR HOME ENTERAL FEEDING PROGRAMS**

By focusing on oral readiness and earlier introduction of feeding interventions, feeding therapists and neonatology teams should now be able to more easily identify preterm infants who may be eligible for an earlier safe discharge on partial PO plus home enteral nutrition. Recently, discharge feeding programs have been established to discharge NICU patients with supplemental tube feedings once their medical needs have stabilized. Although there are no standardized discharge criteria for supplemental tube feedings at present, the Table summarizes discharge criteria and descriptors of several programs. (21)(22)(23)(24)(25)(26)(27) These programs included both extremely preterm infants and infants with medical complexity, but they excluded infants discharged from cardiac intensive care units, those who required parental nutrition, and those who had contraindications to gastric feedings.

In general, programs required infants to demonstrate clinical stability, including temperature and cardiorespiratory stability, with a predetermined length of time receiving oxygen therapy and an apnea-free period off caffeine or on caffeine if discharged with a home monitor. Oral feeding criteria varied: 3 programs required a minimum PO intake of 50% of enteral feedings before discharge, (23)(24)(26) whereas 2 did not require a PO minimum. (21)(25) Although none of the programs required objective studies to evaluate feeding dysfunction before discharge, such as a video fluoroscopic swallow study or fiberoptic endoscopic evaluation of swallowing, programs did assess infants for feeding safety, including back to sleep with NGT (23) and/or absence of apnea with NGT in place. (21)(25) Although none of the programs required objective studies to evaluate feeding dysfunction before discharge, which was typically performed by social workers, to ensure that families had appropriate living conditions, availability of caretakers, and psychosocial stability of caretakers to feed with an NGT: (22)(24)(25) Some programs in the United States offered discharge with supplemental enteral tube feedings as early as 36 weeks’ PMA. (23)(27) Two European studies discharged infants with partial NGT feedings as early as 34 weeks’ gestation without a PMA requirement if they met all other criteria for discharge. (25)(26)

Before discharge, some programs also required parents to complete a checklist that included demonstrating NGT replacement, administering milk and medications via an NGT, and rooming in with the infant to practice using home equipment. (22)(25)(26) Not all programs required the demonstration of NGT insertion, but instead, arranged for families to replace NGTs in outpatient clinics or hospitals. (23)(27) One program provided some infants with a nasal bridle support for the NGT to help reduce accidental dislodgement. (27)
Unfortunately, there is no current standard approach about the type of home feeding tube (NGT vs GT) that should be used in an infant who is unable to achieve full PO feedings and is otherwise ready for discharge. Although NGTs are easy to place, replacement is frequently needed, and appropriate positioning is essential. Although GTs are more stable than NGTs, the GT procedure has associated risks from surgery and anesthesia and can have long-term complications such as soft-tissue infections or a malfunctioning/displaced tube. (22)(28)

Among NICUs in the United States from 2000 to 2012, the overall incidence of GT placement in the pediatric population increased in VLBW infants from 11.5 to 22.9 cases per 1,000 infants. (29) A 2019 study evaluated 114 independent NICUs in the United States from 2010 to 2012 with more than 8,000 NICU inpatients (excluding those with congenital heart disease) and found that the incidence of surgical GT placement ranged from 0.6% to 19.6%. (30) Referral and urban NICUs had a higher incidence of placement in this study. Hatch et al also found that VLBW infants who had a surgical patent ductus arteriosus ligation and/or bronchopulmonary dysplasia (BPD) were more likely to receive a GT before discharge. (29) In the studies that evaluated earlier discharge on home enteral nutrition, common clinical characteristics associated with GT placement included SGA infants and/or lower birthweight (22)(27); those who took less than 20% to 30%

### Table. Description of Earlier Home Enteral Nutrition (HEN) Programs

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cohort Size, No. (estimated per year)</th>
<th>HEN Type (at DC) Exclusion Criteria</th>
<th>PO Minimum (upon DC)</th>
<th>PMA Minimum (upon DC)</th>
<th>Follow-up Options</th>
<th>Median Time to Wean off Tube after DC, days (n)</th>
<th>Tube Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Kampen et al (25)</td>
<td>123 (41)</td>
<td>NGT only</td>
<td>Craniofacial/syndromic abnormalities, social barriers</td>
<td>None</td>
<td>No limit</td>
<td>Weekly home nurse visits, 24/7 telephone access</td>
<td>9 (113) 0 for NGT</td>
</tr>
<tr>
<td>Mago-Shah et al (23)</td>
<td>163 (40)</td>
<td>NGT or GT</td>
<td>Not discharged from NICU; not GT candidates</td>
<td>&gt;36 wk</td>
<td>50%</td>
<td>PCP within 2 days, post-NICU clinic</td>
<td>12 (40) 0 for NGT</td>
</tr>
<tr>
<td>Williams et al (24)</td>
<td>380 (173)</td>
<td>NGT or GT</td>
<td>Nongastric feedings, TPN, GT within 7 days admission</td>
<td>&gt;37 wk</td>
<td>50%</td>
<td>PCP, post-NICU clinic</td>
<td>60 (148) 0 for NGT</td>
</tr>
<tr>
<td>Ermarth et al (22)</td>
<td>183 (122)</td>
<td>NGT or GT</td>
<td>Craniofacial abnormalities, nongastrointestinal feedings, TPN</td>
<td>None</td>
<td>&gt;36 wk</td>
<td>GI/therapy/dietitian clinic</td>
<td>27 (108) NGT &lt; GT</td>
</tr>
<tr>
<td>Stol et al (26)</td>
<td>119 (60)</td>
<td>NGT only</td>
<td>None mentioned</td>
<td>50%</td>
<td>No limit</td>
<td>No limit</td>
<td>8 (47) 0 for NGT</td>
</tr>
<tr>
<td>Lagatta et al (27)</td>
<td>100 (67)</td>
<td>NGT or GT</td>
<td>Craniofacial abnormalities, nongastrointestinal feedings</td>
<td>&gt;25%</td>
<td>36 wk</td>
<td>GI/therapy/dietitian clinic</td>
<td>29 (33) GT &lt; GT</td>
</tr>
</tbody>
</table>

CICU=cardiac intensive care unit; DC=discharge; GI=gastroenterology; GT=gastrostomy tube; NGT=nasogastric tube; PCP=primary care provider; TPN=total parenteral nutrition.
PO by the time of discharge (22)(23)(24); and PMA greater than 45 weeks at the time of discharge. (22)(23)(27)

Although percentage of PO remains a strong predictive clinical characteristic for postdischarge success with achieving PO independence at home (see later section), there is still some controversy over whether programs should use this as a marker for home enteral nutrition decisions. Some programs had no criteria for percentage of PO by discharge, (22)(25) one required 25%, (27) and others did not allow for discharge with NGT unless infants were taking greater than 50% PO. (23)(24)(26)

One program reported that 9% of their GT population (those who did not reach 50% PO by discharge) achieved full PO intake within 60 days after discharge, suggesting that a portion of patients who have lower PO at the time of discharge could avoid this surgical procedure. (24)

For the programs without a PO minimum or less than 50% at discharge, their GT population’s median time to 100% PO was still less than 30 days. (22)(25)(27)

These outcomes suggest that centers with a home enteral nutrition outpatient program and standardized follow-up could consider delaying GT placement until after a trial of home NGT feedings. Furthermore, based on these programs’ outcomes, for those infants who ultimately need GT placement, a preliminary trial of NG feedings at home could give infants the advantages of earlier discharge to the home environment, with the ability to increase their growth safely, and thus may also reduce complications associated with surgical GT placement given that they will be bigger and more developed at the time of surgery.

POSTDISCHARGE PATIENT METRICS

Postdischarge monitoring in the early home enteral nutrition programs can range from primary care physician follow-up to frequent outpatient gastroenterology appointments or multidisciplinary NICU follow-up clinics designed specifically to support the population receiving partial enteral feedings (Table). Some programs offer access to feeding therapists after discharge in addition to medical practitioners. (22)(27)

Another European program provided families with access to weekly home nursing and 24-hours-a-day, 7-days-a-week telephone access to a medical care team. (25) In support of the multidisciplinary follow-up model, an early discharge program in Sweden developed a home home enteral nutrition program with home nursing support and reported reduced parental anxiety at the time of discharge when compared with parents receiving standard outpatient care. (31)(32)

PO INDEPENDENCE PROGNOSIS

When determining the prognosis of long-term oral feeding success in infants being discharged with partial home enteral nutrition, several factors have been identified. One of the strongest indicators for successful transition to complete oral feedings is the proportion of PO an infant is taking on the day of discharge. (21)(22)(23)(24)(25)(26)(27)(28) with higher PO associated with a shorter time to oral independence. However, the risk in setting a minimum PO metric for timing of discharge may lead to an increased length of stay and greater exposure to hospital-associated risks for infants who can go home safely with minimal PO intake. Outcomes with a lower association of achieving feeding tube independence include infants with BPD, a need for antireflux medications, a history of surgical patent ductus arteriosus closure, and/or a history of a high number of ventilator days. (22)(23)(27)(28)(29)(30)

In terms of growth patterns, Matharu et al. recently studied a cohort of infants born at 30 weeks’ gestational age with chronic lung disease (defined as oxygen at 28 days of age) who were discharged from the hospital with partial enteral feedings. (33) The infants in whom GT placement was avoided and only an NGT was used had larger occipitofrontal circumferences and higher length z scores at discharge, suggesting that hospital growth affects postdischarge feeding outcomes. (33) Although these specific growth parameters were different between this particular NGT and GT cohort, other home enteral nutrition programs with larger cohorts showed no differences in adjusted weight at follow-up between tube groups. (22)(23)(24)

Many studies have reported that lower birthweight and SGA status were associated with worse inpatient feeding dysfunction in NICU patients. (10)(22)(23)(30)(34) However, lower birthweight in grams was not always associated with worse outcomes or a longer time to PO independence after discharge in 2 programs. (22)(25) Interestingly, several studies have associated earlier gestational age as a risk factor for in-hospital GT placement (23)(24)(31); however, these studies did not follow these infants after discharge to evaluate whether gestational age was still associated with prolonged time to wean off tube feedings, despite needing a GT. Lower birth gestational age was not found to be a risk factor for the inability to wean off enteral feedings after discharge in 2 studies. (22)(28)

HOME ENTERAL NUTRITION RISKS AND COMPLICATIONS

In NICU infants who are unable to achieve complete PO, the use of home NGT feedings has been shown to be associated with significantly fewer complications than home
GT use. Recent studies support the safety of home NGT feedings; 7% to 13% of tube-related emergency department (ED) visits after discharge occurred in infants with NGT feedings, (22)(24)(28) whereas more than 60% of tube-related ED visits occurred in infants with GTs. (22)(24)(28)(35)(36)(37)(38) Hospital readmissions for NGT-related reasons ranged from 2% to 6% (excluding scheduled hospitalizations or procedures), (22)(23)(24) whereas GT-related readmissions were higher. (22)(23)(24)(27)(28) Other studies showed that the risk of readmissions and ED visits within 90 days after discharge with an inpatient GT placement is 1.6 and 1.7 times more likely than for NGTs, respectively, in preterm infants. (37)

Most of the causes for GT complications requiring ED presentation or rehospitalization include cellulitis, GT displacement, stoma complications, and feeding intolerance. (22)(27)(37)(38)(39)

Accurate quantification of the number of true adverse events in infants discharged with home NGT or GT feedings is difficult, as some studies use only proportions of populations. In addition, there is no accepted timeframe for follow-up; some programs report events up to 12 months, (24) while others report events from 3 to 6 months after discharge. (22)(23)(26)(27)(28) Going forward, more uniform incidence reporting of outcomes for home enteral nutrition should be strongly considered and adopted. One program analyzed adverse events based on “tube exposure days” over time to provide a more standardized measure of reporting. (22) This group calculated an incidence of ED visits and hospital readmissions for all NGT or GT-related events for every 500 tube exposure days in their cohort and showed 1.6 ED visits and 0.8 hospital admissions for every 500 tube days within 6 months of discharge. (22)

QUALITY OF LIFE WITH EARLIER HOME ENTERAL NUTRITION

In programs that measured satisfaction of earlier discharge with home enteral nutrition, parental satisfaction and quality of life were rated highly and anxiety was decreased in parents of early discharge infants compared with parents of infants who were not offered earlier discharge. (21)(25)(26)(27) One study even had similar satisfaction between parents whose infants were rehospitalized (for all causes including scheduled admissions) and those who were not, suggesting that discharging an infant sooner, despite medical complexity, has the advantages of reducing parental stress and improving quality of life for the family-infant dyad. (26) However, given that all programs had variations in follow-up time and support provided, which could affect both the clinical and psychosocial outcomes of families, more studies are needed to accurately assess family satisfaction and infant quality of life after early discharge with home enteral nutrition.

Educating families about GT care before GT placement has been found to lead to lower medical utilization postoperatively by more than 30% compared with families who were educated after GT placement. (40)(41)(42) Three programs that provided GT preplacement family education found a significant reduction in the number of office visits, ED visits, and readmissions at the 12-month postdischarge period, as well as a trend toward reduced medical utilization at the 3-month postdischarge period. (40)(41)(42) In the program established by Devin et al, patients who were discharged with NGT feedings with a plan for GT placement at a later date and had a “follow-up feeding tube medical home” to assist after discharge, found an unintended consequence of decreased GT placements in 5% of the patients, and reduced Nissen fundoplication placement by 2-fold (48% vs 22%). (41) These patients also successfully weaned off NGT feedings before their surgical date in a median time of 4 months. (41) Introducing presurgical family education and medical home resources shows promise toward the reduction of complications and avoidance of unnecessary medical utilization.

Summary

A standardized approach does not exist to provide earlier discharge to NICU patients who are medically stable but still require a feeding tube. However, results from programs currently offering earlier discharge are encouraging and help to reach this goal. Cohort studies of these new programs have shown that the use of home NGT feedings is safe if family education and appropriate home monitoring are prioritized. Enteral tube feedings have been shown to have advantages over home GT placement, such as fewer unplanned ED visits and hospitalizations and patient complications. Because the patient population requiring home enteral nutrition is quite heterogeneous and vulnerable, randomization of feeding practices may never be possible to understand the absolute best practices and/or exact patient selection for home NGT versus GTs. Although these earlier discharge approaches have reported successful outcomes for infants and families, there are still some gaps and controversies in the current medical literature that need to be addressed by future studies and larger patient consortiums.
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1. Preterm infants need to demonstrate physiologic competencies before discharge from the NICU, including sufficient oral feeding to support appropriate growth, ability to maintain normal body temperature, and respiratory control that is sufficiently mature. In a large multicenter, randomized, controlled trial, individualized developmental care of very low birthweight preterm infants was shown to lead to discharge at younger ages. Which of the following statements was NOT a benefit of individualized developmental care in this trial?

A. Fewer days of parenteral feeding.
B. Shorter transition periods to full enteral feeding.
C. Increased height at 42 weeks’ postmenstrual age (PMA).
D. Lower total hospital cost.
E. Decreased incidence of necrotizing enterocolitis.

2. Oral feeding dysfunction remains a main reason for continued NICU hospitalization in medically complex and premature infants. What is the incidence of inpatient oral feeding difficulty in this population?

A. Up to 20%.
B. Up to 40%.
C. Up to 50%.
D. Up to 60%.
E. Up to 80%.

3. The goal of establishing oral independence sooner in the preterm population is a high research priority. Data suggest that individualized intensive oral therapy, including non-nutritive sucking and cue-based feeding approaches, is beneficial in preterm neonates. What is the PMA at which typical preterm neonates are developmentally able to orally feed safely?

A. 29 weeks’ PMA.
B. 31 weeks’ PMA.
C. 32 weeks’ PMA.
D. 34 weeks’ PMA.
E. 36 weeks’ PMA.

4. Preterm infants able to feed orally partially may be eligible for safe earlier discharge from the NICU with a nasogastric tube (NGT) or gastrostomy tube (GT) and the support of a home enteral nutrition program. Which of the following clinical characteristics is NOT associated with a need for GT placement in preterm infants discharged with an NGT?

A. Small for gestational age status.
B. Maternal education level.
C. Oral intake proportion less than 20% to 30% at NICU discharge time.
D. PMA above 45 weeks at NICU discharge time.
E. Lower birthweight.
5. Infants discharged from the NICU with partial oral intake should be closely monitored because of associated risks and complications of home enteral nutrition. What is the rate of hospital readmission in infants discharged with an NGT?

