

# Neonatal Diabetes Mellitus

## An Update on Diagnosis and Management

Michelle Blanco Lemelman, MDa, Lisa Letourneau, MPH, RD, LDNb,  
Siri Atma W. Greeley, MD, PhDc,\*  
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La diabetes mellitus ocurre más comúnmente después del período neonatal y los resultados de

interacciones complejas entre factores de genética ambiental y genética con penetración incompleta. Los avances en genética molecular en la última década aceleraron la aseceración

de que la diabetes que ocurre a una edad muy temprana suele deberse a defectos monogénicos subyacentes, que son trastornos causados por mutaciones en un solo gen. Ahora se sabe que la Diabetes neonatal (o congénita) mellitus (DMN) ocurre en aproximadamente 1 en 90,000 a 160,000 nacidos vivos. Hay más de 20 causas genéticas conocidas para DMN.

DMN puede clasificarse por características fenotípicas en transitorias, permanentes, y formas sindrómicas. En un gran estudio de cohorte internacional de 1020 pacientes clínicamente diagnosticado con diabetes antes de los 6 meses de edad, el 80% tenía un diagnóstico genético conocido. Mutaciones en KCNJ11 y ABCC8 (que afectan al potasio de células beta pancreáticas [K<sup>+</sup>]-ATP channel) puede tratarse con sulfonilureas orales (SU) y dar cuenta de alrededor del 40% de estos pacientes. Los estudios preliminares indican que el tratamiento temprano de SU, en contraste con la insulina, puede mejorar los resultados del neurodesarrollo en pacientes con respuesta a la SU. Es importante diagnosticar la diabetes monogénica tan pronto como sea posible, ya que puede predecir el curso clínico, explicar características clínicas adicionales y guiar manejo para pacientes.

A continuación leer el trabajo completo en inglés.

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Michelle Blanco Lemelman, MD<sup>a</sup>, Lisa Letourneau, MPH, RD, LDN<sup>b</sup>,  
Siri Atma W. Greeley, MD, PhD<sup>c,\*</sup>

### KEYWORDS

• Neonatal diabetes • Monogenic diabetes • Genetic • Insulin • Glyburide

### INTRODUCTION

Diabetes mellitus most commonly occurs after the neonatal period and results from complex interactions between both environmental and incompletely penetrant genetic factors. Advances in molecular genetics over the past decade hastened the realization that diabetes that occurs very early in life is most often due to underlying monogenic defects, disorders caused by mutations in a single gene. Neonatal (or congenital) diabetes mellitus (NDM) is now known to occur in approximately 1 in 90,000 to 160,000 live births.<sup>1</sup> There are more than 20 known genetic causes for NDM.

NDM may be categorized by phenotypic characteristics into transient, permanent, and syndromic forms. In a large international cohort study of 1020 patients clinically diagnosed with diabetes before 6 months of age, 80% had a known genetic diagnosis.<sup>2</sup> Mutations in *KCNJ11* and *ABCC8* (affecting the pancreatic beta-cell potassium [K]-ATP channel) may be treated with oral sulfonylureas (SUs) and account for about 40% of these patients. Preliminary studies indicate that early SU treatment, in contrast to insulin, may improve neurodevelopmental outcomes in SU-responsive patients.<sup>3</sup> It is important to diagnose monogenic diabetes as early as possible, as it can predict the clinical course, explain additional clinical features, and guide appropriate management for patients.<sup>4</sup>

### HYPERGLYCEMIA IN THE NEONATAL PERIOD

Although neonatal diabetes may be recognized within the first few days of life, there are alternative causes of hyperglycemia in neonates, which can make the diagnosis of diabetes difficult. This difficulty is especially true in the preterm or

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<sup>a</sup> Section of Adult and Pediatric Endocrinology, Diabetes, and Metabolism, MC 5053, 5841 South Maryland Avenue, Chicago, IL 60637, USA; <sup>b</sup> Monogenic Diabetes Registry, University of Chicago Medicine, Kovler Diabetes Center, 900 East 57th Street, Chicago, IL 60637, USA;

<sup>c</sup> Section of Adult and Pediatric Endocrinology, Diabetes, and Metabolism, Kovler Diabetes Center, The University of Chicago, 900 East 57th Street, Chicago, IL 60637, USA

\* Corresponding author.

