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Neonatal Hypoglycemia: GLOW at the End of the Tunnel?

Nearly 50 years ago, *The Journal* published a landmark review of hypoglycemia in children by Pagliara, Karl, Haymond, and Kipnis from St. Louis Children's Hospital.[1] This 2-part review focused on recent advances in the physiology of fuel homeostasis during fasting as the foundation for diagnosis and treatment of the many metabolic and endocrine hypoglycemia disorders of childhood. In a short section devoted to neonatal hypoglycemia, the authors noted that fetal glucose is provided by placental transfer from the maternal circulation so that ambient glucose concentrations in the fetus are similar to maternal levels. After delivery, glucose levels decrease to values that would be considered hypoglycemia in older infants and children and remain low for the first few days of life. Pagliara et al considered it unlikely that tissue glucose requirements were different during this brief period of transitional neonatal hypoglycemia and concluded that it was appropriate to use the same glucose standards for treatment of hypoglycemia in newborns as for older infants and children. Their suggestion generated heated letters to the editor from neonatology experts arguing that statistical definitions of "clinically significant" neonatal hypoglycemia (mean – 2 SDs) had been established a decade earlier as a blood glucose of <30 mg/dL for normal birth-weight infants and <20 mg/dL for low-birth-weight infants.[2-4] This controversy rages on down to the present day, owing to our many gaps in knowledge about the mechanism of transitional neonatal hypoglycemia and is reflected by the differences in guidelines from several neonatology and pediatric organizations and by the recommendations published in *The Journal* from the Pediatric Endocrine Society, on which the authors of this editorial were co-authors.[5-8]

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At the time Pagliara et al wrote their review, they believed that the mechanism of transitional neonatal hypoglycemia might reflect delays in development of one or more of the steps in hepatic gluconeogenesis. Attention has recently focused more on insulin as the culprit: evidence in human newborns indicates that the glucose threshold for suppressing insulin release from pancreatic beta-cells is lower in the fetus and early newborn period.[9] This low glucose threshold could be important for maintaining insulin secretion to permit normal fetal growth; it could also explain the stability of low glucose levels during normal newborn transitional neonatal hypoglycemia and its resemblance to hyperinsulinemic hypoglycemia caused by gain-of-function mutations of glucokinase, the beta-cell glucose sensor.[10] Consistent with this finding, islets from fetal and newborn laboratory rodents have been shown to have a lower glucose threshold for insulin release.[11] The mechanism responsible for the low glucose

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threshold of fetal and neonatal beta-cells remains unclear, but suggested explanations include several candidates in the pathways of fuel-mediated insulin secretion (eg, expression of *MCT1* and *LDH*, which are normally disallowed in beta-cells to prevent pyruvate from stimulating insulin release) to terminal steps controlling calcium-regulated release of insulin granules.[12,13] An important feature of hyperinsulinism as the cause of neonatal hypoglycemia is that ketogenesis is suppressed, which contradicts a commonly held presumption that hypoglycemia in newborns can be compensated for by increased supply of ketones as alternative fuel for the brain.[7]

Much of the controversy around neonatal hypoglycemia over the past half century has focused on continued efforts to define hypoglycemia by a specific number. This strategy contrasts with the approach suggested in the Endocrine Society hypoglycemia guidelines for adults, which was also adopted in the Pediatric Endocrine Society recommendations: namely, that hypoglycemia cannot be defined by any specific glucose value, because thresholds for neurogenic (autonomic) and neuroglycopenic brain responses to hypoglycemia occur across a range of glucose concentrations and permanent injury to the brain reflects not only the degree, but also the duration of hypoglycemic insult.[8,14] Recently, efforts have been made to link specific neonatal glucose levels with subsequent neurodevelopmental outcomes; however, such studies have recognized limitations, including the fact that they are merely association, not causation, studies and the fact that neurodevelopmental delays may not be detectable until late childhood.[15-17]