A. Between 2% and 6%.
B. Between 10% and 14%.
C. Between 16% and 20%.
D. Between 25% and 30%.
E. Between 40% and 50%.
Developing a Quality Improvement Feeding Program for NICU Patients

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PRACTICE GAPS

- Evidence-based approaches to feeding premature infants are limited, which leads to practice variation in NICUs.
- A quality improvement program to improve feeding outcomes in premature infants needs to be a priority in NICUs.

OBJECTIVES After completing this article, readers should be able to:

1. Describe the epidemiology of feeding difficulties and physiologic evidence-based approaches that should be incorporated into NICU feeding guidelines.
2. Recognize the steps required to develop a quality improvement feeding program in the NICU.
3. Explain how to sustain a NICU feeding program and affect process change to improve clinical outcomes.

ABSTRACT

Practices in NICUs vary widely, particularly when clinical decisions involve complex tasks and multiple disciplines, which occurs with feeding preterm infants. Neonatal feeding difficulties in preterm infants often lead to prolonged tube feeding and therefore lengthened hospital stays. Education and compliance with evidence-based protocols and guidelines are needed on the initiation of feedings and feeding advancement to transform enteral and oral feeding practices and thus reduce practice variation and improve clinical outcomes.

INTRODUCTION

Feeding difficulties among preterm infants are universally prevalent in NICUs. Challenges can arise at any time between the initiation of enteral feedings soon after birth until the achievement of full oral feedings when infants can be safely discharged from the hospital. Variability in feeding practices is common in
NICUs globally. (1)(2)(3) Clinical guidelines have been used to minimize variability and improve outcomes in clinical practice, but these guidelines need to be developed based on evidence to maximize benefits and avoid harm. (4)

Unfortunately, studies evaluating multiple enteral and oral feeding guidelines developed for preterm infants have found mixed outcomes. (5)(6)(7)(8) The content of these guidelines varies widely, particularly where the evidence is limited or weak. (3)(6)(7)(8) Not surprisingly, a review of oral feeding guidelines in premature infants showed that rigorous research on infant feeding is needed. (5) Clinical guidelines require an evidence-based approach when possible and must also be developed based on the culture of the unit where they will be implemented with goals based on that unit’s needs. For example, a level II NICU in a rural area with only inborn patients will not have the same needs as a level IV NICU in a children’s hospital where infants are transferred from other centers.

We developed the simplified, individualized, milestone-targeted, pragmatic, longitudinal, and educational (SIMPLE) feeding program in our all-referral level IV NICU after we observed variability in preterm infant feeding practices among our clinicians. The program targeted feeding milestones throughout NICU hospitalization, based on available evidence of feeding practices. Infants were included if they were born at less than or equal to 32 weeks’ gestational age (GA) and were excluded if they had surgical necrotizing enterocolitis (NEC), intraventricular hemorrhage with ventricular dilation or intraparenchymal involvement, chromosomal abnormalities, or gastrointestinal (GI) or neurologic surgery. This program significantly increased the number of infants who received trophic feedings, decreased the time to full enteral feedings, increased weight gain velocity, and decreased length of hospital stay (LOHS) compared with a baseline group of infants before the program was implemented. (9)(10) The program was developed and sustained in a process undertaken by a group that was passionate about infant feeding, with the main goal of improving clinical outcomes related to feeding in the NICU.

A practice guideline such as the SIMPLE program can be established in any NICU regardless of size or patient population. When developing preterm feeding guidelines, it is important to understand the epidemiology of feeding difficulties, establish physiologic evidence-based approaches, and customize the program to the individual unit. Sustaining the program and effecting process change can be accomplished by tracking feeding milestones, examining compliance metrics, providing targeted education to bedside feeding clinicians, and specifying the roles of parents and clinicians. With an individualized feeding program, any NICU can improve clinical outcomes as defined by the unit’s aims. In this review, we provide an overview of the evidence that we incorporated into our feeding program’s guidelines to allow other units to establish a similar, but unit-specific, program.

Epidemiology and Physiology-Based Infant Feeding Guidelines

All preterm births (ie, <37 weeks’ gestation) account for approximately 15 million births globally each year, which is associated with increased morbidity, mortality, and socioeconomic burden. (11) The total cost of preterm births in the United States was $25.2 billion dollars in 2016. The cost for an infant born at less than 28 weeks’ GA is more than 12 times the cost of an infant born at 32 to 36 weeks’ GA. (12) After discharge, feeding problems affect approximately 42% of premature infants without significant comorbidities, and this number is likely higher in the presence of multisystemic comorbidities. (13) Furthermore, preterm infants comprise approximately 40% of infants referred to clinics for chronic feeding issues. (14)

One of the most important determinants of preterm infant growth and development is providing timely enteral nutrition, which is often a challenge in the NICU setting. Preterm infants often need central venous catheters to provide adequate parenteral nutrition, which places them at increased risk for nosocomial bloodstream infections because of their immunocompromised state. To decrease the length of central catheter use, preterm infants need to begin gastric feedings and advance to full enteral nutrition as early as possible. Early attainment of full enteral nutrition is often delayed in premature infants because of perceived intolerance or concerns for risk of NEC, though a Cochrane review showed that slow advancement of intragastric feedings (15–20 mL/kg per day, compared with 30–40 mL/kg per day) did not decrease the risk of NEC in very preterm or very low-birthweight infants. (15)

The initiation of oral feedings and the progression to full oral feedings have also been found to be delayed in preterm infants. These delays are often attributed to cardiorespiratory instability or inadequate pharyngeal-esophageal motility and airway protective mechanisms that need time for maturation. (16) In a prospective study of 6,017 moderately premature infants still hospitalized at 36 weeks’ postmenstrual age (PMA), one-third of the infants who were born at 29 to 33 weeks’ GA remained hospitalized solely because of inadequate oral intake. (17) Prenatal
and postnatal physiology, as well as limited opportunities for oral feeding experiences, affect the advancement to full oral feedings in hospitalized preterm infants and could prolong hospital stay or lead to discharge with tube feedings.

The American Academy of Pediatrics identifies oral feeding competency to sustain growth as 1 of 3 physiologic criteria for hospital discharge of preterm infants with nasogastric feeding as a limited option for discharge in select cases. (18) However, recently many centers are discharging preterm infants who are receiving nasogastric feedings. Given the complexity of the NICU patient, identifying the appropriate patient, the ideal family, a safe home environment, and the ability for close follow-up are important for establishing successful home nasogastric feedings. Home nasogastric feedings also pose postdischarge charge risks such as trauma from placement, dislodged or misplaced tube, clogging of tube, and aspiration, all of which lead to an increase in hospital and clinic visits. (19)

Preoral Feeding

Trophic Feeding. Multiple studies have examined the benefits and risks of trophic feeding in both animal and human models. Trophic feeding is defined by McClure as “the practice of feeding nutritionally insignificant volumes of enteral substrate to the compromised newborn infant in order to stimulate and supply nutrients to the developing GI system.” (20) In a review of randomized controlled trials in preterm infants, trophic feeding was shown to 1) elevate gastrin, enteroglucagon, and motilin, which stimulate GI growth, function, and motility; 2) increase enteric blood flow; 3) enhance proximal intestinal motor activity; 4) decrease the amount of time to reach full enteral feedings; 5) decrease the risk of sepsis; and 6) decrease the LOHS. (20) In contrast, a Cochrane review of randomized controlled trials in preterm infants born at less than 32 weeks’ GA at birth, kangaroo care was shown to significantly increase the length of breastfeeding time from 2 to 5 months and significantly increase exclusive breastfeeding at multiple time points (up until 6 months). (26)

Preoral Interventions. Although enteral feeding is extremely important to the preterm infant, there are preoral interventions that can enhance feeding-related outcomes. Oral care with colostrum and expressed breast milk is an intervention that has the potential to provide improved immunity, better feeding tolerance, and decreased time to full enteral feeding. (24)(25) Kangaroo care is another treatment that should be provided to all preterm infants. (3) In a randomized controlled trial of preterm infants of 32 to 36 weeks’ GA at birth, kangaroo care was shown to significantly increase the length of breastfeeding time from 2 to 5 months and significantly increase exclusive breastfeeding at multiple time points (up until 6 months). (26)

Introduction to Oral Feeding

The timing of introducing oral feedings to the preterm infant can vary based on practice variation, clinician preference, the infant’s clinical condition, and other factors. Clear guidelines for when to initiate oral feeding should be based on preterm physiology and available evidence.

Fetal Development of Sucking and Swallowing. The development of sucking and swallowing begins in utero. Swallowing of amniotic fluid begins around 11 to 12 weeks’ gestation and is an important regulator of amniotic fluid volume. Sucking movements develop by 18 to 20 weeks’ gestation. (27) The fetus swallows approximately 250 mL/kg per day of amniotic fluid by 28 weeks’ gestation. (28) After birth, preterm infants are able to swallow their own saliva and secretions, but they are no longer receiving the in utero experience of swallowing large volumes of amniotic fluid continually, which would continue to develop their swallow function. (28) A study that investigated the role of swallowing during sleep found that preterm infants only swallow about once per minute in active sleep at
term PMA, illustrating the limited number of swallowing opportunities if they are not being orally fed. (29)

Swallowing evolves as early as 11 weeks’ gestation, however, studies show that coordination of the processes involved with oral feeding begin by 33 to 34 weeks’ PMA and continue to mature beyond term PMA. (30) The attainment of these skills is influenced negatively by the presence of neurologic, aerodigestive, and pulmonary comorbidities. This was shown by a retrospective study of premature infants of less than 35 weeks’ gestation that found lower gestational age, history of hypotension, and increased duration of ventilation all correlated with later attainment of full oral feeding. (16)

**Initiation of Oral Feeding.** The introduction of oral feeding is usually attempted in clinically stable infants at approximately 32 to 34 weeks’ PMA when they potentially have the maturation to control and coordinate the complex feeding process of sucking and swallowing a bolus feed while demonstrating respiratory rhythm regulation. (30) Many studies use multiple criteria for determining the time to begin oral feeding in premature infants. In a randomized controlled study of 29 infants of less than 30 weeks’ gestation, infants in the intervention group initiated oral feeding 48 hours after achieving full enteral feedings (120 kcal/kg per day) whereas the timing of oral feeding of infants in the control group was left to the discretion of the attending physician. (31) The intervention group initiated and achieved full oral feeding significantly sooner than the control group. (31) Another randomized controlled study by Pickler et al examined 4 feeding strategies starting either at 32 or 34 weeks’ PMA and oral feeding either with every feeding or gradually increasing from 2 to 8 feedings per day over 2 weeks. (32) The authors found that the group with the later start (ie, 34 weeks’ PMA) who received 8 oral feedings per day took significantly fewer days to advance to full oral feedings. (32) As all infants mature at a slightly different rate, tools are necessary for evaluating when to begin oral feedings in preterm infants. A Cochrane review of tools to assess readiness for oral feeding did not find any studies to inform clinical practice in this area. (33)

**Cue-based Feeding.** Infant-driven feeding, also known as cue-based feeding, has become common in most NICUs but is often loosely interpreted and adapted. Most data are based on retrospective reviews of quality improvement projects. (34)(35) Cue-based feeding involves using a feeding readiness scale to determine infant readiness for oral feeding and then evaluating the quality of each feeding based on an assigned quality score. The focus is on the quality of the feeding rather than the volume of the feeding.

In the development of our SIMPLE program, cue-based feeding readiness scores were based on the system used by Davidson et al, which were adapted from Ludwig and Waitzman. (36)(37) In this approach, the feeding readiness scale consisted of a 5-point scale that was condensed into a 3-point scale as the program evolved (Table 1) to make it simpler and more user-friendly, such that parents could calculate a score. With the new scale of 0, 1, and 2, oral feeding is only offered with a readiness scale of 2. To initiate cue-based feedings, the infant needs a score of 2 for at least 50% of the feedings during a 24-hour period. The feeding quality score is based on 5 categories to provide a quantitative value to the oral feeding quality, as shown in Table 1. (36) That number can be tracked over multiple feedings or days to indicate improvement or regression with feedings without relying solely on the feeding volume and is not used as a marker of when to hold oral feedings.

**Oral Feeding with Respiratory Support.** Although there are mixed results on the safety and feasibility of oral feeding when an infant requires nasal continuous positive airway pressure (NCPAP) and high-flow nasal cannula (HFNC), it has been shown to be feasible in stable infants. A survey in Australia and New Zealand showed varied practices regarding oral feeding of infants and children receiving NCPAP and HFNC. (38) Oral feeding of children receiving NCPAP was reportedly done often, sometimes, and rarely in 2%, 45%, and 22% of respondents, respectively. Oral feeding while receiving HFNC support was done often, sometimes, and rarely in 38%, 41%, and 17% of respondents, respectively. (38) A study of infants born between 24 and 27 weeks’ GA who were receiving NCPAP at 37 to 42 weeks’ PMA compared 26 infants who were orally fed to 27 infants who were exclusively gavage fed until discontinuing NCPAP. The study showed significantly earlier achievement of full oral feeding by more than 2 weeks with no incidence of clinically significant aspiration pneumonia in the infants who were orally fed while receiving NCPAP. (39) Mechanistic studies using manometry evaluation of pharyngoesophageal reflexes and airway safety supported the presence of basal and adaptive aerodigestive reflexes in infants receiving noninvasive respiratory support. (40) A retrospective analysis of infants receiving NCPAP who were either fed orally with cues or not offered oral feeding showed no statistical difference in outcomes or morbidities in either group. (41) A quality improvement effort to achieve breastfeeding and bottle
feeding competence in a safe gradual manner developed an algorithm for offering and advancing oral feeding in all stable infants at 32 weeks’ PMA with or without CPAP. They compared their data from the first 6 months of implementing the algorithm to a baseline group 6 months before implementation and found significantly lower PMA at first oral feeding and first breastfeeding in the intervention group, but no significant difference was found with feeding method used at discharge. The group did not observe any cases of suspected aspiration or increased distress related to the oral feeding opportunities. (42)

**Oral Feeding to Discharge**

Once oral feeding is initiated in preterm infants, it can be advanced based on clinician-driven limitations or on the infant’s cues. Allowing preterm infants to eat based on cues ensures that no feeding opportunities are missed when they demonstrate signs of readiness. If oral feeding does not progress, it is necessary to examine potential barriers. Preterm infants with multiple comorbidities such as bronchopulmonary dysplasia, patent ductus arteriosus, NEC, sepsis, and severe intraventricular hemorrhage can have significantly delayed feeding milestones and may require more time than the preterm infant without significant comorbidities. (27) This high-risk group may also require some oral feeding method modifications such as pacing and different positioning, as well as instrumental testing to evaluate for gastroesophageal reflux disease (eg, pH impedance) and/or intestinal dysmotility (eg, esophageal motility testing). Aspiration can also occur in preterm infants when a bolus penetrates below the vocal cords. This can be antegrade (during oral feedings) or retrograde (during proximal gastroesophageal reflux). Both of these require objective diagnostic testing with personalized treatments. (43)(44) Some infants simply require prolonged tube feedings because of dysmaturity.

Thickening of feedings should be reserved for infants with older PMAs and only if clinically indicated. Adding cereal or other additives to formula or breast milk should be avoided, if possible, because of the higher osmolality, which is not recommended for preterm infants. (45)(46) Premature introduction of cereal or other prepared thickeners is also associated with

### Table 1. Oral Feeding Readiness Scale (Original and Revised)

<table>
<thead>
<tr>
<th>Scale</th>
<th>Original</th>
<th>Revised</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Needs increased oxygen (from patient’s baseline) for care</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Sleeps through care, no hunger cues</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>Briefly alert with care, no hunger cues</td>
<td>2*</td>
</tr>
<tr>
<td>4*</td>
<td>Drowsy or alert once handled, able to elicit rooting or takes pacifier</td>
<td>5*</td>
</tr>
</tbody>
</table>

Revised scale modified from original. (36) Original scale used with permission from Elsevier. *Oral feeding should be offered.