E-mail address: [sgreeley@peds.bsd.uchicago.edu](mailto:sgreeley@peds.bsd.uchicago.edu)

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low-birth-weight infant.<sup>5</sup> The prevalence of high glucose levels in preterm infants is 25% to 75%.<sup>6,7</sup> Neonatal hyperglycemia is more common in the first 3 to 5 days after birth but can be found in infants at up to 10 days of life; it usually resolves within 2 to 3 days of onset.<sup>8</sup>

Typical causes for hyperglycemia in this group include increased parenteral glucose administration, sepsis, increased counter-regulatory hormones due to stress, and medications, such as steroids.<sup>8</sup> There is some evidence of insufficient pancreatic insulin secretion and relative insulin resistance in hyperglycemic and nonhyperglycemic critically ill preterm neonates.<sup>6,9</sup> However, there is no clear consensus related to the treatment of neonatal hyperglycemia; many institutions may follow personalized approaches. In the neonatal intensive care unit at the University of Chicago, patients are commonly placed on insulin when point-of-care dextrose persistently reaches 300 mg/dL or greater. Related literature suggests that intervention may be warranted when blood sugar levels are greater than 180 mg/dL. However, because of the low risk of short-term hyperglycemia in neonates and the high risk of insulin-induced hypoglycemia, Rozance and Hay<sup>8</sup> recommend reserving insulin therapy for severe hyperglycemia, defined as glucose levels greater than 500 mg/dL. Another consideration is that significant osmotic changes leading to ventricular hemorrhage may occur at glucose levels greater than 360 mg/dL.<sup>9</sup> Regardless of the cause of hyperglycemia, the authors recommend intervention with insulin when glucose levels are persistently more than 250 mg/dL. Irrespective of the glucose threshold, patients with persistent elevations should be started on an intravenous insulin infusion, although in some circumstances subcutaneous insulin could be considered (discussed in detail later).

Term infants and premature infants born at greater than 32 weeks' gestational age (GA) are more likely to have a monogenic cause for their diabetes than are very premature infants born at less than 32 weeks' GA.<sup>5</sup> However, according to the same study, 31% of all preterm infants with diabetes born at less than 32 weeks' GA were diagnosed with a monogenic cause, strongly suggesting that such infants should have genetic testing.<sup>5</sup> These preterm infants also tend to present earlier with diabetes (around 1 week of age) compared with full-term infants (around 6 weeks of age). Data gathered from the Monogenic Diabetes Registry at the University of Chicago and others show that patients with transient forms of neonatal diabetes present earlier on average (most often within days of birth) as compared with those with permanent forms.<sup>1,10,11</sup>

NDM should be considered in infants with insulin-dependent hyperglycemia, with blood glucoses persistently greater than 250 mg/dL, without an alternative cause. Neonatologists should become suspicious of diabetes when hyperglycemia persists for longer than 7 to 10 days. Some literature alternatively suggests pursuing genetic testing when hyperglycemia persists beyond the first 2 to 3 weeks of life.<sup>9</sup> However, genetic testing should be sent immediately in patients who present with acute extreme hyperglycemia (serum glucose >1000 mg/dL) without an identified cause, regardless of the time course. Of note, some forms of NDM, such as 6q24, may be transient, presenting only for a few days to weeks before resolving. The authors recommend sending genetic testing immediately, even if hyperglycemia resolves.

The initial assessment of children with suspected disease should include laboratory assessment of urine ketones, serum glucose, C peptide, and insulin. A pancreatic ultrasound should be performed, as the presence or absence of a pancreas will guide diagnosis and therapy considerations. The timing of the appearance of diabetes-related autoantibodies in neonates has not been well studied. Literature analyzing antibodies in the offspring of parents with type 1 diabetes (T1D) conclude that maternal antibodies may be present in the neonate for up to 6 months. In addition, specific detection of insulin antibodies after 6 months of age was associated with

developing disease.<sup>12</sup> The authors would, therefore, suggest that testing for autoantibodies within the first 6 months of life will not change the decision about mandatory genetic testing and, thus, may not be essential.

Neonatal diabetes may not always present in the immediate neonatal period. More recent studies show that monogenic forms of NDM may still occur at up to 12 months of age, albeit at a reduced frequency.<sup>1,13</sup> The likelihood of monogenic diabetes causing hyperglycemia in children older than 12 months of age is much lower. Patients may present insidiously (with polyuria, polydipsia, or failure to thrive), acutely (with ketoacidosis or altered mental status), or incidentally without symptoms.<sup>14</sup>

The odds of presenting with diabetic ketoacidosis (DKA) increases with age; this is likely the result of the difficulty recognizing early signs of diabetes in infancy.<sup>1</sup> Currently there is very little published regarding presenting signs and symptoms of diabetes in infancy. A recent study at the University of Chicago reported that 66.2% of subjects with monogenic diabetes, of all types, presented with DKA.<sup>1</sup> When patients present between 6 and 12 months of life, monogenic diabetes is less likely; but genetic testing should still be pursued. Antibodies for T1D should be drawn, including glutamate decarboxylase, zinc transporter-8, insulin, and islet antigen-2 autoantibodies. Laboratory assessment should also include urine and serum ketones, serum glucose, serum insulin, and C-peptide levels. Incidence studies in Europe show that the number of predicted new cases of T1D in the zero to 5-year age group will double by the year 2020.<sup>15</sup> Making the distinction of neonatal diabetes from T1D as early as possible is paramount for management and treatment decisions.

## TYPES OF DIABETES

Prognosis and treatment options for monogenic forms of NDM depend heavily on which gene is affected. Advances in genetic testing have allowed for more efficient and comprehensive testing to be readily available.<sup>16</sup> Despite the fact that genetic testing is expensive, in the case of neonatal diabetes, it is clearly cost-effective largely because of the high proportion of patients whose treatment will improve by such testing.<sup>17</sup> Therefore, genetic testing is indicated for all cases of diabetes diagnosed at less than 12 months of age. Here the authors provide details on some of the most common forms of infancy-onset diabetes (**Table 1**).