In this volume of *The Journal*, Harris et al present the results of the Glucose in Well Babies (GLOW) Study which represents the first accurate study of Transitional Neonatal Hypoglycemia in normal newborn babies.[18] Harris et al meticulously tracked the changes in blood glucose levels of normal babies after birth using both twice-daily laboratory quality determinations of plasma glucose concentrations as well as continuous interstitial glucose monitoring using an indwelling glucose sensor. The GLOW results indicate that the period of postnatal hypoglycemia in these mostly breast-fed babies resolved by day 4 of life. Although consistent with previous data in newborn infants, the GLOW Study is a landmark in its efforts to combine accurate glucose measurements with rigorous statistical analysis to describe the transitional period of hypoglycemia in a well-defined, relatively large group of 67 normal newborns and reflects previous studies by this group from Auckland, New Zealand, led by Professor Jane Harding. The observation that the period of transitional hypoglycemia can normally last until day 4 of life answers a major question faced when drafting recommendations for the Pediatric Endocrine Society on when the possibility of a persistent hypoglycemia disorder could be excluded in an at-risk baby; the GLOW Study makes clear that the current practice of earlier discharge may need modification for these at-risk neonates. The GLOW Study also found that patterns of glucose concentrations in individual babies varied widely. Thus, early measurements of glucose did not predict later low or high plasma glucose concentrations. This observation has important implications for designing screening tests for persistent hypoglycemia disorders, such as perinatal stress-induced hyperinsulinism or children with genetic congenital hyperinsulinism, who are at high risk of permanent brain injury if not identified early.[19,20] It is encouraging that careful scientific studies of neonatal hypoglycemia, exemplified by the GLOW Study, and, especially, of its mechanism(s) are beginning to emerge that may finally resolve the many long-standing controversies about neonatal hypoglycemia. ■

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Realizing the Improvement Potential of the Value in Inpatient Pediatrics Network

The gap between evidence-based practice and current clinical care is seen across the spectrum of hospitalized pediatric patients.[1,2] The field of quality improvement (QI) was born out of this gap. QI promotes the use of improvement methodologies to both decrease variation and improve the delivery of high-quality care as measured by nationally endorsed benchmarks. Part and parcel to improvement methodologies is the dissemination of the local plan-do-study-act cycle and the importance of starting small in any implementation. In fact, the Institute for Healthcare Improvement's Prioritization Matrix recommends starting with at most a small-scale test for 9 of the 12 categories in their prioritization matrix evaluating readiness to make change and perceived benefit of change.[3] This focus on small-scale testing is a hallmark of QI and is undoubtedly a driver to the many local improvement initiatives that we find throughout clinical settings.

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Although local improvements are encouraged to continue in multiple settings, the implementation of interventions found to be beneficial from local improvements across multiple sites is not as commonly seen. Dissemination of evidence-based interventions across diverse sites is a goal of multiple collaboratives, including the Value in Inpatient Pediatrics (VIP) network.[4]

The VIP is a collaborative network that resides within the American Academy of Pediatrics with the mission of improving care to pediatric inpatients by supporting implementation of clinical practice guidelines by hospitalists who might not otherwise have organizational resources to conduct QI initiatives on their own.[4] Since its initiation, the VIP has supported 7 multisite collaboratives. The first was the Quality Collaborative for Improving Hospitalist Compliance with the AAP Bronchiolitis Guideline in 2013. The current active collaborative on Standardization of Fluids in Inpatient Settings is set to be completed in 2020.[4] Although the goal of these collaboratives has been to foster hospitalists' adoption of evidence-based practice outlined in published clinical practice guidelines, the structure of each of these collaboratives has varied. Elements that have been constant throughout the VIP collaboratives are the dissemination of a toolkit and a platform for data sharing. A toolkit is often a collection of best practice interventions identified by the evidence to support the change that is desired. This toolkit is generally sent electronically to sites that are involved in collaboratives for their individual evaluation and potential application. Data sharing across sites with the ability to benchmark is a strong lever for many collaboratives because it allows the measurement of both local and aggregate improvements over the timeline of the study on primary outcome metrics carefully determined by collaborative leadership.

One multisite collaborative, Pathways to Improve Pediatric Asthma Care (PIPA), used a multifactorial support structure: (1) A toolkit offering sites examples of pathways and order sets pertaining to 3 predefined core pathway interventions (asthma severity assessment tools for emergency department triage, order sets and pathways at emergency department triage to trigger administration of

PIPA	Pathways to Improve Pediatric Asthma Care
QI	Quality improvement
VIP	Value in Inpatient Pediatrics

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