### Table 2. Feeding Quality Scale

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alert state</td>
<td>Maintains alert state, or if drowsy, suckles without reminders/stimulation</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Sleepy; able to wake, but falls asleep due to limited capacity for alertness</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Unable to wake; may be unstable; does not initiate sucking on own</td>
<td>0</td>
</tr>
<tr>
<td>Suck/swallow/breathe coordination</td>
<td>Maintains safe suck/swallow/breathe coordination throughout</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Immature skill; requires pacing, positioning, or nipple change</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Uncoordinated suck/swallow/breathe, resulting in apnea/bradycardia/desaturation</td>
<td>0</td>
</tr>
<tr>
<td>Fluid loss</td>
<td>Minimal loss; typical drooling/leaking</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Intermittent fluid loss that does not occur with each suck burst</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Excessive fluid loss, as evidenced by fluid loss with each suck/swallow</td>
<td>0</td>
</tr>
<tr>
<td>Work of breathing</td>
<td>No increased work of breathing</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Increase in work of breathing, as evidenced by increased retractions, tachypnea, or head bobbing</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Significant increase in work of breathing, requiring discontinuation of feed</td>
<td>0</td>
</tr>
<tr>
<td>Volume</td>
<td>100% volume taken</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>50%–99% volume taken</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&lt;50% taken</td>
<td>0</td>
</tr>
<tr>
<td>Total score</td>
<td></td>
<td>0-10</td>
</tr>
</tbody>
</table>

Quality scale used with permission from Elsevier.
infection risks, constipation, and risk for childhood obesity. (47) The associated decrease in breast milk or breastfeeding found with thickened feedings is not ideal as breast milk has shown benefits of immune defense, GI development, better nutrition, and improved neurologic outcomes, particularly with preterm infants in the hospital. (49) In some infants, cereal or other thickeners can lead to excessive effort to extract thickened milk via the nipple, which may be particularly difficult for infants with lung disease. Appropriate cleaning of bottles, nipples, and inserts when using thickened milk can also be difficult and may predispose infants to infections. Added rice starch formulas can lead to decreased availability of calcium, zinc, and protein compared with preterm discharge formulas. (46)

Most cases of feeding dysfunction in preterm infants resolve with maturation of oral skills and esophageal function in the presence of good nutrition and growth. As preterm infants mature, they establish more regulated apneas during the act of deglutition and increased strength and number of pharyngeal contractions. All of this leads to the improvement of esophageal peristalsis and propagation, bolus clearance, and lower esophageal sphincter relaxation to empty boluses into the stomach (Fig 1). During this time of maturation, the number of consistent oral feeding experiences may be the most important intervention, which requires diligence and patience from both parents and clinicians.

The definition of full oral feeding volume varies among populations and ranges from 120 to 200 mL/kg per day with varying caloric densities, as certain medical conditions, such as cardiorespiratory illness, are managed with restricted total fluid volume and increased caloric density. The volume and calories to achieve full oral feedings need to be personalized to the individual needs of the infant based on comorbidities, tolerance, and growth. Premature infants who do not need to be fluid restricted should be discharged on ad lib oral feedings with follow-up with both a primary physician and a developmental follow-up clinic for close monitoring of their growth and nutrition. They should be monitored on full ad lib oral volumes for 1 to 2 days before discharge to ensure adequate weight gain (10–20 g/kg per day) with their current intake. (50) It is important to ensure growth of weight, length, and head circumference during and after a NICU stay. This requires a discharge plan with reliable follow-up of feeding, growth, and developmental milestones to avoid a disconnect in transition from the NICU to the community.

Preterm infants may not reach full oral feedings before discharge and as a result, may require long-term home tube feeding. Home tube feeding can be provided with a nasogastric or gastrostomy tube. Units that discharge infants from the hospital with nasogastric feeding should define eligibility criteria as well as outline a postdischarge management plan. (19) (51) To promote eventual full oral feeding, a feeding plan should be developed with the parents to optimize oral feeding opportunities at home and provide them with the knowledge to care for their infant with home tube feedings. Both family education and follow-up are imperative; families

Figure 1. Oral feeding challenge showing that biomarkers improved with maturation over a 4-week period. This figure shows results of an oral feeding challenge during high-resolution esophageal manometry (with 3- and 2-dimensional views) in a representative 29-week gestational age infant at time 1 (44.14 weeks’ PMA, left panel) and at time 2 (48.14 weeks’ PMA, right panel). This infant was receiving gavage feedings at time 1 and full oral feedings at time 2. An oral feeding challenge was done for 3 minutes and the infant took 3 mL/min at time 1 and 9 mL/min at time 2. Observations at time 2 showed improved regulation of breathing, improved regulation and coordination of pharyngeal waveforms, and increased strength and propagation of esophageal contractile peristalsis. LES=lower esophageal sphincter, PMA=postmenstrual age, UES=upper esophageal sphincter.
need reliable, knowledgeable resources at their disposal once they are home.

DEVELOPMENT OF THE SIMPLE FEEDING PROGRAM: A QUALITY IMPROVEMENT INITIATIVE

A quality improvement feeding program such as SIMPLE can be established in any NICU regardless of the size or complexity of the patient referral pattern. The milestones and goals to be attained need to address the targeted population in the specific NICU. When establishing a feeding program, it is first necessary to develop common accepted feeding milestones as goals, based on all available data and evidence from the individual unit. The feeding milestones used for the initial SIMPLE feeding program are listed in Table 3. These milestones are targets and encompass all infants of less than or equal to 32 weeks’ GA admitted to an all-referral level IV children’s hospital. Milestones may be slightly different for a NICU with a different population and should be modified over time based on any new emerging evidence. The process for the successful development and implementation of a feeding program is described below and summarized in Fig 2.

Steering Committee

A steering committee should be developed, which includes representatives from the following areas: hospital administration, unit leadership, medical staff (physician and/or nurse practitioner), nursing leadership, and quality improvement (data analyst). This group should include a physician leader who can infuse enthusiasm and pathophysiology-based knowledge about safe feeding approaches into the program. Without the support of the institution and administration, the program will not have the financial support and credibility that it needs to succeed. The steering committee needs to have the common goal of decreasing practice variability while identifying problem areas with feeding in their unit. The problem areas will differ based on the patient population and unit culture and may include increased gastrostomy tube rates, minimal parent involvement with feedings, lack of consistency with feeding management, increased NEC rates, or lack of breast milk use at the time of discharge, among other parameters. Once these issues are recognized, specific aims can be identified, and a key driver diagram can be developed. This diagram includes specific aims (what the program is trying to accomplish in exact measurable terms), key drivers (factors needed to achieve the aims) and interventions (specific changes in practice to be implemented). The key driver diagram in our SIMPLE feeding program included the specific aim of reaching full oral feedings by 38 weeks’ PMA and decreasing LOHS by 10 days over a 12-month period. (9) Before coming up with specific aims, it is necessary to collect baseline data, which is where a quality improvement analyst can help determine the number of baseline patients needed and the specific data that need to be collected. To measure improvements, it is necessary to establish a baseline before the intervention. For the SIMPLE feeding program, data were collected on a baseline population of infants matching the criteria of infants included in the program.

Core Group

Once the steering committee agrees on the feeding problems to be addressed and develops a key driver diagram, the committee needs to identify a core group of people who are passionate about improving feeding outcomes. The core group should meet on a regular basis to develop appropriate interventions and education as well as to collect and monitor data, including baseline data. The core group should include 2 to 3 physicians, nurse practitioners, and/or physician assistant champions; 2 to 3 nurse champions; a quality improvement specialist; a dietitian; a lactation consultant; and possibly a parent and feeding therapist. This group may vary based on the unit’s composition of patients, parents, staff, and specialists as well as the unit’s specific needs. The core group should meet at least monthly to review data, develop educational tools, review available evidence, and identify any new feeding issues. They should recognize active barriers to implementation and determine solutions to resolve them. The core group can also arrange formal trainings to keep staff engaged, provide evidence-based updates, and share data.

Feeding Champions

Feeding champions should be identified to educate individuals and provide support for the program. These champions

Table 3. Feeding Milestones

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start of trophic feedings</td>
<td>≤3 d after birth</td>
</tr>
<tr>
<td>Full enteral feedings (defined as 120 mL/kg/day)</td>
<td>≥28 d after birth</td>
</tr>
<tr>
<td>First oral feeding</td>
<td>≥34 wk PMA</td>
</tr>
<tr>
<td>Full oral feedings (oral intake of at least 120 mL/kg/day)</td>
<td>≥38 wk PMA</td>
</tr>
</tbody>
</table>

PMA=postmenstrual age.
typically are the bedside staff who feed patients and possibly parents involved in the program. They provide support for the program, educate the rest of the NICU and parents, and participate in discussions about feeding.

NICU Education and Implementation
Before implementing the program, all staff members need to be educated about the program’s goals and the planned interventions. Formal education can begin with the feeding champions, who then can provide individualized training to the rest of the NICU staff and parents.

Focus Groups
Focus groups can be established when the need arises and can consist of a small group of interested participants who identify solutions to more specific feeding problems. For example, our SIMPLE program included focus groups for gastrostomy tube use, medication use, education, and cue-based feeding. Each of these groups contained a member from the core group as well as feeding champions. As the groups defined ideas for improvement, these ideas were discussed in the core group and then implemented as needed. Often these projects were also discussed in quarterly educational sessions for the NICU staff.

METHODS TO SUSTAIN A SUCCESSFUL FEEDING PROGRAM
To maintain a feeding program and adapt to changing needs, it is necessary to track feeding milestones, achieve process change in the NICU, provide targeted education, track accountability and compliance, and identify the roles of parents and clinicians. These are all necessary for sustaining a feeding program with ever-changing staff and families. Feeding milestones should be tracked on a regular basis by someone with protected time to ensure accurate data. The data can be extracted electronically with computerized charting but should be stored in a database and verified for accuracy. Sharing data on a regular basis with the team encourages buy-in and acceptance of the program. Data sharing and teaching can occur with the use of bulletin boards, newsletters, educational rounds, and formal educational sessions. Monitoring accountability and compliance with the milestones also is a priority.

Feeding rounds provide an opportunity for members of the feeding core group to discuss each infant individually with the physician and/or advanced practitioner, bedside nurse, dietitian, feeding therapist, and parent(s). In our program, feeding rounds included the patient care team and the parents and occurred twice a week. Our rounds were facilitated by a nurse who collected specific information before rounds. The data included the infant’s age, PMA, comorbidities, respiratory support, growth velocity, feeding status, and parental involvement, including kangaroo care and breastfeeding. The team then determined if the infant was meeting targeted feeding milestones and offered suggestions for improving feeding outcomes. Whenever the team was not following established feeding guidelines for reaching the milestones, discussions were

Figure 2. The organizational structure for successful development and execution of the simplified, individualized, milestone-targeted, pragmatic, longitudinal, and educational (SIMPLE) feeding program is shown. Roles and members of the steering committee, core group, and feeding champions are described in the text.
focused on reestablishing goals and expectations while understanding potential challenges of meeting the goals. Acceptance of clinical guidelines and process change can be difficult in the NICU setting. For some aspects of clinical care, there is a long history of providing care the way that it has always been done because of a lack of rigorous evidence in this population. To establish buy-in from staff, they must be shown the potential benefits of change and actively engage as a part of that change.

**CLINICALLY MEANINGFUL OUTCOMES FOR IMPROVED OVERALL UNIT OUTCOMES**

The goal of any feeding program should be to improve clinical outcomes for patients and families while lowering economic burden. A primary feeding outcome goal is achieving full oral feedings before discharge. Discharging a patient with nasogastric tube feedings carries the risk of multiple complications, such as nasal trauma, obstruction, septal deviation, or congestion; nasogastric tube dislodgement; and recurrent hospitalizations, as well as an added burden of stress for the family. Similarly, gastrostomy feeding carries a risk of complications such as leaking, infection, and dislodgement. Better neurologic/developmental outcomes at 18 to 24 months of age were found in infants who had achieved full oral feedings at discharge compared with those who received a gastrostomy tube. (13) The presence of a gastrostomy tube without complications also carries an added economic burden of close to $50,000 in the first year and $180,000 in the first 5 years due to the cost of placement, supplies, follow-up, etc. (44)

One goal of the SIMPLE feeding program is to have infants achieve full oral feedings before discharge; however, another important goal is to improve the quality of life for infants and their families. Decreasing the LOHS is primarily seen as an economic benefit, but it also significantly improves the quality of life for the family. Parents struggle with a lengthy NICU stay, balancing the need to be with their child while trying to maintain their life at home and work. Feeding can be a major source of stress for parents and providing them with the education and ability to improve their infant’s feeding outcome can help them immensely. Earlier discharge allows the family to be home, bonding with their family unit. Decreasing the LOHS decreases morbidities from exposure to hospital-acquired infections, decreases the cost of the hospital stay, and frees up scarce hospital resources for other infants who need to be hospitalized.

The quality of life can be affected for those infants and families who require long-term tube feeding after discharge. The impact of home gastrostomy feedings was assessed by a qualitative study that interviewed families and identified some key challenges for families including disturbed sleep, inability to go out and take vacations, lack of child care, family division, negative attitudes of others, and the missed experience of bonding via bottle or breastfeeding (52) The goal of discharge with full oral feedings as a result of a feeding program has the potential to improve the quality of life for infants and their families.

**LESSONS LEARNED AND FUTURE DEVELOPMENT**

In developing the SIMPLE feeding program and observing its evolution over the past 10 years, our group has learned many lessons that may benefit other units developing similar quality improvement initiatives. Our program has attempted to transition clinicians from multiple disciplines into an interdisciplinary team. For that to happen, everyone needs to practice as a team rather than in silos. Ideally, NICUs would transition from an interdisciplinary to a transdisciplinary approach in which all disciplines are working as one with common goals. This would eliminate confusion and inconsistencies often experienced by parents and staff.

Feeding problems have become more complex in the NICU as technology has allowed the treatment of infants of younger gestational age. The complexity of patients makes personalized plans for feeding problems imperative, allowing teams to account for an infant’s history, comorbidities, medications, stage of development, and social dynamics. Feeding rehabilitation in these infants needs to be based on objective evidence and personalized to their exact pathophysiology. Parents should be educated early and provided anticipatory guidance to understand feeding difficulties so that they can be a part of the interventions to improve feeding outcomes from the very beginning. Clinicians also need to be aware of the factors that influence feeding milestones and outcomes. It is important to empower bedside caregivers to feel comfortable with the feeding approach because they are at the bedside for every care. Feeding guidelines need to be based on relevant evidence with the ability to personalize the plan for the complex infant. The institutional administration also needs to provide structural and financial support to sustain the program.

Multiple factors are required to modify infant feeding difficulties in the NICU and improve feeding outcomes. (53) These factors are listed in Fig 3 and include:

1. Physiology: Understand how neurologic and aerodigestive functions change as preterm infants mature.
2. Pathophysiology: Identify the underlying mechanisms associated with feeding difficulties.

3. Patient characteristics: Take into account the risk factors and comorbidities that vary with every patient.

4. Parental involvement: Account for varied parental involvement, attitudes, culture, and resources when providing education.

5. Providers: Recognize that multiple clinicians have varied experiences and knowledge about preterm infant feeding and they need to use objective evidence to provide interdisciplinary care.

6. Procedures: Complete standardized, timely, and properly interpreted procedural evaluations for infants with feeding challenges.

7. Precision medicine: Institute innovative treatment approaches for specific objective diagnoses.

8. Personalization: Provide therapies that are specific to the needs of the parent-clinician-infant triad.

9. Pragmatism and humanism: Recognize that management approaches can alter clinical outcomes.

10. Policy: Tailor institutional policies based on the needs of the specific NICU.

TAKE-HOME POINTS

- Consensus of care with evidence-based feeding guidelines can lead to improved clinical outcomes of infants in the NICU.
- Feeding guidelines in NICU infants need to be based on developmental physiology and available evidence.
- Premature infants have rapidly changing neurologic and aerodigestive physiology that makes timely interventions imperative.
- The development of an effective NICU feeding program requires a stepwise process that includes all stakeholders.
- The maintenance of a feeding program for preterm infants requires enthusiastic participants who are dedicated to tracking feeding milestones, affecting process change, providing targeted education to families and staff, and tracking accountability and compliance.
References


46. Eichenwald EC; Committee on Fetus and Newborn. Diagnosis and management of gastroesophageal reflux in preterm infants. *Pediatrics.* 2018;141(1):e20181061


1. Among preterm infants with no significant comorbidities, what is the approximate proportion who have feeding problems after discharge and are referred to long-term feeding clinics?

A. 5%
B. 10%
C. 25%
D. 40%
E. 75%

2. An enteral feeding protocol may help to reduce the duration of central catheter placement for providing parenteral nutrition and also optimize nutrition. A Cochrane review on the advancement pathways for advancing nasogastric feedings showed which of the following regarding necrotizing enterocolitis (NEC)?