### ***KCNJ11, ABCC8***

Activating heterozygous mutations in the genes encoding either of the subunits of the ATP-sensitive K channel ( $K_{ATP}$  channel; *KCNJ11* or *ABCC8*) of the pancreatic beta-cell are the most common causes of permanent neonatal diabetes and the second most common cause of transient NDM.<sup>2</sup> Combined, these mutations account for more than 50% of all cases of NDM.<sup>18</sup>

#### ***Mechanism of action***

In the normal pancreatic beta-cell, increased glucose across the GLUT 2 transporter is metabolized by the enzyme glucokinase, resulting in increased production of ATP. This causes closure of the  $K_{ATP}$  channel, which, in turn, depolarizes the cell membrane, activating the influx of calcium through voltage-gated calcium channels that subsequently allows for exocytosis of insulin granules. *KCNJ11* encodes for the inner subunit (Kir6.2) of the  $K_{ATP}$  channel, whereas *ABCC8* encodes for the outer subunit (SUR1). Mutations in either gene cause the  $K_{ATP}$  channels to remain inappropriately stuck open even in the presence of hyperglycemia. Without channel closure, the cell membrane is not able to depolarize effectively; thus, insulin cannot be released from the beta-cell.

Gene	Transient vs Permanent	Inheritance	Features	Treatment
KCNJ11	Either	Spontaneous (80%), AD (20%)	Low birthweight, developmental delay, seizures (DEND syndrome), may have other neurologic features	Insulin SU
ABCC8	Either	Spontaneous, AD	Low birthweight	Insulin SU
6q24	Transient	Spontaneous, AD for paternal duplications	Low birth weight, possible IUGR, diagnosed earlier than channel mutations (closer to birth), relapsed cases may respond to SU	Insulin
INS	Either	Spontaneous (80%), AD (20%) AR (rare: T or P)	Low birthweight	Insulin
GATA6	Permanent	Spontaneous, AD	Pancreatic hypoplasia or agenesis, exocrine insufficiency, cardiac defect	Insulin
EIF2AK3 <sup>a</sup>	Permanent	Spontaneous, AR	Wolcott-Rallison syndrome, skeletal dysplasia (1–2 y old) Episodic acute liver failure, exocrine pancreatic insufficiency	Insulin
GCK <sup>a</sup>	Permanent	Spontaneous, AR (neonatal diabetes), AD (GCK-MODY)	Low birthweight	Insulin
PTF1A	Permanent	Spontaneous, AR	Neurologic abnormalities, exocrine insufficiency, kidney involvement	Insulin
FOXP3	Permanent	X-linked	Autoimmune thyroid disease, exfoliative dermatitis, enteropathy (IPEX syndrome)	Insulin
ZFP57	Transient	Spontaneous, maternal Hypomethylation Imprinting	Variable phenotype Low birth weight, macroglossia, developmental delay	Insulin
GLIS3 <sup>a</sup>	Permanent	Spontaneous, AR	Hypothyroidism, kidney cysts, glaucoma, hepatic fibrosis	Insulin

*(continued on next page)*

<b>Table 1</b> <b>(continued)</b>				
<b>Gene</b>	<b>Transient vs</b>		<b>Features</b>	<b>Treatment</b>
	<b>Permanent</b>	<b>Inheritance</b>		
PDX1	Permanent	Spontaneous, AR (neonatal diabetes), AD (PDX1-MODY)	Pancreatic hypoplasia or agenesis, exocrine insufficiency	Insulin
SLC2A2	Either	Spontaneous, AR	Fanconi-Bickel syndrome (hepatomegaly, RTA)	Insulin
SLC19A2	Permanent	Spontaneous, AR	Neurologic deficit (stroke, seizure) Visual disturbance; cardiac abnormality	Insulin Thiamine (rarely)
GATA4	Permanent	Spontaneous, AR	Pancreatic hypoplasia or agenesis, exocrine insufficiency, cardiac defect	Insulin
NEUROD1	Permanent	Spontaneous, AR	Neurologic abnormalities (later), learning difficulties, sensorineural deafness	Insulin
NEUROG3	Permanent	Spontaneous, AR	Diarrhea (due to lack of enteroendocrine cells)	Insulin
NKX2-2	Permanent		Neurologic abnormalities (later), very low birth weight	Insulin
RFX6 <sup>a</sup>	Permanent	Spontaneous, AR	Low birthweight, intestinal atresia, gall bladder hypoplasia, diarrhea	Insulin
IER3IP1 <sup>a</sup>	Permanent	Spontaneous, AR	Microcephaly, infantile epileptic encephalopathy	Insulin
MNX1 <sup>a</sup>	Permanent	Spontaneous, AR	Neurologic abnormalities (later)	Insulin
HNF1B	Transient	Spontaneous, AD	Pancreatic atrophy, abnormal kidney, and genitalia development	Insulin

*Abbreviations:* AD, autosomal dominant; AR, autosomal recessive; DEND, developmental delay, epilepsy, and neonatal diabetes; DM, diabetes mellitus; IUGR, intrauterine growth restriction; MODY, maturity onset diabetes of the young; RTA, renal tubular acidosis; SGA, small for gestational age.