A. Feeding protocols that did not initiate enteral feedings until day 7 led to the lowest rate of NEC.
B. A 10 mL/kg per day advancement is the optimal rate for prevention of NEC.
C. A 20 mL/kg per day advancement is the optimal rate for prevention of NEC.
D. 40 mL/kg per day advancement is the optimal rate for prevention of NEC.
E. The review did not find a specific advancement rate that led to a decrease in NEC.

3. Which of the following is considered by the American Academy of Pediatrics Committee on Fetus and Newborn as 1 of 3 physiologic criteria for hospital discharge for preterm infants?

A. Oral feeding volumes that sustain appropriate growth.
B. Mature newborn reflexes in all extremities.
C. Visual tracking of 180-degree fields.
D. Ability to roll over from supine to prone position to facilitate appropriate positioning during sleep.
E. Absence of preatrial contractions

4. Trophic feeding of preterm infants has been shown to lead to which of the following?

A. Decrease in gastrointestinal motility.
B. Increases in gastrin, enteroglucagon, and motilin levels.
C. Decrease in enteric blood flow.
D. Slight increase in early-onset necrotizing enterocolitis, but reduction in late-onset necrotizing enterocolitis.
E. No impact on amount of time to reach full enteral feeding.

5. Sucking and swallowing movements develop during the fetal period. Which of the following statements describe typical fetal development?

A. Swallowing of amniotic fluid begins around 4 to 6 weeks’ gestation.
B. Sucking movements begin around 18 to 20 weeks’ gestation.
C. The fetus swallows approximately 100 mL/kg per day of amniotic fluid at 28 weeks’ gestation.
D. The coordination of the processes involved with oral feeding begins at 37 to 39 weeks’ gestation.
E. Fetal swallowing occurs at a rate of approximately once per second.
Seizures in a Term Newborn

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PRESENTATION

A 31-year-old gravida 7, para 4 woman delivers a male infant via vaginal delivery without the use of forceps or vacuum extraction after induction of labor at 39 weeks and 2 days of gestation. The pregnancy was complicated by tobacco use throughout gestation. The mother received routine prenatal care and her laboratory findings were negative for infections, including group B Streptococcus. Membranes ruptured 2 hours before delivery, and the amniotic fluid was meconium stained. Resuscitation is routine, and the neonate’s Apgar scores are 8 and 9 at 1 and 5 minutes, respectively. The infant’s birthweight of 3,465 g places him in the 50th to 75th percentile for age and his length and head circumference are greater than the 90th percentile for age. He undergoes triage in the well-baby nursery where his admission physical examination findings are normal. He remains with his mother until approximately 22 hours after birth when he develops apnea and respiratory distress.

Radiographs of the chest and abdomen are normal. The infant is transferred to the NICU. On admission, he is noted to have left face and eyelid twitching and left upper extremity stiffening associated with apnea and hypoxemia concerning for seizures. These episodes last 20 to 40 seconds and resolve spontaneously. The patient is given an intravenous phenobarbital load. An arterial blood gas measurement and complete blood cell count are within normal limits. A complete metabolic panel shows normal serum electrolytes, glucose, creatinine, and liver enzymes. A urine toxicology screen is negative. Bacterial blood culture and blood herpes simplex virus (HSV) polymerase chain reaction (PCR) are performed, and a lumbar puncture is attempted but unsuccessful. Umbilical artery and venous catheters are inserted, and intravenous ampicillin, gentamicin, and acyclovir are started. The infant is transferred to a level IV NICU for subspecialty care.

DISCUSSION

Differential Diagnosis

The differential diagnosis of seizures in the newborn includes the following:
ever, FVIII activity is low, at 12% (normal 50%–100%).

The patient is found to have a suboccipital craniectomy and cerebellar hemorrhage evacuation and expansive duraplasty on day 2 after birth, without major complications. The neonate receives 10 mL/kg of fresh frozen plasma (FFP) before the procedure.

Although there was no family history of bleeding disorders, given the severity of the bleed, a bleeding diathesis evaluation is initiated. The patient is found to have a slightly prolonged prothrombin time of 16.9 seconds (normal 10.1–15.9 seconds [1]) and a significantly prolonged activated partial thromboplastin time of 78 seconds (normal 31.3–54.5 seconds [1]). International normalized ratio and fibrinogen are normal. Plasma clotting factor VIII (FVIII), factor IX, and factor XIII activity assays are obtained approximately 6 hours after the patient received FFP. Factors IX and XIII activity are normal for age; however, FVIII activity is low, at 12% (normal 50%–178% [1]).

On postoperative day 1, FVIII replacement therapy is started. The patient receives therapy for a total of 12 days and FVIII activity remains more than 100% while receiving inpatient replacement therapy. Serial postoperative head imaging studies show residual blood in the central nervous system and a decrease in the size of the ventricles without additional hemorrhage.

The patient has no additional seizures and phenobarbital is discontinued. He undergoes extubation on postoperative day 2 and is quickly weaned to room air. The blood culture is without growth and the HSV PCR from the blood is negative. Antibiotics and acyclovir are discontinued on day 3 after birth.

The patient is discharged from the hospital on day 15 after birth without major neurologic deficits. FVIII activity is less than 1% at 1 and 2 months of age consistent with severe hemophilia A. The patient has 1 bleeding episode since discharge lasting several hours after cutting his finger which resolves without medical intervention. He continues to be followed in the hematology and neurosurgery clinics.

**The Condition**

Hemophilia A is an inherited bleeding disorder caused by a functional deficiency of FVIII, a plasma protein necessary for the generation of thrombin and fibrin. (2) Two-thirds of patients with hemophilia have a family history of the disorder, whereas the other one-third of patients represent sporadic cases. (2) Hemophilia A is inherited in an X-linked fashion and is caused by variants in F8, located at the distal portion of the X chromosome. (2) The prevalence of hemophilia A is estimated to be 1 in 4,000 male births in developed countries, with severe hemophilia A accounting for approximately one-third of cases. (3)

The diagnosis of hemophilia A is often made in the setting of a positive family history or after a significant bleeding event in sporadic cases. Coagulation studies often reveal a prolonged partial thromboplastin time (PTT), and the diagnosis is confirmed with plasma factor activity (also called concentration or level). Hemophilia A is classified as mild, moderate, or severe based on the plasma activity of FVIII. (4) If plasma FVIII activity is less than 1% of normal, the hemophilia is designated as severe; if FVIII activity is 1% to 5% of normal, the hemophilia is designated as moderate; and if FVIII activity is greater than 5% but less than 40% of normal, the hemophilia is designated as mild. (4) The severity of clinical manifestations is often proportional to the concentration of factor present. (3) Diagnosing hemophilia in the newborn period presents unique challenges, as neonates have prolonged PTT due to a physiologic reduction in factor IX and other vitamin K-dependent factors. (2) Furthermore, the stress of birth may transiently increase FVIII concentration, further confusing the clinical picture. (2)

Although ICH during the newborn period is infrequent in the general population, it remains a potentially life-
threating complication in patients with hemophilia. (5) The first estimate of the incidence of ICH in patients with hemophilia in the newborn period was made by Baehner and Strauss in 1966. (6) In a cohort of 192 patients with hemophilia, only 1 patient experienced ICH in the newborn period. More recent attempts to quantify the incidence of ICH in the newborn period in patients with hemophilia have placed the number much higher. In a review of several case studies, Ljung estimated the true incidence of ICH in the newborn period in patients with hemophilia in developed countries to be 3.5% to 4%. (7) This is much higher than the ICH incidence in the general population, which occurs in 1 in 1,900 (0.05%) spontaneous vaginal deliveries, 1 in 907 (0.11%) cesarean sections during labor, and 1 in 860 (0.12%) deliveries after vacuum extraction. (8) Like newborns without hemophilia, the risk of ICH and extracranial hemorrhage (subgaleal hemorrhage or cephalohematoma) increases after prolonged delivery or with use of forceps or vacuum extraction. (7)(9) While minimizing trauma in the perinatal period decreases the likelihood of ICH in patients with hemophilia, it does not wholly eliminate the risk, as evidenced by reports of newborns with hemophilia experiencing ICH after elective cesarean section without labor. (10) Although the optimal mode of delivery in infants suspected of having hemophilia remains a topic of debate, it is generally agreed that prolonged labor, difficult deliveries, and use of instrumentation should be avoided if possible. (11)(12)

The neurologic prognosis of newborns with hemophilia who have ICH varies widely among case series. For example, Yoffe and Buchanan reported that 62% of patients in their cohort of newborns with hemophilia and early ICH went on to develop chronic neurologic sequelae. (5) In contrast, Ljung et al had a similar cohort with no patients who developed persistent neurologic sequelae. (13) Most case series report that at least some newborns with early ICH in the setting of hemophilia suffer long-term neurologic consequences, such as seizures, paralysis, and focal neurologic deficits. (5)(7)(9)

Lessons for the Clinician

- Medical providers should be open to the possibility of a diagnosis of bleeding disorders in newborns with ICH even in the absence of pertinent family history or difficult or assisted delivery.
- The risk of early ICH appears to be exacerbated by difficult labor and the use of instrumentation, such as forceps or vacuum extraction, but can occur even in the absence of labor.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Understand the differential diagnosis and evaluation of neonatal seizures.
- Understand the clinical manifestations of neonatal seizures, and their prognosis.
- Know the inheritance patterns of the common coagulation factor deficiencies.
- Know the causes and pathophysiology of acquired defects in hemostasis.
- Know the clinical manifestations, laboratory findings, and management of congenital defects in hemostasis.
References


Hepatosplenomegaly and Periventricular Cyst in a Neonate with Direct Hyperbilirubinemia

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CASE PRESENTATION

An infant is born at 36 weeks to a 27-year-old gravida 4, para 3 woman via precipitous vaginal delivery through meconium-stained amniotic fluid. The pregnancy had been complicated by diet-controlled gestational diabetes. The mother works as a daycare teacher and had traveled to Europe 12 weeks before delivery. She had clinical symptoms of an acute upper respiratory illness 3 weeks before delivery. The neonate’s physical parameters include weight of 2.085 kg (13th percentile), length of 43 cm (38th percentile), and head circumference of 31 cm (16th percentile).

Initial blood glucose level is 23 mg/dL (1.28 mmol/L), and the neonate is given a D10 bolus and maintenance intravenous fluids are started. The neonate’s initial platelet count is 37 × 10³/mL (37 × 10⁹/L) with no active bleeding or oozing. He is noticed to be thrombocytopenic on subsequent complete blood cell counts. A sepsis evaluation is done, blood specimens for culture are drawn, and ampicillin and gentamicin are started. Initial C-reactive protein is 6 mg/dL (60 mg/L) and white blood cell count is 15,000/mL (15 × 10⁹/L). An initial total bilirubin is 18.8 mg/dL (321.5 µmol/L) and direct bilirubin is 10 mg/dL (171 µmol/L). Results of a liver function panel are as follows: alanine aminotransferase (ALT) 117 U/L (1.9 mkat/L), aspartate aminotransferase (AST) <5 U/L. Abdominal ultrasonography reveals hepatosplenomegaly. Result of urine cytomegalovirus (CMV) test is pending at the time of transport.

The infant is transferred to our tertiary NICU for multidisciplinary management of neonatal direct hyperbilirubinemia and transaminitis. Physical examination findings are notable for hepatomegaly, splenomegaly, and petechiae on the abdomen and back. Admission laboratory findings are significant for calcium less than 5 mg/dL (1.25 mmol/L), magnesium 0.6 mg/dL (0.25 mmol/L), albumin 2 g/dL (20 g/L), total bilirubin 23 mg/dL (393 µmol/L), direct bilirubin greater than 16 mg/dL (273.6 µmol/L). ALT 106 U/L (1.7 µkat/L), AST <5 U/L
pregnancy results in the occurrence of cirrhosis in cases defined as neonatal acute liver failure (NALF). All neonatal liver failure is “acute” by definition. The common differential diagnostic considerations include viral infections (20%-30%), hemophagocytic lymphophagocytosis, mitochondrial cytopathy, and gestational alloimmune liver disease, which is the most common cause. HSV is the most common viral agent associated with NALF. Neonates with HSV-associated NALF may have disseminated HSV with or without central nervous system infection. In either of those cases, neonates often lack cutaneous manifestations; therefore, a high index of suspicion is required. CMV is very rarely associated with NALF, but more often with less fulminant hepatitis and prominent cholestasis. Enterovirus should be a consideration in evaluating any neonate with a combination of necrotizing enterocolitis and NALF.

In our case, the urine CMV result from the birth hospital was positive, consistent with a diagnosis of congenital CMV (CMV) and the neonate was subsequently started on ganciclovir. The repeat blood and urine samples tested for CMV at our NICU confirmed the diagnosis, and EBV polymerase chain reaction (PCR) (initially 350 copies/mL and then 1,500 copies/mL) was positive as well. Ganciclovir was switched to oral valganciclovir on postnatal day 6. The neonate failed the otoacoustic emissions test bilaterally. The eye examination performed as part of the evaluation for toxoplasmosis, other infections, rubella, CMV, and HSV (TORCH) syndrome showed posterior embryotoxon. Re-examination after the diagnosis of CMV was made showed no chorioretinitis.

The Condition

Congenital CMV. Human CMV is a human-specific DNA virus of the Herpesviridae family. In the developed world, congenital CMV is the leading nongenetic cause of sensorineural hearing loss (SNHL) in children and accounts for 21% and 24% of cases of hearing loss at birth and 4 years of age, respectively. (i) In addition, congenital CMV is the leading viral cause of neurodevelopmental delay.

The clinical spectrum of congenital CMV varies widely, from asymptomatic infection to potentially life-threatening disseminated disease. Presentation can be with intrauterine growth restriction, preterm labor, petechiae, jaundice, hepatomegaly, splenomegaly, and microcephaly. Laboratory and imaging findings include thrombocytopenia, transaminitis, direct hyperbilirubinemia, SNHL, periventricular calcifications, and rarely, chorioretinitis. Radiographic findings are abnormal in 50% to 70% of children with symptomatic infections at birth and include intracranial calcifications, ventricular dilation, cysts, lenticulostriate vasculopathy, choroidal plexus cyst, and echogenic bowel.

Because infants with congenital CMV shed large amounts of virus in saliva and urine, saliva (at least 1 hour after breast feeding) or urine PCR is used for diagnosis. The treatment of symptomatic congenital CMV disease is...
with intravenous ganciclovir or the oral prodrug valganciclovir. Neonates receiving valganciclovir for 6 months had a 2.6-times higher likelihood of improved total hearing at 12 and 24 months than those who received only 6 weeks of valganciclovir treatment. (2) Neurodevelopmental outcomes on the language composite of the Bayley Scale III were improved with longer duration of therapy.

EBV Infection in Neonates and Pregnancy. Whether the infection with EBV in our case was a coincidence or contributed to the disease severity remains uncertain. EBV is a herpes virus associated with infectious mononucleosis, nasopharyngeal carcinoma, Burkitt lymphoma, B-cell lymphoma, and posttransplant lymphomas. Infection with EBV is extremely common and 90% of adults in the United States are seropositive before the age of 30 years. Purtilo and Sakamoto (3) reported that EBV reactivation in pregnancy is a much more common occurrence than primary infection due to the high rates of seroprevalence.

Transmission of EBV is usually horizontal, requiring close contact with the saliva of an infected person; vertical transmission is felt to be rare. Several case reports of fetal outcomes of EBV infection during pregnancy have been published, but there is no specific syndrome that can be described as an outcome of EBV infection during pregnancy.

In a cohort of 500 women whose serum samples were studied for EBV nuclear antigen early in pregnancy, 28 neonates had anomalies. Of these, 16 had minor anomalies and 12 had major anomalies including congenital heart disease, microcephaly, anencephaly, meningomyelecele, and achondroplasia. (4) In a case report by Brown and Stenchever, (5) severe congenital anomalies were described in an infant exposed to EBV infection from conception to delivery. Another case report described congenital anomalies such as cryptorchidism, micrognathia,
cataract, and hypotonia in a male infant exposed to EBV during pregnancy. Two other reports described liver and bile duct anomalies in infants exposed to EBV during pregnancy. A case control study of 403 infants born to mothers with EBV infection at 12 to 14 weeks of gestation suggested an increased risk for leukemia.

To our knowledge, this is the third case in literature to report coinfection with CMV and EBV in neonates. Two previous cases were reported by Joncas et al (Table). (6) Although congenital CMV could explain all of this infant’s findings, the severity may have been due to concurrent in utero infection with CMV and EBV.