<sup>a</sup> Autosomal recessive forms may be more likely in populations or families with known consanguinity.

### **Presentation**

Although *KCNJ11/ABCC8* mutations typically lead to the onset of diabetes before 6 months of age, a diagnosis after 6 months is also possible. In a recent study of subjects diagnosed at less than 1 year of age, the median age at diagnosis for subjects with *KCNJ11/ABCC8* was 9.6 weeks (interquartile range [IQR] 6.1–18.3 weeks).<sup>1</sup>

Estimates of DKA frequency at the diagnosis vary between 30% and 75%.<sup>1,19,20</sup> Intra-uterine growth restriction (thus, small-for-gestational age birthweight) is common in patients with these conditions.

### **Treatment**

Although many patients may be managed with insulin during the initial hospitalization and diagnosis, most patients with mutations in these genes can be treated with high-dose SU medications (typically 0.5–1.0 mg/kg/d of glyburide or even greater, depending mostly on the specific mutation). SUs act on the  $K_{ATP}$  channel to promote closure, allowing for insulin to be released from the beta-cell. The use of SUs in pediatric patients is considered an off-label use and is discussed later in more detail.

### **Associated features**

Because of the presence of  $K_{ATP}$  channels in the brain, patients with mutations in *KCNJ11*, particularly those with permanent forms, may exhibit increased frequency of attention-deficit/hyperactivity disorder, sleep disruptions, developmental delays, and seizures.<sup>21,22</sup> Effects may vary from mild delays without seizures to more severe delays with seizures (developmental delay, epilepsy, and neonatal diabetes [DEND] syndrome). Patients with certain mutations may have such mild delays that they remain unnoticed by their caregivers and health care providers until they emerge later in life as specific deficits become apparent when compared with their unaffected siblings.<sup>21</sup> SU therapy may improve neurologic function in addition to improving glycemic control,<sup>23–25</sup> and earlier initiation of SUs may offer more benefit.<sup>3</sup> These associations have not been as well characterized in patients with permanent *ABCC8* mutations or in transient forms of either gene.

## **6q24-Related Neonatal Diabetes Mellitus**

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Overexpression of genes at chromosome 6q24 is the most common cause of transient neonatal diabetes.<sup>26</sup>

### **Mechanism of action**

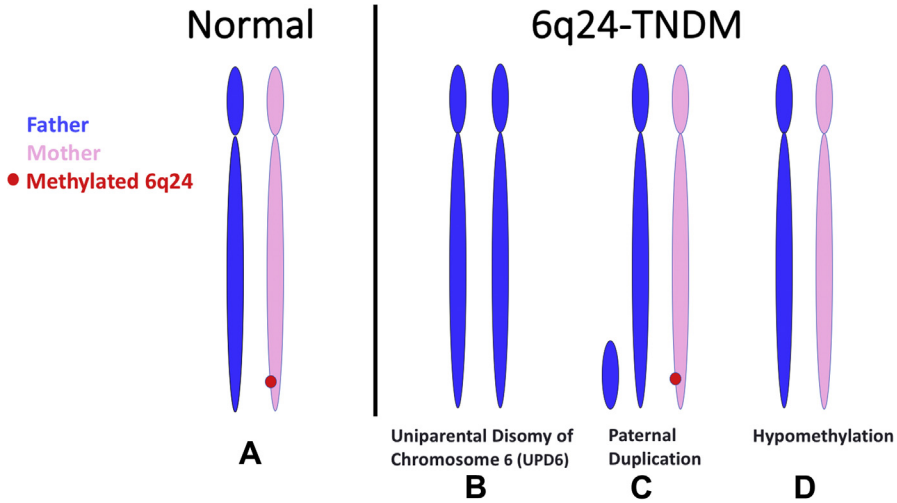
This NDM disorder can occur through any of 3 distinct mechanisms (Fig. 1), most often epigenetic: uniparental disomy of chromosome 6 (in which there are only 2 copies of 6q24 but both come from the father), duplication of the paternal 6q24 allele (in which there are 3 copies of 6q24, but 2 are from the father), or loss of maternal methylation (in which there is a defect in the silencing of the maternal allele, which can be recessively inherited). Paternal duplications are autosomal dominant and, thus, carry a 50% transmission risk when inherited from the father.<sup>27</sup>

### **Presentation**

Patients with 6q24-related NDM typically present within the first few days or weeks of life,<sup>28</sup> usually without DKA.<sup>1</sup> Although the patients' hyperglycemia may go away within the first year or so of life, hypoglycemia is possible during the remission period.<sup>29</sup> Although the exact risk is uncertain, it seems to be highly likely that the hyperglycemia will return during the teenage years; this persists into adulthood in most cases.<sup>28</sup>