Follow-up

Our patient was discharged on postnatal day 17, with infectious disease, hepatology, ophthalmology, and audiology follow-up. Currently, at 2 years of age, he has not undergone brainstem auditory evoked response testing but has speech delay.

Lessons for the Clinician

- Congenital CMV should be considered in the differential diagnosis of neonates born with cholestasis and thrombocytopenia.
- Maternal history can serve as an important clue to guide postnatal evaluation. In the case described herein, the maternal history of working as a daycare teacher and developing symptoms of upper respiratory infection before delivery was important.

### American Board of Pediatrics

**Neonatal-Perinatal Content Specifications**

- Know the various etiologies, including bacterial, viral, and protozoal agents, and clinical manifestations of hepatitis in the newborn.
- Know the incidence, causes, risk factors, and management of congenital hearing loss in the neonate.

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**Table.** Coinfection with EBV and CMV During Pregnancy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Findings</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current case</td>
<td>Case report: neonatal coinfection with CMV and EBV</td>
<td>Hepatitis, thrombocytopenia, direct hyperbilirubinemia, petechiae, hepatosplenomegaly</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diagnosis: PCR blood for CMV and EBV</td>
<td>Follow-up with resolution of hepatitis but the infant developed progressive developmental delay and SNHL</td>
</tr>
<tr>
<td>Joncas et al (6)</td>
<td>2 case reports: infant with CMV/EBV</td>
<td>Petechial rash, hepatosplenomegaly, thrombocytopenia, periventricular calcification. Diagnosis: Positive IgM titers for CMV and EBV</td>
<td>Gross motor delay with speech delay</td>
</tr>
</tbody>
</table>

CMV=cytomegalovirus; EBV=Epstein-Barr virus; IgM=immunoglobulin M; PCR=polymerase chain reaction SNHL=sensorineural hearing loss.
References


A Floppy Infant with Facial Dysmorphism

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HISTORY

A male neonate was born small for gestational age with a birthweight of 2.36 kg to a 32-year-old gravida 2 woman in a third-degree consanguineous marriage. The mother’s history included a spontaneous abortion at 10 weeks of gestation in the previous pregnancy. The current pregnancy was a product of spontaneous conception. The antenatal period in this pregnancy was uneventful, with regular follow-ups. The mother also took iron and folic acid supplementation along with tetanus toxoid immunization. She has no history of fever, rash, or any teratogenic exposure during pregnancy. Screening for gestational diabetes, hypertension, and thyroid disorders in this pregnancy found no abnormalities. Targeted imaging for fetal anomalies at 20 weeks of gestation had normal findings. Subsequent growth scans showed polyhydramnios but the growth pattern was appropriate for gestational age. The neonate was delivered at 37 weeks and 6 days of pregnancy via emergency caesarean section in view of decreased fetal movements. The amniotic fluid was clear at the time of birth. The neonate did not cry immediately after birth and required positive pressure ventilation for 30 seconds. His Apgar scores were 7, 8, and 8 at 1, 5, and 10 minutes, respectively. Cord arterial blood gas analysis revealed a pH of 7.23, base excess −5.6 mmol/L, PCO₂ 46 mm Hg (6.12 kPa), PO₂ 24 mm Hg (3.19 kPa), and lactate 1.8 mmol/L (0.2 mmol/L). There is no significant history suggestive of unexplained death or any genetic disease in other family members.

PRESENTATION

In view of the respiratory distress, the neonate was transferred to the NICU. Oxygen support was started in the form of nasal prongs. Vital signs on examination were as follows: heart rate 128 beats/min, respiratory rate 62 breaths/min, temperature 97.7°F (36.5°C), oxygen saturation 98% via nasal prongs, and blood pressure 66/50 mm Hg (mean 42 mm Hg). On examination, the neonate’s weight, length, and head circumference were 2,360 g (5th percentile), 48 cm (30th percentile), and 32.5 cm (20th percentile), respectively. On general examination, facial dysmorphism was noted in the form of large fontanels with wide sutures, low-set ears, hypertelorism, periorbital puffiness with hazy cornea,
depressed nasal bridge with broad nose, and high arched palate (Fig 1A). There was a redundant skinfold over the nape of the neck. Simian crease and bilateral clubfoot were also noted (Fig 1B). The testes were undescended. Detailed neurologic examination revealed a lethargic neonate with diminished arousal response and markedly diminished motor responses. Deep tendon reflexes were also difficult to elicit, with weak cry and poor sucking and swallowing reflex. The neonate was grossly hypotonic with significant head lag and shoulder hypotonia (Fig 1C). Prolongation of secretions was also noted, with minimal response to light and sound. Abdominal examination revealed a firm liver that was palpable 2 cm below the right subcostal margin with a smooth surface and no splenomegaly.

As breathing became shallow and respiratory distress increased, with oxygen saturation falling below 90%, the neonate was moved to oxygen via high-flow nasal cannula with a flow of 6 L/min. The breathing pattern improved later and respiratory supports were weaned off. The neonate was moved on free flow oxygen intake to the mother's side in a postnatal room. Supportive therapies were started in the form of oromotor stimulation, physiotherapy, and non-nutritive sucking. Gradually, he started to feed through a cuplike utensil with a narrow tip used for feeding in India (“paladai”) from day 3. Minimal improvement was seen in tone and level of consciousness by day 7. He was discharged on day 15 after birth after the mother learned how to care for him. He developed seizures at 1 month of age, which required readmission, and he was started on antiseizure medication. He did not attain any milestones on follow-up and died at 5.5 months of age due to respiratory illness.

**EVALUATION**

The neonate was initially evaluated with arterial blood gas analysis, sepsis screening, measurement of serum glucose, calcium, and electrolytes, and expanded newborn screening for neonatal sepsis and metabolic derangements. Laboratory investigation revealed normal arterial blood gas analysis, sepsis screening (total white blood cell count 4,000/μL [4 × 10⁹/L]), C-reactive protein 0.04 mg/dL [0.4 mg/L]), and basic metabolic panel (serum glucose 65 mg/dL [3.6 mmol/L], total serum calcium 9.7 mg/dL [2.4 mmol/L], serum sodium 141 mEq/L [141 mmol/L], and serum potassium 4.2 mEq/L [4.2 mmol/L]). Liver function parameters revealed a total bilirubin of 7.8 mg/dL [133.4 μmol/L], aspartate aminotransferase 24 U/L [0.4 μkat/L], and alanine aminotransferase 34 U/L [0.6 μkat/L]. Thyroid-stimulating hormone was 1.45 μIU/mL on day 3. Titers for toxoplasmosis, other agents, rubella, cytomegalovirus, and herpes simplex (TORCH) syndrome were also within normal limits. Findings of expanded newborn screening and tandem mass spectrometry were normal, with no metabolic derangements. Total creatine phosphokinase level was 158 U/L (2.6 μkat/L; reference value <652 U/L [10.9 μkat/L]). Neurosonography revealed bilateral pseudocysts of germinal matrix with mild ventriculomegaly. Ophthalmologic evaluation revealed hypopigmented iris and fundus with hazy cornea. Two-dimensional echocardiography indicated a 1-mm closing patent ductus arteriosus on day 2. Abdominal ultrasonography revealed mild hepatomegaly with bilateral mild pelviectasis in the kidneys without any cystic changes. Skeletal survey showed a narrow chest (Fig 2A) with punctuate calcifications at the knee joint.

**Figure 1.** A. Facial dysmorphism. B. Bilateral varus deformity. C. Floppy infant.

**Figure 2.** A. Radiograph showing bell-shaped thorax. B. Infantogram showing punctate calcifications at knee joint.
Magnetic resonance imaging (MRI) and genetic testing confirmed the diagnosis.

**DIAGNOSIS**

Brain MRI showed cysts in the caudothalamic groove bilaterally, abnormal sulcation in the frontal and parietal lobes with extensive polymicrogyria of both, and sylvian fissure with no evidence of hypoxic injury (Fig 3A and 3B). Based on all these findings, a presumptive diagnosis of peroxisomal disorder was made.

Clinical exome sequencing showed a pathogenic homozygous variant, c.589C>T (p.Gly197Ter) (NM_001199319), in exon 4 of the PEX26 gene known to cause Zellweger syndrome. This variant was absent from population databases with low minor allele frequency in the in-house database. In-silico predictions reported it to be damaging, with a combined annotation-dependent depletion score of 36.0, and a codon that was conserved across mammalian species. This variant was consistent with the presumptive diagnosis of the child. Both parents are heterozygous carriers for the same variant identified in the child.

**DISCUSSION**

Peroxisomal disorders comprise a wide spectrum of clinically and genetically heterogeneous disorders. They are classified into 2 subgroups: peroxisome biogenesis disorders and single peroxisomal enzyme deficiency. The prototype of peroxisomal biogenesis disorders is classic Zellweger syndrome. Zellweger syndrome, also known as cerebrohepatorenal syndrome, is a rare genetic disorder which comes under the group of peroxisomal biogenesis disorder.

It is an autosomal recessive disorder characterized by a defect in peroxisome biogenesis caused by a mutation in one of the PEX genes (i). PEX genes encode proteins called peroxins and are involved in either peroxisome formation or peroxisomal protein import or both (ii). These mutations in PEX genes result in deficiency of functional peroxisomes. These gene defects were earlier named to the spectrum of disorders known as Zellweger syndrome, neonatal adrenoleukodystrophy (ALD), infantile Refsum disease, and rhizomelic chondrodysplasia punctata. (iii) Among the first 3 disorders, Zellweger syndrome is the most severe, infantile Refsum the least severe, and neonatal ALD is of intermediate severity. Defective peroxisomal function can lead to impaired fatty acid metabolism, leading to the accumulation of very long chain fatty acids, phytanic and pristanic acids, C27-bile acid intermediates, and pipecolic acid in plasma, and can have deficiency of plasmalogens in erythrocytes. (iv) Accumulation of all these metabolites leads to multiorgan dysfunction including neurodevelopmental delay, liver dysfunction, developmental delay, adrenocortical dysfunction, and hearing and vision impairment.

Facial profile is also characteristic in the early phase of infancy. (v) In our case, the neonate's facial profile was not similar to that seen with Zellweger syndrome, but he had central hypotonia and characteristic MRI brain findings. (vi) Increased levels of very long chain fatty acid and phytanic acid and urinary metabolites like pipecolic acid were not detected in our case. Patients with mild Zellweger syndrome disorders may have near-normal biochemical findings in plasma and urine. (vii) Among the differential disorders to consider, single peroxisomal enzyme deficiencies especially Acyl-CoA oxidase type 1 deficiency and D-bifunctional protein deficiency show several overlapping clinical features. (viii) At present, there is no curative treatment for Zellweger syndrome. Treatment is mainly supportive like ensuring proper calorie intake by means of a proper feeding protocol, physiotherapy, and early stimulation and interventions for sensory and motor system and intake of fat-soluble vitamins with phytanic acid–restricted diet. Holistic care requires involvement of a multidisciplinary team including pediatricians, neurologists, audiologists, ophthalmologists, and orthopedists. Preventive measures should be taken against acquiring respiratory tract infections. The cause of death usually is gastrointestinal bleeding and liver failure.

**Lessons for the Clinician**

Zellweger syndrome should be considered in the differential diagnosis of a neonate with central hypotonia with dysmorphism. Confirmation of the diagnosis requires good clinical expertise with adequate collaborative efforts of the neonatologist, geneticist, pediatric neurologist, and radiologist.
American Board of Pediatrics
Neonatal-Perinatal Content
Specifications

- Know the disorders for which molecular genetic studies are clinically indicated, such as cystic fibrosis, and how to interpret test results.
- Recognize the diagnostic implications of single vs. multiple anomalies.
- Recognize the clinical features and know how to diagnose and manage congenital anomalies of the lower extremities, such as metatarsus adductus, talipes equinovarus, syndactyly, polydactyly, limb reduction.
- Know the clinical features and inheritance patterns of common syndromes or associations that can be recognized in the newborn period (eg, VATER association and DiGeorge syndrome).
- Know the indications, limitations, and techniques for newborn screening for genetic disorders.
- Know physical findings indicative of neonatal encephalopathy.
- Know the basis for (including genetic, clinical and laboratory features (including associated abnormalities), differential diagnosis, evaluation, management, and outcomes of neonatal hypotonia/neuromuscular weakness.

References

Whole Genome Sequencing: Early Diagnostic Tool in Newborns with Refractory Seizures

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THE CASE
A term male infant born at an outlying hospital to nonconsanguineous parents was transferred immediately after birth due to facial dysmorphisms and limb abnormalities (Figs 1A, 1B, 1C).

Prenatal and Birth History
- Born to a 24-year-old gravida 1, para 0 white woman.
- Pregnancy complicated by mild oligohydramnios at 36 weeks’ gestation that resolved with hydration; prenatal ultrasonography findings unremarkable with consistent fetal movement throughout pregnancy
- Cesarean section at 38 weeks’ gestation for breech presentation
- Prenatal maternal laboratory findings: Group B Streptococcus negative, hepatitis B surface antigen negative, rubella immune, HIV negative, rapid plasma reagin nonreactive
- Apgar scores: 4 and 9 at 1 and 5 minutes, respectively

Presentation
The infant was cyanotic and hypotonic at birth with no respiratory effort. He required positive pressure ventilation for approximately 2 min and was then transitioned to nasal cannula oxygen. His tone improved by 5 minutes of age. He was transported to a level 3 NICU for evaluation of his dysmorphic features.

PROGRESSION
Vital Signs (Newborn Day)
- Heart rate: 160 beats/min
- Respiratory rate: 40 breaths/min
- Blood pressure: 57/41 mm Hg
- Oxygen saturation: 97% (on high-flow nasal canula 5 L/min, fraction of inspired oxygen 0.3)
- Temperature: 99.1°F (37.3°C)
Physical Examination (Newborn Day)
- Birthweight: 2,640 g (10th percentile), length: 48.5 cm (37th percentile), head circumference: 35.8 cm (85th percentile)
- Head: Cranial molding; microcephaly; retrognathia; micrognathia; long, downward-slanting palpebral fissures; low-set ears; prominent nose; broad nasal bridge
- Cardiovascular: Regular rate and rhythm; normal S1, S2; no murmurs
- Lungs: Clear and equal bilaterally; no respiratory distress
- Chest wall: Pectus carinatum, wide-spaced nipples
- Abdomen: Soft, nontender; no masses; 3-vessel cord
- Genitourinary: Normal male genitalia; testes descended; patent anus
- Skeletal: Ulnar deviation of bilateral wrists; arachnodactyly; bilateral talipes equinovarus; arthrogryposis
- Skin: Bruising of bilateral lower extremities; no sacral tufts or dimples
- Neurologic: Awake, alert with spontaneous movement of all extremities with increased tone and contractures; intermittent myoclonic movements with tactile stimulation

On the second day after birth, he was observed to have myoclonic events that were associated with vital sign instability and staring that lasted 10 to 15 seconds. Video electroencephalography confirmed epileptiform activity. The seizures were multifocal, brief, and clustering, with multiple episodes in a 12-hour period. He was supported with orogastric feedings and high-flow nasal cannula while an extensive evaluation was initiated.

Laboratory Studies
Investigative studies within normal limits:
- Infectious evaluation: C-reactive protein, blood and urine cultures, cerebrospinal fluid (CSF) meningoencephalitis panel

Figure 1. A. Photograph showing the infant’s overall appearance, including a broad nose, micrognathia, arthrogryposis of the upper and lower extremities and bilateral talipes equinovarus. B. Photograph showing retrognathia and low-set ears. C. Photograph showing a broad chest with wide-spaced nipples.
Abnormal laboratory findings with unclear significance:

- CSF triene/tetraene ratio 0.099 (normal 0.017–0.083)
- CSF linoleic acid 288 nmol/mL (normal 30–170 nmol/mL)
- Serum taurine 7 nmol/mL (normal 8–48 nmol/mL)
- Serum α-amino-n-butyric acid 5 nmol/mL (normal 7–28 nmol/mL)
- Serum ammonia 40.6 μg/mL (28 μmol/L; normal 75.5–126 μg/mL [54–90 μmol/L])
- Serum 3-methylhistidine 3 nmol/mL (normal <1 nmol/mL)

Radiographic Studies

- Radiography (Fig 2) showed prominent cardiothymic silhouette and mild thoracolumbar scoliosis
- Brain magnetic resonance imaging (MRI) without contrast showed diffuse, mild undersulcation and underopercularization; mildly prominent extra-axial CSF; thinning of posterior corpus callosum (Figs 3 and 4)

The infant continued to have subclinical seizures despite multiple antiepileptic drugs (AEDs), including phenobarbital, levetiracetam, phenytoin, and topiramate. Due to the risk of respiratory depression with additional medications, the care team decided to not increase the AED dosages any further and monitor clinically for seizure activity. Given that the extensive laboratory and radiographic studies were unrevealing, the team decided to perform additional genetic testing. A family history revealed that the parents were non-consanguineous. A maternal aunt had died at 8 months of age from a presumed seizure disorder present from birth and a maternal uncle had died at several weeks of age of sudden unexpected infant death. Parental consent was obtained for rapid whole genome sequencing (rWGS), which was performed during the infant’s second week of age, and results were obtained within 5 days.