### **Treatment**

Insulin is typically used during the early neonatal phase, although there is a possibility of a response to SU in some cases.<sup>30</sup> The best treatment option during the later relapse phase remains unclear; but these patients have been shown to have the ability to produce insulin and, thus, should not be treated as though they have T1D. Although



**Fig. 1.** Mechanisms of overexpression of imprinted genes causing 6q24-related neonatal diabetes. Diabetes in all cases results from overexpression of genes that are normally either silenced by maternal methylation or expressed when paternally inherited (A). Overexpression, thus, occurs when (B) both copies are paternally inherited in uniparental paternal disomy (UPD6, which can be either complete disomy or hetero-disomy), (C) an additional copy is paternally inherited because of a duplication that includes 6q24, or (D) there is a defect in maternal methylation (which can be due to recessive mutations in ZFP57). Although the parent of origin determination or detection of duplication can be possible through a variety of methods, the most comprehensive direct way of testing of overexpression of genes at 6q24 from any cause is methylation-specific multiplex ligation-dependent probe amplification or methylation-specific polymerase chain reaction/sequencing-based and is rarely offered in most commercial laboratories.

insulin has often been used in these older patients, recent studies have shown that noninsulin therapies used for type 2 diabetes may be highly effective.<sup>31,32</sup>

#### **Associated features**

Patients with 6q24-related neonatal diabetes may also present with macroglossia or umbilical hernia.

#### **Insulin Gene**

Alterations in the insulin gene (*INS*) are the second most common cause of permanent neonatal diabetes.<sup>33</sup>

#### **Mechanism of action**

Mutations in the insulin gene seem in most cases to lead to misfolding of the insulin protein. These proteins accumulate in various subcellular compartments and seem to increase endoplasmic reticulum (ER) stress and subsequent beta-cell death.<sup>34–36</sup>

#### **Presentation**

Patients with *INS* mutations may appear clinically similar to patients with early onset T1D. Although most cases will be diagnosed before 6 months of age, cases diagnosed near 12 months of age and even into the toddler years have been reported. Letourneau and colleagues<sup>1</sup> found a median age at diagnosis of 10 weeks (IQR 6.1–17.4) with 30% presenting in DKA.



**Treatment**

Patients will require insulin therapy. Anecdotal evidence suggests that early, aggressive treatment with insulin may help to preserve some beta-cell function.

**Associated features**

No other specific features are known to be associated with *INS*-related neonatal diabetes.

**Less Common Forms**

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Mutations in more than 20 genes are now known to cause diabetes onset within the first year of life, but most of these are exceedingly rare recessive conditions. Among these rarer causes, a few are relatively more common and are worth mentioning, because early recognition of associated features can be important for long-term outcomes.

***GATA6, PDX1***

*GATA6* and *PDX1* are transcription factors critical to pancreatic development. Mutations in either gene can result in a varying degree of pancreatic hypoplasia, including possible complete agenesis.<sup>37</sup> Insulin therapy, as well as pancreatic enzyme replacement therapy, is necessary for appropriate growth and glycemic control.

***EIF2AK3***

Homozygous mutations in *EIF2AK3* induce ER stress and, thus, beta-cell death and are the most common cause of NDM among consanguineous families.<sup>2</sup> Several other features may include episodic hepatic dysfunction and skeletal dysplasia; however, because these are not usually apparent in the neonatal phase, early genetic testing will help guide monitoring and management.<sup>38</sup> Insulin treatment is required.

***FOXP3***

Mutations in *FOXP3* cause a monogenic form of autoimmune diabetes, most often as part of the immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome..<sup>39,40</sup> Because the associated features of IPEX are severe enough to often cause death within the first year of life, stem cell transplantation is often considered. Early genetic diagnosis would be essential in guiding clinical decision-making.

***Early Onset Autoimmune Type 1 Diabetes***

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Most patients diagnosed with diabetes after 6 months of age will have autoimmune T1D. Among subjects diagnosed at less than 1 year of age, those with likely T1D had a median diagnosis at 42.6 weeks of age (IQR 37.4–50.4) and 87.5% presented in DKA at diagnosis.<sup>1</sup> They may be less likely to have a low birth weight. Most of these patients will test positive for at least one diabetes autoantibody. For those who have a negative autoantibody and/or genetic testing, a T1D genetic risk score assessment (most often done on a research basis) may be helpful to discern the true cause.<sup>37</sup> There is some evidence to suggest that patients with early onset T1D may experience more aggressive beta-cell decline than those diagnosed at older ages.

**MANAGEMENT CONSIDERATIONS**

The initial approach to hyperglycemia includes assessing the quantity of glucose being administered and reducing the glucose infusion rate when it does not affect patients' nutrition and growth. In the neonate, ideal glucose infusion rates should be 6 to 12 mg/kg/min to maintain appropriate minimums for growth without inefficient

conversion of energy to fat.<sup>9</sup> Patients with hyperglycemia are initially managed on an intravenous insulin infusion. Guidelines for dosing and titrating insulin infusions in neonates are lacking in the literature. In studies assessing early insulin therapy in very-low-birth-weight infants, an initial dosage of 0.05 units per kilogram per hour was commonly used.<sup>6</sup> However, other studies show effective glucose control with insulin rates ranging as low as 0.02 units per kilogram per hour, much lower than the standard dosage of 0.1 units per kilogram per hour used in older children in DKA.<sup>41</sup> In infancy, insulin infusion rates should be titrated by small increments of 0.01 units per kilogram per hour in response to glucose levels less than 200 (decrease infusion rate) or greater than 250 mg/dL (increase infusion rate). However, dosing should ultimately be guided by clinical judgment. The capillary blood glucose (BG) level should be monitored at least every hour while on intravenous insulin infusion. When hyperglycemia is persistent and insulin dependence is established, the provider should consider transition to subcutaneous insulin injections, in part to avoid complications related to central venous catheters. Treatment should be guided by recommendations from a pediatric endocrinologist.

### ***Subcutaneous Insulin***

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The initial subcutaneous doses of insulin should be given conservatively, when BG levels are at least greater than 200 to 250 mg/dL. The authors would recommend starting with preprandial short-acting doses in the amount of 0.1 to 0.15 units per kilogram per dose or doses guided by the response to intravenous insulin. The dose should be given before feeds when blood sugars are greater than 200 to 250 mg/dL. Because of the frequency of oral intake in newborns, insulin should only be given preprandially. All preprandial blood sugars should be checked at least initially, but insulin doses may only be needed with every other feed (3–4 times per day). The smallest, feasible subcutaneous dose of any insulin, including long acting (glargine) and short acting (lispro or aspart), without dilution is 0.5 units.

Smaller doses of U-100 (100 units of insulin per 1 milliliter of liquid) that would otherwise be immeasurable are possible by dilution, preferably with an insulin-specific compatible diluent (typically available through the manufacturers). Diluting one part of aspart or lispro to 9 parts diluent will yield a concentration of one-tenth of the original concentration (U-10). Therefore, doses of 0.1 to 0.9 U-100 may be used as subcutaneous injections. Such a preparation of lispro may be used for up to 28 days when stored at 41°F (and up to 14 days when stored at 86°F),<sup>42</sup> whereas the preparation of aspart may be used for up to 28 days when stored at 86°F or less.<sup>43</sup> Of note, U-10 insulin aspart may be stable for up to 7 days at 98.6°F or less when used in a continuous subcutaneous insulin infusion (CSII) pump (insulin pump).<sup>44</sup> However, diluted insulin is typically not necessary for use with insulin pumps because they are capable of administering very small doses of U-100 preparations (see later discussion). Clinical personnel, patients, and families should use caution with diluted preparations in the hospital and at home because of the potential for dosing errors.

Whether using diluted or undiluted insulin subcutaneously, the authors would recommend against the use of intermediate-acting insulins, such as regular and NPH, which have been associated with an increased risk of hypoglycemia compared with short- and long-acting analogues.<sup>45</sup> Although infants are feeding frequently and clinicians may be tempted to cover basal and bolus requirements with an intermediate insulin, when the feeding schedule ultimately becomes more spaced out, these infants will be at a higher risk of hypoglycemia. Just as with older patients, infants should also be placed on a regimen of multiple daily injections of insulin (MDI) with daily or twice-daily long-acting insulin and multiple daily doses of rapid-acting insulin to cover

hyperglycemia and carbohydrate intake (ultimately using carbohydrate counting when feasible).

Carbohydrate estimation for breastfed infants can be challenging. If patients are fed pumped breastmilk, the carbohydrate content can be estimated at approximately 2.1 g per ounce of breastmilk. Resources are available to help caregivers estimate the quantity of breastmilk and, subsequently, the carbohydrates consumed.<sup>46</sup>

### ***Continuous Subcutaneous Insulin Infusion Therapy***

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During the neonatal period, dosing can be difficult because of the frequent intake and variability in quantity. In addition, infants with neonatal diabetes are susceptible to hypoglycemia because of the relatively low insulin requirements.<sup>47</sup> Subcutaneous insulin infusions allow for very small accurate doses to be given in a physiologic way, with a continuous basal dose (as low as 0.025 units per hour) that may be adjusted hourly. In addition, pump technology allows for frequent hyperglycemia or carbohydrate bolus coverage (with doses typically as low as 0.05 units) while minimizing the potential for dangerous stacking of boluses.