DIFFERENTIAL DIAGNOSIS

- Congenital brain malformation (anencephaly, Chiari malformation, holoprosencephaly, Dandy Walker spectrum, agenesis of the corpus callosum)
- Neuromuscular disorder (spinal muscular atrophy with progressive myoclonic epilepsy)
- Congenital disorders of glycosylation
- Essential fatty acid disorder
- Urea cycle disorder
- Amino acid disorder
- Chromosomal abnormality
- Single gene or multifactorial genetic disorder

ACTUAL DIAGNOSIS

Single gene or multifactorial genetic disorder

The results of the infant’s rWGS showed maternal heterozygous mutation of the c.294dup (p.Leu99ThrfsTer92) variant and paternal heterozygous mutation of the c.638dup (p.Val214GlyfsTer18) variant. These results were consistent with a compound heterozygous BRAT1 mutation that is associated with rigidity and multifocal seizure syndrome, lethal neonatal (RMFSL). A multidisciplinary care conference was held that included the neonatologist, pediatric neurologist, social worker, nurse, and case manager. The team discussed with the parents that this diagnosis is rare, and as a result, it is difficult to provide a definitive prognosis for the infant. Various management options were discussed with the family which included, but were not limited to, continuing full support with escalating care if needed and comfort care with home hospice.

Figure 2. Radiograph showing prominent cardiophymic silhouette and mild thoracolumbar scoliosis.
The parents elected to continue current management in addition to trying a ketogenic diet to attempt to lessen the infant’s seizure burden.

At 2 weeks of age, the infant was transferred to a facility with expertise in a ketogenic diet. The infant continued to have myoclonic activity with tactile stimulation, and contractures of his extremities were still present but slightly improved. He continued to have multiple clinically significant seizures and ultimately developed respiratory failure requiring intubation. After 5 days on the ketogenic diet, the infant had not achieved ketosis. The parents elected to proceed with hospice care. He died of cardiopulmonary failure at 1 month of age.

**WHAT THE EXPERTS SAY**

We describe a white term male infant born to nonconsanguineous parents with facial dysmorphisms, limb abnormalities, and AED-resistant seizures requiring respiratory and enteral support and who was found to have a compound heterozygous BRAT1 mutation.

The infant’s brain MRI on the first day after birth showed diffuse cerebrum underdevelopment. There were no other structural abnormalities indicating a disorder of dorsal induction, ventral induction, or myelination. Serum analysis of essential fatty acids and amino acids was part of the diagnostic evaluation as these components have been implicated in poor neurologic development. As seen in the infant’s laboratory studies, he had elevated levels of essential fatty acids with low levels of ammonia and specific amino acids. The significance of these results was not clear and did not result in a specific diagnosis.

BRAT1 mutations have been associated with RMFSL and neurodevelopmental disorder with cerebellar atrophy, with or without seizures. We conducted a literature review and found that since 2012, BRAT1 mutations have been reported in 26 patients, all with a spectrum of neurodevelopmental and phenotypic anomalies but 1 common variable of refractory seizures (Table). Many of these cases have also reported abnormalities on the brain MRI consistent with global underdevelopment of the cerebrum and cerebellum. These findings include mild hypoplasia of the frontal lobes, delayed or decreased myelination, thin corpus callosum, cerebellar hypoplasia, and prominent pericerebral extra-axial space. The cases in which the patient survived long enough to have serial imaging reported a progressive atrophy. The magnitude of the abnormality noted on brain MRIs was not found to be predictive of prognosis. In prior case reports, 12 infants died at or before age 6 six months, 5 before age 2 years, and 1 at age 5 years. (1)(2)(3)(4)(5)(6)(7)(8) Eight patients were reported to have milder symptoms and lived until their childhood years. (3)(9)(10)(11)(12) One study suggested the possibility that homozygous mutations may have a more severe presentation than compound heterozygous. (8) However, our patient presented with severe disease in the neonatal period despite having a compound heterozygous mutation. The extent to which the inheritance pattern affects the severity of the RMFSL may be more complex than initially thought, as patients with both homozygous and compound heterozygous mutations can present with severe symptoms. This raises the question as to whether the true diagnosis is a single gene disorder or multifactorial disorders.
**Table.** Summary of Case Reports of Patients with RMFSL from 2012–2019

<table>
<thead>
<tr>
<th>Reference (No. of Patients)</th>
<th>Timing of WES/WGS</th>
<th>Dysmorphic Facies</th>
<th>Microcephaly</th>
<th>Seizure Type and Onset (If not Neonatal)</th>
<th>Abnormal Brain MRI</th>
<th>Treatments Leading to Clinical Improvement</th>
<th>Invasive Interventions</th>
<th>Age at Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puffenberger et al (1) (n=3)</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Yes</td>
<td>Multifocal</td>
<td>Yes</td>
<td>N/A</td>
<td>Tube feeding</td>
<td>All less than 4 mo</td>
</tr>
<tr>
<td>Saunders et al (13) (n=1)</td>
<td>After 5 weeks; patient already placed on comfort care at that time</td>
<td>Yes</td>
<td>Yes</td>
<td>Focal</td>
<td>No</td>
<td>Transient improvement with pyridoxine</td>
<td>Intubation</td>
<td>2 mo</td>
</tr>
<tr>
<td>Saitou et al (2) (n=2)</td>
<td>Pt 1: Not performed</td>
<td>Yes</td>
<td>Yes</td>
<td>Pt 1: GTC and myoclonic</td>
<td>Yes</td>
<td>Improvement in apneic spells with zonisamide</td>
<td>Not specified</td>
<td>21 mo and 3 mo</td>
</tr>
<tr>
<td>Mundy et al. (9) (n=1)</td>
<td>Not specified</td>
<td>Yes</td>
<td>Yes</td>
<td>3 mo</td>
<td>Yes</td>
<td>N/A</td>
<td>Not specified</td>
<td>Alive at 6 y</td>
</tr>
<tr>
<td>Hanes et al (11) (n=1)</td>
<td>Around age 2 y</td>
<td>Yes</td>
<td>Yes</td>
<td>Focal onset impaired awareness</td>
<td>Yes</td>
<td>Valproic acid</td>
<td>N/A</td>
<td>Alive at 3 y</td>
</tr>
<tr>
<td>Straussberg et al (5) (n=2)</td>
<td>Not specified</td>
<td>Yes</td>
<td>Yes</td>
<td>Myoclonic</td>
<td>No</td>
<td>N/A</td>
<td>Gastrostomy tubes in both patients</td>
<td>5 mo and 6 mo</td>
</tr>
<tr>
<td>Van de Pol et al (14) (n=3)</td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3, 17, and 2 mo</td>
</tr>
<tr>
<td>Srivastava et al (12) (n=4)</td>
<td>Not specified</td>
<td>Yes</td>
<td>Yes</td>
<td>Pt 1: No seizures</td>
<td>Yes</td>
<td>Pt 3: Levetiracetam</td>
<td>Pt 4: Tracheostomy, gastrostomy</td>
<td>Pt 1: Alive at 10 y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pt 2: Staring spells</td>
<td></td>
<td></td>
<td></td>
<td>Pt 2: Alive at 6 y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pt 3: Staring spells</td>
<td></td>
<td></td>
<td></td>
<td>Pt 3: Alive at 4 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pt 4: Focal/tonic; focal electrographic status epilepticus</td>
<td></td>
<td></td>
<td></td>
<td>Pt 4: Alive at 16 mo</td>
</tr>
<tr>
<td>Smith et al (3) (n=2)</td>
<td>Not specified</td>
<td>Yes</td>
<td>Yes</td>
<td>Onset at 4 and 8 mo</td>
<td>Pt 1: Yes</td>
<td>N/A</td>
<td>Not specified</td>
<td>Pt 1: 15 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pt 2: Not reported</td>
<td></td>
<td></td>
<td></td>
<td>Pt 2: Alive at 4 y, 4 mo</td>
</tr>
<tr>
<td>Horn et al (4) (n=2)</td>
<td>Not specified</td>
<td>Yes</td>
<td>Yes</td>
<td>Pt 1: Myoclonic, started at 5 mo</td>
<td>Pt 1: No</td>
<td>N/A</td>
<td>Pt 1: Gastrostomy</td>
<td>5 y and 2 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pt 2: Myoclonic</td>
<td>Pt 2: No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pt 2: NG tube, muscle biopsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fernández-Jaén et al (10) (n=1)</td>
<td>Not specified</td>
<td>No</td>
<td>Yes</td>
<td>No seizures; developmental delay only</td>
<td>Yes</td>
<td>N/A</td>
<td>N/A</td>
<td>Alive at age 4 y</td>
</tr>
<tr>
<td>Celik et al (8) (n=1)</td>
<td>Not specified</td>
<td>No</td>
<td>Yes</td>
<td>Myoclonic</td>
<td>Yes</td>
<td>N/A</td>
<td>Gastrostomy, tracheostomy</td>
<td>10 mo</td>
</tr>
<tr>
<td>Van Ommeren et al (6) (n=1)</td>
<td>Not reported; results led to initiation of palliation</td>
<td>Yes</td>
<td>Yes</td>
<td>Myoclonic</td>
<td>Yes</td>
<td>N/A</td>
<td>Intubation; palliation from 6 wk</td>
<td>10 wk</td>
</tr>
<tr>
<td>Szymańska et al (7) (n=2)</td>
<td>Not specified</td>
<td>Yes</td>
<td>Reported in 1 of 2 patients</td>
<td>Myoclonic, polymorphic</td>
<td>Yes</td>
<td>N/A</td>
<td>Not reported</td>
<td>6 mo and 12 mo</td>
</tr>
<tr>
<td>Current patient</td>
<td>2 weeks</td>
<td>Yes</td>
<td>Yes</td>
<td>Myoclonic</td>
<td>Yes</td>
<td>N/A</td>
<td>Intubation, NG feeding</td>
<td>2 mo</td>
</tr>
</tbody>
</table>

GTC=generalized tonic-clonic, MRI=magnetic resonance imaging, N/A=not available, NG=nasogastric, Pt=patient, WES=whole exome sequencing, WGS=whole genome sequencing.
In most of the previous case reports, the timing of genetic testing relative to the onset of symptoms was not clear. Many of these infants had progressed to requiring interventions such as gastrostomy tube and/or tracheostomy and underwent multiple studies that yielded results of unknown significance. (4)(5)(6)(8)(12) In infants with AED-refractory seizures in the NICU, the use of rWGS has yet to become an established norm during the evaluation. WGS has become more cost-effective with a shorter test-result time and high analytic specificity and sensitivity of more than 99.5%, making it one of the most comprehensive tests currently available.

A spectrum of clinical severity has been found to be associated with RMFSL. Our patient had findings most consistent with a severe form of RMFSL that results in early death at 2 months of age. Several affected individuals, including our patient, have common features of intractable seizures, facial dysmorphisms, and brain underdevelopment. Other congenital brain malformations were less likely in this case as no other structural abnormalities were noted on the brain MRI. Certain neuromuscular disorders were ruled out with a normal newborn screen and no specific laboratory result confirmed a disorder of glycosylation, fatty acid metabolism, or urea cycle or amino acid metabolism. The chromosomal array did not detect any gene duplication or deletion.

Although some patients with RMFSL present with later onset of disease, attenuated symptoms, and prolonged survival, others present with early onset, severe symptoms, and early death. This report aims to raise awareness of RMFSL and its variable presentations and to recognize the usefulness of rWGS in cases of intractable seizures from an unknown cause. Early identification of a genetic diagnosis may facilitate discussions between care teams and families and help guide often difficult management decisions. More frequent utilization of rWGS may reveal a higher prevalence of RMFSL than previously reported, which in turn, may create advocacy for research into possible treatments and facilitate the development of a support network for families affected by this rare disease.

**American Board of Pediatrics Neonatal-Perinatal Content Specifications**

- Know when to obtain karyotypes on the subject, parents, or other family members.

**References**


A male infant with a birthweight of 2,500 g (between the 3rd and 10th percentile) is born at 37 weeks gestation to a 27-year-old primigravida woman with severe polyhydramnios (amniotic fluid index of 37 cm). After delivery, the neonate is vigorous, with Apgar scores of 8 and 9 at 1 and 5 minutes of age, respectively. He develops excessive frothy oral secretions, and the neonatology team is unable to pass a nasogastric tube. Chest radiography shows the coiling of a nasogastric tube with air in the stomach suggestive of esophageal atresia (EA) with tracheoesophageal fistula (TEF).

On day 4 of age, a primary surgical repair of the TEF with eso-esophageal anastomosis is performed under mild tension. Initially, the neonate receives minimal ventilator settings (mean airway pressure 8 cm H₂O, positive end-expiratory pressure of 5 cm H₂O, and fraction of inspired oxygen [FiO₂] 0.21) for 4 days. Three days after surgery, the neonate undergoes extubation to noninvasive positive pressure ventilation and is then weaned to high-flow nasal cannula on postoperative day 4. Soon after extubation, the infant develops intermittent stridor but is weaned to high-flow nasal cannula by postoperative day 4. The stridor progresses over the next 48 hours, and a video of the infant at that time is shown (Video 1).

QUESTION 1

The stridor in this infant occurs in which of the following phases of respiration?

A. Inspiratory phase
B. Expiratory phase
C. Biphasic

The infant’s stridor was present at rest but worsened with crying. There was no significant decrease in stridor with neck extension and prone position. An intravenous dexamethasone trial was given after extubation for 3 days with no clinical improvement. The neonate’s baseline oxygen saturation in room air was between 90% and 92%; however, with high-flow nasal cannula (flow of 5 L, FiO₂ 0.21), the oxygen saturations increased to 94% to 98%. To determine the
cause of the stridor, flexible bronchoscopy was done transnasally using a 2.8-mm video bronchoscope (Video 2); this procedure was performed with minimal sedation to ensure spontaneous respirations.

QUESTION 2

Based on this infant’s clinical course and findings in the flexible bronchoscopy, the most likely diagnosis in this infant is:

A. Double aortic arch
B. Laryngomalacia
C. Subglottic edema or stenosis
D. Tracheomalacia
E. Vocal cord palsy

DISCUSSION

In infants with stridor, a careful clinical assessment of the stridor can provide information about the type, severity, and level of obstruction. In Video 1, the infant has inspiratory stridor during agititation that is associated with supra-sternal and sternal retractions and oxygen desaturations. In addition, the infant’s hoarse cry suggests vocal cord swelling or injury. Of note, bronchoscopy (Video 2) reveals that the infant has reduced and paradoxical vocal cord movements (Figs 1 and 2), suggestive of bilateral vocal cord paralysis (VCP). The video also demonstrates the presence of a repaired TEF in the posterior wall of the midtrachea (Figs 3 and 4) with nonpulsatile narrowing of the trachea. There was no variability with respirations, thus ruling out tracheomalacia. The lower trachea appeared normal. The infant’s improvement in oxygen saturations with high-flow cannula was likely because of the airway stents. The infant was discharged with orogastric feedings at 3 weeks; he did not have any stridor and was feeding well on follow-up at 3 months of age.

VCP is the absence of movements of the vocal folds following dysfunction of the recurrent laryngeal nerve. This nerve is a branch of the vagus nerve that runs along the lateral surfaces of the trachea near the tracheoesophageal groove and is vulnerable to injury during surgeries of the neck and thorax. (1) Similar to the patient in this case, bilateral VCP presents with inspiratory stridor at rest that worsens upon agitation. VCP has been reported to occur in 3% to 11.2% of patients following EA/TEF repair. (1)(2) According to a retrospective review, 48% of the postoperatively diagnosed cases were bilateral, and the etiology was mostly (43%) iatrogenic. (3)(4)

A double aortic arch is a rare cause of stridor in infants and is known to be associated with EA/TEF. (5) The mean
Age at diagnosis for this vascular ring is 6 months, but it can present earlier. The clinical features are related to compression of the esophagus and trachea, such as dysphagia or difficulty in feeding and stridor in the expiratory phase. Computed tomography angiography is considered the gold standard for diagnosis. In children with a double aortic arch, flexible bronchoscopy may show pulsatile compression in the midtrachea.