All pediatric patients with diabetes (including neonatal diabetes) are candidates for CSII regardless of age.<sup>48</sup> Most observational studies have noted a decreased rate of hypoglycemic events, as well as reduced hemoglobin A<sub>1c</sub>, in those receiving CSII rather than MDI.<sup>44</sup>

When deciding on the type of insulin pump to use, the following should be considered:

- Small basal rate increments allow for a lower hourly infusion rate; different varieties of insulin pumps may have the lowest setting of 0.025 units per hour versus 0.05 units per hour. It may also be important to consider using a pump that can be programmed to deliver no insulin (0.00 units per hour).
- Consider whether there is communication with a home glucose meter, whereby data collected from the glucometer is electronically communicated to the pump directly.
- Consider the types of infusion sets and tubing. For babies with less subcutaneous fat, infusion sets using a steel needle, or sets with a 30° insertion with a shorter cannula, may be more effective. Similar to older patients who have more lean mass and less fat, such catheters may be more effectively threaded into the subcutaneous tissue manually rather than using an inserter device. However, if using sites that have more fat, including the buttocks, a 90° insertion set may be used. One should consider that the buttocks may be a problematic site because of friction with clothing and diapers and exposure to stool. Of note, shorter tubing is generally preferred for small dose administration.
- Determine if there are alarm features.
- Waterproof casing in active children is important.

In general, assessment of capillary blood sugars in early infancy can be difficult because of the limited surface area and trauma-related concerns. Continuous glucose monitoring can be a very helpful tool for glucose control and parental reassurance, regardless of treatment modality. Studies with continuous glucose monitoring systems (CGMS) in very-low-birth-weight infants reveal a higher prevalence of abnormal glucose levels as compared with standard sampling methods. A study by Iglesias Platas and colleagues<sup>49</sup> showed no adverse events associated with CGMS and, with less associated fibrosis as compared with adults, sensors may be placed for longer

periods of time in preterm infants. The thigh and upper buttock area in patients with little subcutaneous fat provide ideal insertion sites for insulin pumps and CGMs.<sup>50</sup>

### **Sulfonylureas**

SU-responsive mutations are the most common cause of neonatal diabetes. Up to 90% to 95% of patients with NDM caused by *KCNJ11* may be successfully transitioned completely off of insulin therapy with a significant decrease in glycated hemoglobin levels.<sup>19</sup> In addition to the importance of the specific mutation, 2 large studies have also shown an association of improved and expedited response with initiation of therapy at an earlier age; this may result from impaired perinatal expansion or reduced replication of beta-cells with age.<sup>51,52</sup>

A significant proportion of patients exhibit a spectrum of neurodevelopmental disability related to the expression of mutated K-ATP channels in the brain, where SU therapy may also lead to beneficial effects on neurocognitive development.<sup>53,54</sup> Patients with *KCNJ11* mutations have reduced general intellectual ability, including reasoning, vocabulary, reading, and auditory working memory, as compared with sibling controls.<sup>21</sup> There is some evidence for improved neurocognitive outcomes with SU therapy, but the degree of benefit may depend on earlier age of treatment.<sup>23,47</sup>

A trial of glyburide may be considered in newly diagnosed neonatal diabetes because of the relatively high chance of having a mutation responsive to treatment (Fig. 2). In patients referred to the Monogenic Diabetes Registry, the authors found

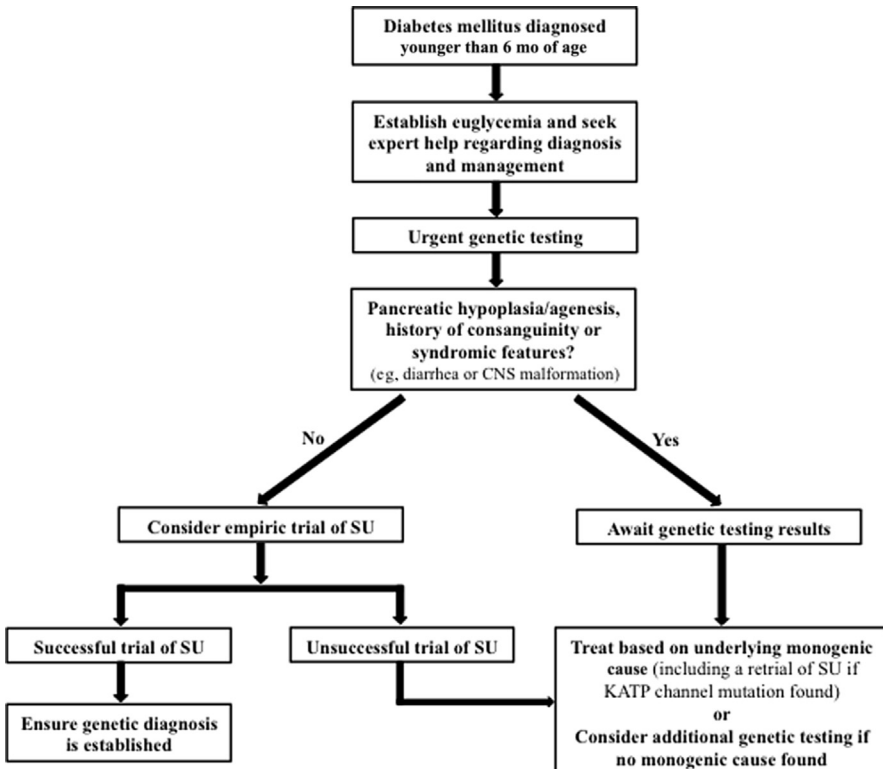


Fig. 2. Algorithm for considering SU trial. CNS, central nervous system.