Laryngomalacia typically presents with inspiratory stridor and is the most common cause of congenital stridor in neonates. (6) Affected patients typically have inspiratory stridor that increases with feeding, crying, agitation, supine positioning, and upper respiratory tract infections. In patients with laryngomalacia, the inspiratory stridor decreases with neck extension and in the prone position. In this case, the infant had stridor mainly when crying, with no significant decrease in stridor with neck extension and prone position, making laryngomalacia less likely. (7) In a retrospective study, laryngeal anomalies were associated with approximately 30% of cases of TEF, and of these, 4.3% were found to be laryngomalacia. (8) Movements of laryngeal structures should be analyzed in a spontaneously breathing infant to diagnose laryngomalacia. During bronchoscopy, an omega-shaped epiglottis with inspiratory supraglottic tissue collapse is the hallmark of laryngomalacia. (6) However, in our case, flexible bronchoscopy did not demonstrate these findings, thus ruling out laryngomalacia.

Subglottic stenosis can be congenital or acquired. Acquired subglottic stenosis has been recognized as a postoperative complication in 12.9% of TEF patients. (8) It has also been seen as a result of subglottic injury caused by endotracheal intubation, especially if prolonged. The presence of stridor during both phases of respiration remains the most common symptom of a subglottic lesion, which was not noted in our patient. Flexible bronchoscopy ruled out the possibility of stenosis or edema.

The incidence of congenital tracheomalacia has been reported to be at least 1 in 2,100 and has been found to be associated with EA. (4) Indeed, a retrospective study found that tracheomalacia is the most common airway finding in 37.4% of patients with TEF. (8) Localized secondary tracheomalacia may occur due to compression from a vascular malformation (such as a double aortic arch). (5) Acquired forms of tracheomalacia may develop as a result of prolonged ventilation, tracheostomy, or severe tracheobronchitis. Intrathoracic tracheomalacia causes excessive trachea collapse during expiration, whereas extrathoracic tracheomalacia causes tracheal collapse during the inspiratory phase. This leads to the presence of monophonic (expiratory) wheezing in patients with intrathoracic tracheomalacia and inspiratory or biphasic stridor in patients with extrathoracic tracheomalacia. In addition to these symptoms, a ‘barking cough’ and increased work of breathing is often present. In a patient with tracheomalacia, bronchoscopy typically shows dynamic tracheal compression with respiration, which was not found in our patient. Preoperative bronchoscopy is not a routine practice; instead, it is need-based.

Correct Responses:

**Question 1:** A. Inspiratory phase

**Question 2:** E. Vocal cord palsy

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**American Board of Pediatrics Neonatal-Perinatal Content Specifications**

- Know the clinical features of an infant with airway obstruction.
- Plan appropriate diagnostic evaluation and management for an infant with airway obstruction.
Acknowledgment
We wish to thank Dr Ramji Bhardwaj and Dr Manazir Hasan Rahmani for producing and editing the video.

References
2. Mortellaro VE, Pettiford JN, St Peter SD, Fraser JD, Ho B, Wei J. Incidence, diagnosis, and outcomes of vocal fold immobility after esophageal atresia (EA) and/or tracheoesophageal fistula (TEF) repair. *Eur J Pediatr Surg.* 2011;21(6):386–388
Follow-up for a Preterm Infant with Beckwith-Wiedemann Syndrome

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Divisions of Newborn Medicine* and Genetics and Genomics,† Department of Pediatrics, Boston Children’s Hospital and Harvard Medical School, Boston, MA

We are excited to introduce this new NeoReviews feature: Outcomes of NICU Graduates. In this article, authors describe the clinical course of a NICU graduate who is receiving care in a specialty clinic. After providing a brief overview of the NICU hospitalization, the authors review the infant’s post-discharge clinical course including recommended follow-up and treatments. The article concludes with a short summary of major take-home lessons from the case as well as a discussion of expected outcomes for the specific condition. We hope that neonatal clinicians will benefit from these case presentations by gaining insight into the outpatient management and long-term outcome of a wide range of NICU diagnoses. If you are interested in submitting a case, please contact neoreviewseditorial@aap.org.

—Dr. Dara Brodsky, Editor in Chief, and Dr. Santina Zanelli, Associate Editor, Outcomes of NICU Graduates

CASE PRESENTATION

In this article, we describe a female child born preterm with a postnatal diagnosis of Beckwith-Wiedemann syndrome (BWS) who has been followed in our multidisciplinary infant follow-up program.

The infant was born at 31 and 3/7 weeks’ gestation via vaginal delivery to a 30-year-old gravida 2, para 1 woman following spontaneous preterm labor. The pregnancy had been unremarkable, with a normal second-trimester fetal survey. The infant initially emerged vigorous with good tone and spontaneous respiratory effort, though soon after, she had apnea and bradycardia. She ultimately required intubation in the delivery room and was transferred to a level III NICU for further evaluation and management. Her Apgar scores were 6 and 7 at 1 and 5 minutes of age, respectively. Her birth parameters were notable for a length of 47 cm (~90th percentile), head circumference of 27.5 cm (~90th percentile), and weight of 2,108 g (~50th percentile).

She underwent extubation and was transitioned to continuous positive airway pressure by 24 hours of age and subsequently to room air by 4 days of age. She continued to have occasional apnea/bradycardia/desaturation spells both at rest and with feedings that were initially attributed to prematurity. She was started on nasogastric feedings that were advanced without difficulty and she transitioned to

AUTHOR DISCLOSURE Dr Wojcik has worked as a consultant for Change Healthcare. Dr Bresnahan has disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/ investigative use of a commercial product/device.
full oral feedings by about 1 month of age. Her head ultrasound scan at 7 days of age was normal and she passed her newborn hearing screen.

She continued to have spells both with feedings and at rest despite reaching term postmenstrual age. At 6 weeks of age, the neonatology team had observed that her tongue was large and thought that her spells may have an obstructive component. She was seen by the genetics team for macroglossia, mild hypotonia, and unique facial features. She was clinically diagnosed with BWS, based on her features of macroglossia, forehead and glabellar nevus simplex, ear creases and pits, umbilical hernia, bilateral infraorbital creases, and generalized overgrowth (Fig 1A). Genetic testing to determine the underlying molecular etiology of the infant's clinical diagnosis included a karyotype, chromosomal microarray and methylation analysis (via methylation-sensitive Multiplex Ligation-Dependent Probe Amplification, Mayo Clinic Laboratories, Rochester, MN), all of which were nondiagnostic.

Due to the clinical diagnosis of BWS, tumor surveillance with serum α-fetoprotein (AFP) levels and abdominal ultrasonography was recommended. The initial serum AFP was elevated at 17,500 ng/mL (17,500 µg/L), but this was not unexpected for a former preterm infant with a diagnosis of BWS because both prematurity and BWS are associated with elevated AFP levels. (1)(2) Following this initial AFP, a sharp downtrend was observed (Fig 2). Initial liver ultrasonography showed multiple hypoechoic lesions (Fig 3), suspected to be hemangiomas (she was also noted to have a hemangioma on her posterior scalp), and a splenic cyst.

The infant was transferred to our institution at 2 months of age for a sleep study that showed mixed sleep-disordered breathing with a prominent obstructive component that was well-controlled with bilevel positive airway pressure (BiPAP). A modified barium swallow study showed oropharyngeal dysphagia and aspiration when she was fed upright with a regular-flow nipple, but this did not occur when she was fed side-lying with a slow-flow nipple. She was discharged to a rehabilitation facility at 2.5 months of age and ultimately went home at 3 months of age to continue to use BiPAP during naps and overnight sleep.

Our genetics team counseled the family extensively about the diagnosis of BWS based on her clinical features. The family was appropriately concerned about the potential for medical complications such as intra-abdominal tumors. They were also worried about issues related to the macroglossia, which they were reassured should improve over time and for which follow-up was arranged with surgical subspecialists in the event that a surgical intervention was needed.

**FOLLOW-UP COURSE**

The infant is now 20 months old (Fig 1C) with a corrected age of 18 months and has been followed in our multidisciplinary infant follow-up program by genetics, physical therapy, and pediatric psychology in addition to other subspecialists including pulmonology (for history of sleep-disordered breathing) and plastic and oral surgery (for history of macroglossia). Her home BiPAP was discontinued at 5 months of age after a normal sleep study. Her AFP levels continue to trend downward and are now in the normal range, and subsequent ultrasonography over the first 18 months of age demonstrated resolution of all but 1 of the hepatic lesions. The most recent ultrasound scan at 18 months of age showed resolution of the final liver lesion with a stable splenic cyst. Her growth curve continues to demonstrate overgrowth (Fig 4).

The plastic and oral surgery team monitored the child’s macroglossia, which was thought to become less clinically and cosmetically significant over time without intervention (Figs 1B and 1C); therefore, their plan is to continue to observe until 2 to 3 years of age before considering a tongue debulking procedure. She had a slight delay in oral motor skills for which she was followed by the outpatient feeding and swallowing team with no further clinical concerns for aspiration. After her last visit to this clinic at 18 months of age, she was noted to be doing wonderfully with her oral feeding skills and was discharged from their clinic with follow-up on an as-needed basis only.

Developmentally, she continues to make excellent progress. She is a bright and determined child with a loving
and nurturing attachment to her parents. Neuropsychological testing using the Bayley Scales of Infant and Toddler Development, 4th edition (Pearson, London, England) at 20 months of age (18 months’ corrected age) demonstrated gross and fine motor skills that are age-appropriate, cognitive skills that are also within the normal range, and a receptive and expressive language delay of 6 to 7 months (accounting for prematurity). She had some atypical self-stimulatory behaviors and social interactions noted during the most recent evaluation that deserve further monitoring. It is unclear whether the language delay is related to mechanical challenges associated with her macroglossia, or overall, whether the developmental assessments reflect a predominant influence of the preterm delivery versus BWS, or likely both. She continues to receive early intervention services for developmental support, and increased frequency of speech therapy has been recommended.

The search for the genetic cause of the child’s BWS has yet to be successful. Additional testing has included CDKN1C sequencing (Genetic Diagnostic Laboratory, University of Pennsylvania, Philadelphia, PA), a genome-wide methylation study (EpiSign, Greenwood Genetics, Greenwood, SC), and MLPA with pyrosequencing (Greenwood Genetics). All of these results were nondiagnostic with no epigenetic pattern classic for BWS. Due to a potential for mosaicism, should she undergo the tongue debulking procedure, the excised tissue sample may be sent for genetic testing.

**Figure 2.** $a$-fetoprotein (AFP) levels over time. Graph shows a sharp decrease in the neonatal period followed by normalization over the next year.

**Figure 3.** Liver imaging. Transverse (left) and sagittal (right) views of the liver on ultrasonography showing a small hypoechoic lesion measuring 5.1 x 4.2 x 4.5 mm in the right lobe of the posterior liver. At least 4 other smaller lesions were noted in the left lateral lobe, right lobe of the anterior liver, right lobe of the liver dome, and the inferior right lobe of the liver with normal directional color Doppler flow in the hepatic vasculature. These lesions were thought to likely represent multiple small liver hemangiomas.
DISCUSSION

BWS is an overgrowth disorder with a varied presenting phenotype that is attributed to disorders of genomic imprinting of the 11p15 chromosomal region. Interestingly, children with BWS are often born preterm. (3) BWS can be diagnosed clinically using major and minor findings associated with this condition:

- **Major findings:** Macrosomia, macroglossia, linear/transverse ear lobe creases and/or posterior pits, lateralized overgrowth or hemihyperplasia, cleft palate, omphalocele or umbilical hernia, cardiomyopathy, embryonal tumors such as Wilms tumor or hepatoblastoma, visceromegaly (enlargement of the intra-abdominal organs), adrenal cortex cytomegaly, renal abnormalities, placental mesenchymal dysplasia, and positive family history

- **Minor features:** Prematurity, hypoglycemia, nevus simplex or hemangiomas, infraorbital creases, cardiac abnormalities, diastasis recti, and advanced bone age

Using these criteria, a clinical diagnosis of BWS can be established in an individual who meets either (a) 3 major or (b) 2 major and at least 1 minor criteria. (4) This infant’s macroglossia, umbilical hernia, ear creases, and pits meet the major criteria (3 major), and her history of preterm delivery, nevus simplex and hemangiomas, and infraorbital creases are minor criteria (3 minor). With 3 major and 3 minor findings associated with BWS, she meets the criteria for a clinical diagnosis of BWS.

More recently, to recognize the variable clinical presentations and molecular etiologies of BWS, the term “BWS spectrum” (BWSp) has been adopted. (5) A recent international consensus group (5) has abandoned the terminology of major and minor associated findings and introduced “cardinal” and “suggestive” features of BWSp as well as a scoring system to diagnose clinical BWSp. Cardinal features include macroglossia, lateralized overgrowth (hemihyperplasia), omphalocele, multifocal Wilms tumor or nephroblastomatosis, hyperinsulinism, and other features seen on clinical pathologic examination such as placental mesenchymal dysplasia and adrenal cortex cytomegaly. Suggestive features, or features that also occur frequently in those without a BWSp diagnosis, include polyhydramnios or placentomegaly, increased birthweight for gestational age (>2 standard deviations above the mean), transient hypoglycemia, facial nevus simplex, ear creases or pits, umbilical hernias or diastasis recti, nephromegaly or hepatomegaly, and embryonal tumors. In this scoring system, 2 points are given for each cardinal feature and 1 point per suggestive feature. A score of greater than or
equal to 4 points is consistent with a clinical diagnosis of BWSp. (1) The infant in this case has 1 cardinal feature (macroglossia) and 3 suggestive features (nevus simplex, ear creases and pits, and umbilical hernia) scoring a total of 5 points. In her initial genetic evaluation, a possible right leg length discrepancy was noted, which would lead to a score of 7, though this finding has not persisted.

On a molecular level, BWSp is associated with various abnormalities in chromosome region 11p15 that affect imprinted genes. Methylation abnormalities make up the most common subgroup, with loss of methylation (LOM) at the maternal IC2 allele (IC2 LOM) found in 50% of individuals with BWSp and gain of methylation (GOM) at the material IC1 allele (IC1 GOM) in 5% to 10% of cases with BWSp. (5) Other underlying molecular etiologies include paternal uniparental isodisomy (pUPD) of 11p15.5 in 20% of cases, pathogenic sequence variants in the CDKN1C gene in 40% of familial and 5% of sporadic cases, and other chromosomal abnormalities affecting 11p15 in less than 5% of cases. (6) Determining the molecular etiology of BWSp can better predict the familial recurrence risk, the risk of tumor development, and health surveillance needs. (1) In pursuing a molecular diagnosis of BWSp, various genetic tests can be used, including methylation analysis (often via MLPA), chromosomal microarray analysis, karyotype analysis, and single gene testing of CDKN1C. (2) It is recommended that the first line of molecular testing should include methylation analysis, because methylation abnormalities are present in approximately 80% of individuals with BWSp. (7) Methylation testing would indicate the presence or absence of the IC2 LOM and IC1 GOM subtypes. Chromosomal microarray analysis can detect microdeletions, microduplications, and pUPD subtype, and a karyotype can test for inversions or translocations of the 11p15 region. Single gene testing including sequencing and deletion/duplication analysis of the CDKN1C gene in the 11p15 region is recommended, particularly in familial cases of BWSp. (4)

In the present case, as noted earlier, the first line of genetic testing (ie, methylation analysis, chromosomal microarray analysis, and karyotype analysis) and the second round of genetic testing (ie, CDKN1C sequencing and further epigenetic testing) were nondiagnostic. Thus, despite extensive genetic testing, the molecular etiology of the child’s BWSp remains unknown. This patient is not alone, as about 20% of patients with a clinical BWSp diagnosis do not have a molecular diagnosis. (6) One explanation is related to potential mosaicism, where the pathogenic variant is present in some cells of the body—such as those affected by overgrowth—but not others. In most sporadic cases of BWSp, the underlying molecular defect is mosaic at a low enough level where it may not be detected in the peripheral blood genetic testing. (8)

Many individuals with BWSp present in the NICU or newborn nursery, particularly as hypoglycemia related to hyperinsulinism (not seen in our case) and preterm delivery (as seen in our case) are common features. Following the recognition of this diagnosis, an AFP measurement and abdominal ultrasonography are recommended to assess for intra-abdominal malignancy. Evaluation for issues related to macroglossia such as poor feeding or sleep-disordered breathing should be pursued depending on the clinical presentation. Intubation may be challenging depending on the severity of macroglossia. Cardiac evaluation, including electrocardiography and echocardiography, may be performed if abnormalities are suggestive on examination to assess for a possible association with cardiomyopathy, however, a proportion of individuals with BWSp have cardiomegaly that resolves spontaneously. (4)

Tumor surveillance is of utmost importance for patients with BWSp because of the increased risk of tumor development associated with this syndrome. Tumor surveillance can vary based on the molecular etiology of the BWSp, another motivation to determine the underlying etiology. The overall risk of developing a tumor is lowest in the IC2 LOM subtype (2.6%), CDKN1C subtype (6.9%), and in BWSp with no detectable molecular defect (6.7%) and highest in the pUPD subtype (16%) and the IC1 GOM subtype (28.1%). (1) Wilms tumor is most frequent in the IC1 GOM subtype as well as the subtype with negative molecular tests. Hepatoblastoma occurs mostly in the IC2 LOM and pUPD subtypes. In the CDKN1C subtype, neuroblastoma is the most common tumor. (9) This risk of malignancy decreases with age and in general, the associated tumors are treatable with favorable outcomes provided they are detected early. Abdominal ultrasonography every 3 to 4 months until age 8 years is the preferred method of tumor screening, with serum AFP levels added for increased sensitivity to detect hepatoblastoma; however, this recommendation has more recently been called into question. (4)(10)(11) Particularly, many families have difficulty with blood draws every 3 months for the first 4 years of age, and without evidence of substantial benefit over a detailed abdominal ultrasound scan, it is thought to be safe to perform surveillance with ultrasonography alone. In our case, the initial persistence of the liver lesion prompted continuing surveillance using AFP levels, though the lesions have spontaneously resolved as expected with the presumed diagnosis of hemangioma.
Adults with BWSp are expected to have normal intelligence and a normal lifespan, though little research has been conducted on health outcomes in adulthood. An older study surveying 87 children with BWSp (mean age 9.7 years) and their parents noted higher scores than the general population on a social/behavioral questionnaire indicating a higher frequency of behavioral issues. Six children, or 6.8% of the cohort, had a diagnosis of autism spectrum disorder, higher than the general population. (12) Another study has shown developmental delay and mild intellectual disability in about 26% of 34 adults with BWSp, though this was usually referring to mild speech delay. For the rare cases with severe delays, co-occurring perinatal events such as severe hypoglycemia or hypoxic-ischemic encephalopathy also affected these outcomes. Most medical issues in adulthood reflect the evolution of BWSp features noted in infancy or the consequences of surgical intervention. (13) This highlights the need for preventive follow-up care and treatment of associated medical problems during childhood. Many features of BWSp such as macroglossia and lateralized overgrowth improve with age but can potentially cause lasting effects into adulthood such as speech and swallow difficulties or orthodontic abnormalities, scoliosis, or back pain related to lateralized overgrowth. (1)(13) One study, with substantial limitations such as a small sample size, showed an increased risk of tumor development in adults with BWSp, though it is more generally believed that there is not enough evidence to make this claim or change any tumor surveillance protocols. (13)

**TAKE HOME LESSONS**

Recognizing the clinical features of BWSp in the neonatal period is important, as tumor surveillance in these cases may be lifesaving. The overall prognosis for this condition is excellent, and the clinical and cosmetic impact of issues such as macroglossia and asymmetric overgrowth tends to wane over time. Developmental surveillance may aid in management due to the higher risk of developmental delays or other neuropsychological challenges associated with this condition, though further research into the associated neurodevelopmental outcomes is needed. In our case, the combination of preterm birth and clinical diagnosis of a genetic syndrome prompted referral to a specialized developmental follow-up program at our institution for infants with genetic conditions where developmental service needs have been identified.

**American Board of Pediatrics Neonatal-Perinatal Content Specifications**

- Know the evolution of neurodevelopmental impairments during development and the difference between transient and permanent impairments in NICU graduates (eg, developmental delay vs. intellectual disability; tone abnormalities vs. cerebral palsy).
- Know the value and limitations of the Bayley Scales of Infant Development and other tests of psychomotor development in assessing current function and predicting long-term outcomes.
- Know the etiology, molecular phenotype, and clinical manifestations of disorders associated with genetic imprinting, such as Prader-Willi syndrome.
- Know the etiology, molecular phenotype, and clinical manifestations of disorders associated with uniparental disomy.

**Acknowledgment**

The authors thank the child’s family for their willingness and enthusiasm to participate in this report. They also thank the multidisciplinary team of the NICU Growth and Developmental Support Program (NICU GraDS) at Boston Children’s Hospital for their thoughtful and insightful care of this child and her family.

ANSWER KEY FOR JANUARY 2022 NEOREVIEWS

Maternal Facial Nerve Palsy and a Perinatal Infection

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ELECTRONIC FETAL MONITORING CASE REVIEW SERIES

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, the terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women’s Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate (FHR) patterns, interpretation, and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal arterial umbilical cord gas values and indications of acidosis are defined in the Table.

ASSUMPTIONS FROM THE NICHD WORKSHOP

Definitions are developed for visual interpretation, assuming that both the FHR and uterine activity recordings are of adequate quality.
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of FHR do not occur alone and generally evolve over time

DEFINITIONS

Baseline FHR
- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate

AUTHOR DISCLOSURES

Drs Lueck and Young have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/ investigative use of a commercial product/device.
Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min.

Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude.

Baseline Variability
- Fluctuations in the baseline FHR of ≥2 cycles per minute, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute.
- Classification of variability: Absent: Amplitude range is undetectable. Minimal: Amplitude range is greater than undetectable to 5 beats/min. Moderate: Amplitude range is 6–25 beats/min. Marked: Amplitude range is >25 beats/min.

Accelerations
- Abrupt increase in FHR above the most recently determined baseline.
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes.
- Before 32 weeks’ gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds.
- Prolonged acceleration lasts ≥2 minutes but <10 minutes.

Late Decelerations
- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions.
- Considered a periodic pattern because it occurs with uterine contractions.

Early Decelerations
- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction.
- Also considered a periodic pattern.

Variable Decelerations
- Abrupt decrease in FHR (onset to nadir <30 seconds).
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes.
- May be episodic (occurs without a contraction) or periodic.

Prolonged Decelerations
- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline.
- Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period.
- Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent.

Sinusoidal FHR Pattern
- Visually apparent, smooth sine wave-like undulating pattern in the baseline with a cycle frequency of 3 to 5 per minute that persists for ≥20 minutes.

Uterine Contractions
- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes. Normal: ≤5 contractions in 10 minutes. Tachysystole: >5 contractions in 10 minutes.

Interpretation
A 3-tier FHR interpretation system has been recommended as follows:

<table>
<thead>
<tr>
<th>pH</th>
<th>Pco₂ (mm Hg)</th>
<th>Po₂ (mm Hg)</th>
<th>Base Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal*</td>
<td>≥7.20 (7.15 to 7.38)</td>
<td>&lt;60 (35 to 70)</td>
<td>≥20</td>
</tr>
<tr>
<td>Respiratory acidosis</td>
<td>&lt;7.20 &lt;60 Variable</td>
<td>≤–10</td>
<td></td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>&lt;7.20 &lt;60 Variable</td>
<td>≥–10</td>
<td></td>
</tr>
<tr>
<td>Mixed acidosis</td>
<td>&lt;7.20 &gt;60 Variable</td>
<td>≥–10</td>
<td></td>
</tr>
</tbody>
</table>

Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:
- Baseline rate: 110 to 160 beats/min
- Baseline FHR variability: Moderate
- Late or variable decelerations: Absent
- Early decelerations: Present or absent
- Accelerations: Present or absent

Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:
- Bradycardia not accompanied by absent variability
- Tachycardia
- Minimal or marked baseline variability
- Absent variability without recurrent decelerations
- Absence of induced accelerations after fetal stimulation
- Recurrent variable decelerations with minimal or moderate variability
- Prolonged decelerations
- Recurrent late decelerations with moderate variability
- Variable decelerations with other characteristics, such as slow return to baseline

Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:
- Absent variability with any of the following:
  - Recurrent late decelerations
  - Recurrent variable decelerations
  - Bradycardia

Variability: Moderate
Baseline rate: 150 beats/min
Episodic patterns: None
Periodic patterns: None
Uterine contractions: None


We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

THE CASE

Presentation
A 33-year-old gravida 1, para 0 woman had an uncomplicated pregnancy until 32 weeks’ gestation when she developed malaise, fever, and a mildly elevated blood pressure at home. She also reported neurologic symptoms of transient tingling in her extremities and a nonpositional headache. She was evaluated and noted to be afebrile and normotensive. Given her reported mild-range blood pressure at home and headache, she was evaluated for preeclampsia. Serum laboratory results demonstrated transaminitis with an alanine aminotransaminase (ALT) of 60 U/L (1 μkat/L; normal <40 U/L [0.67 μkat/L]). During her evaluation, the patient developed a noticeable unilateral facial palsy and slurred words due to her facial droop. A code stroke was called and she had an emergent evaluation by neurology including a noncontrast head computed tomography scan. This urgent head imaging was unrevealing; she was diagnosed with Bell palsy of unclear etiology. She was administered betamethasone for fetal benefit and transferred to our facility for further evaluation. The fetal nonstress test performed on arrival at our facility is shown in Fig 1.

Figure 1. Electronic monitoring strip 1.
Interpretation: Category I
Differential diagnosis: The FHR tracing is reassuring with moderate variability and accelerations; there are no signs of fetal distress
Action: Expectant management and ongoing evaluation

The patient was admitted and initially underwent evaluation to identify the cause of the Bell palsy and for possible preeclampsia. She remained normotensive and had no proteinuria. Serial laboratory evaluation demonstrated increasing ALT up to 400 U/L (6.68 μkat/L). Neurology and infectious disease consultations were obtained. Head magnetic resonance imaging was unrevealing. The patient was started on acyclovir for empiric treatment of a possible viral infection causing her Bell palsy. Evaluation for an infectious process continued with serologic testing for Lyme disease and cytomegalovirus (CMV). An inpatient fetal nonstress test at 32 weeks and 4 days is shown in Fig 2.

- Variability: Moderate
- Baseline rate: 140 beats/min
- Episodic patterns: None
- Periodic patterns: None
- Uterine contractions: None

Interpretation: Category I
Differential diagnosis: The FHR tracing is reassuring with moderate variability and accelerations; there are no signs of fetal distress
Action: Expectant management and ongoing evaluation

Serologic testing for Lyme disease returned positive results; given her neurologic symptoms, a lumbar puncture was recommended because of the potential risk for Lyme meningitis. She was started on ceftriaxone for empiric treatment of disseminated Lyme disease. Ultimately, confirmatory Lyme studies returned negative, and CMV serologies demonstrated a positive immunoglobulin (Ig)M and positive IgG with an intermediate avidity IgG. Primary CMV during pregnancy could not be excluded. The fetal nonstress test at 32 weeks and 6 days of gestation is shown in Fig 3.

- Variability: Moderate
- Baseline rate: 140 beats/min
- Episodic patterns: None
- Periodic patterns: None
- Uterine contractions: Irritability
- Interpretation: Category I
Differential diagnosis: The FHR tracing is reassuring with moderate variability and accelerations; there are no signs of fetal distress.

Action: Expectant management and ongoing evaluation

The patient was discharged after an 8-day hospitalization with spontaneously improved transaminitis and improvement in her facial palsy. She received outpatient management with close maternal and fetal surveillance until a scheduled early-term induction of labor. She was induced at 37.5 weeks’ gestation; her induction was uncomplicated. A representative FHR tracing during her induction is demonstrated in Fig 4.

Variability: Moderate
Baseline rate: 140 beats/min
Episodic patterns: None
Periodic patterns: Variable decelerations
Uterine contractions: Every 3 to 4 min
Interpretation: Category II
Differential diagnosis: The FHR tracing has reassuring variability, but showed recurrent variable decelerations with contractions
Action: Re-position patient, intravenous fluid bolus, consider intrauterine pressure catheter/amnioinfusion

Outcome
The patient delivered a female infant via uncomplicated spontaneous vaginal delivery with Apgar scores of 9 and 9 at 1 and 5 minutes, respectively; the neonate had a birthweight of 2,465 g (22nd percentile) with a normal head circumference for gestational age. The neonate had no rashes or petechiae. Results of polymerase chain reaction testing of the neonate’s urine and serum samples were positive for CMV. The urine demonstrated a viral count of 5,658 U/mL. A neonatal head ultrasound scan was normal. Following pediatric infectious disease consultation, the neonate was started on valganciclovir for primary CMV treatment with planned outpatient infectious disease follow-up.

DISCUSSION
CMV is a perinatal infection that has a risk of adverse teratogenic effects for the neonate. CMV is a double-stranded DNA herpes virus transmitted by contact with bodily fluids (blood, saliva, semen, vaginal fluid, or feces.). CMV is a common childhood infection and it is estimated that up to 70% of children in day care will acquire the virus. (1) However, many adults do not have immunity and therefore remain susceptible to the virus. In adults, infections range from asymptomatic to systemic symptoms including fevers, malaise, headache, myalgias, or facial nerve palsy. While there is a chance of CMV reactivation, the vast majority of fetal implications from CMV infection in pregnancy are caused by primary infection. It is estimated that the incidence of primary CMV infection in pregnant women ranges from 0.7% to 4%. (2)

CMV is one of the most common congenital infections in the United States, occurring in approximately 1 in every 150 live births. (3) Transmission to the fetus is far more likely for a primary infection than a secondary infection, and the infection risk increases with each trimester. Although the likelihood of fetal infection is highest in the third trimester, the risk of symptomatic illness and long-term sequelae in the infant is highest when transmission occurs during the first trimester. (3)

About 11% of infants born with congenital CMV will develop symptoms or long-term sequelae. (3) CMV is the leading cause of congenital nonfamilial sensorineural hearing loss in the United States. (1)(2) Symptomatic infants may be small for gestational age or have microcephaly, ventriculomegaly, chorioretinitis, jaundice, hepatosplenomegaly, or petechiae/thrombocytopenia. Long-term sequelae include hearing loss, vision loss, and cognitive impairment.

Maternal CMV infection is evaluated using serologic testing with confirmatory testing requiring amniotic fluid. Testing is done either in the setting of maternal illness suspicious for CMV infection, such as mononucleosislike
symptoms, or if congenital CMV is suspected after abnormalities, such as lateral ventriculomegaly, microcephaly, echogenic bowel, hepatosplenomegaly, intracranial calcifications, ascites and fetal hydrops, are noted on fetal ultrasound. The presence of IgM antibodies with low avidity IgG antibodies is most indicative of primary infection. (1)(4)

Universal screening for CMV is not recommended given the lack of treatment during pregnancy, high false-positive rates, and risk of secondary infection in women with an existing seropositive status. (1)

Currently there is no standard treatment for CMV infection during pregnancy or established medical intervention to prevent transmission of CMV to the fetus. Very limited data support the use of antiviral medications, such as ganciclovir or valacyclovir during pregnancy to treat infection or prevent transmission to the fetus. (1) In addition, multiple studies have looked at the use of CMV hyperimmune globulin infusions during pregnancy to prevent transmission to the fetus. In a recent study, the administration of CMV hyperimmune globulin did not result in a lower incidence of congenital CMV infection compared with placebo. (5)

Primary prevention strategies to decrease the risk of CMV infection during pregnancy include frequent handwashing with soap and warm water, careful handling of used diapers and other possibly infected items, and avoiding sharing utensils. Given the high prevalence of CMV among young children, especially those in day care, pregnant women should be especially vigilant of handwashing and hygiene around young children. (1)

In this case, a broad differential diagnosis for the maternal clinical presentation of facial nerve palsy helped diagnose primary CMV and optimize prompt treatment in the newborn period.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Understand the rationale, interpretation, and limitations of maternal detection of fetal movement, of the biophysical profile, the non-stress test, and the contraction stress test as means of assessing fetal well-being
- Know the epidemiology, prevention, and pathogenesis of perinatal infections with herpes 1, herpes 2, cytomegalovirus, Epstein-Barr virus, and varicella-zoster
- Know the clinical manifestations, diagnostic features, management, and complications of perinatal infections with herpes 1, herpes 2, cytomegalovirus, Epstein-Barr virus, and varicella-zoster
References