that there was a mean delay of 10 weeks from the time of the diabetes diagnosis to the genetic diagnosis of NDM (range 1.6–58.2 weeks).<sup>30</sup> Because of the potential neurocognitive effects of delaying therapy, the authors, thus, suggest that a trial of SU therapy can be considered even before a genetic diagnosis is made, although genetic testing must be done in all cases. In patients with NDM who are responsive to SU therapy, glycemic outcomes are favorable and side effects are minimal.<sup>19</sup> There is some risk of hypoglycemia, although the risk seems to be much lower compared with insulin therapy.<sup>30</sup>

### ***Approach to Transitioning from Insulin to Oral Glyburide***

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If patients are on CSII (pump), the basal rate should be reduced by 50% before glyburide administration.<sup>19</sup> The basal rate may be adjusted or suspended as needed to prevent hypoglycemia during transition. Glyburide tablets can be crushed and readily prepared in aqueous suspension; although the stability has not been well studied, the authors have not experienced any problems with the use of such a suspension for 14 days. An initial dosage of 0.1 mg per kilogram per dose twice daily before meals is most often used. The point-of-care BG should be assessed at least before a meal and at bedtime. On each subsequent day, if the BG is greater than 200 mg/dL at the time glyburide is due, the dose can be increased by 0.1 mg per kilogram per dose. The dose may, thus, be increased each day, progressing up to a dosage of at least 1 mg/kg/d (usually achieved within 5–7 days) if the premeal capillary blood sugars continue to be greater than 200 mg/dL.<sup>30</sup> If the patients' point of care glucose is less than 200 mg/dL, the usual prandial insulin dose should be reduced by at least 50%. In addition, doses of insulin should only be administered at least 2 to 3 hours after glyburide is dosed to avoid hypoglycemia. **Table 2** summarizes the authors' general approach to transition from insulin to oral glyburide therapy.

The original protocol<sup>19</sup> used a BG of 126 mg/dL as a threshold for dose titration. In the authors' experience it is often better to allow a reasonable level of hyperglycemia so as to avoid hypoglycemia while insulin is also being given, especially in neonates. Although it is very important to avoid extreme hyperglycemia, we have found 200 mg/dL to be a reasonable threshold for dose titration, but this may be altered based on specific clinical scenarios and the clinical judgment of the treating team.

Response to oral medications should be achieved in those with channel mutations including *KCNJ11* and *ABCC8*. However, some nonchannel mutations, such as 6q24, have been responsive to SU therapy as well.<sup>31</sup> If the desired effect is difficult to assess, glucose and C-peptide levels may be drawn before a meal and again 90 to 120 minutes after a meal is eaten (and glyburide is given). Patients with appropriate response to glyburide should have an appreciable increase in C-peptide level following glyburide dosing and a meal. If no clinical response or appreciable C-peptide difference is seen, then SU treatment should be discontinued and the patient managed on insulin therapy until genetic testing results are available.

Glyburide transition may also be done as an outpatient, depending on the families' comfort level with diabetes and insulin management. Once insulin has been completely discontinued, or a steady dose of glyburide has been achieved, patients should continue to monitor the BG levels before meals and at bedtime. Patients should also see their provider monthly for the first 6 months, followed by every 3 months thereafter.

Table 2

## Transition from insulin to oral sulfonylurea therapy (specifically glyburide)

Day	Glucose Monitoring	Insulin Adjustments	Glyburide Dosing
Prep	Monitor the capillary BG before meals, 2 h after meals, bedtime, and 2 AM. Monitor the ketones when BG >300. Have a plan for hypoglycemia.	Maintain usual insulin regimen via pump or customary basal-bolus injections. Reduce the basal insulin by 50% (pump: decrease before breakfast on day 1; long-acting: reduce in the evening before transition)	Tablets available (may be halved) are as follows: 1.25, 2.5, or 5.0 mg. For infants, tablets may be crushed and suspended in formula or water.
1	Monitor the capillary BG before meals, bedtime, and 2 AM. If BG <i>before a meal</i> is >200 mg/dL (11.1 mmol/L) → <200 mg/dL (11.1 mmol/L) →	Administer rapid-acting bolus insulin as needed based on the capillary BG (unless glyburide is given within the last 2 h <sup>a</sup> ): Give the usual bolus dose. Give 50% of the usual insulin dose.	Start with 0.1 mg/kg before breakfast and dinner (total 0.2 mg/kg/d). Depending on BG at the second dose, consider skipping a dose if BG is trending low.
2–7	Monitor the capillary BG before meals, bedtime, and 2 AM. If BG <i>before SU</i> dose is >200 mg/dL (11.1 mmol/L) → <200 mg/dL (11.1 mmol/L) →	Continue to wean down the basal dose as tolerated. Administer rapid-acting bolus insulin as needed based on the capillary BG: Give bolus dose from the previous day. → Decrease the bolus dose by 50%. →	Each day the dose will increase by 0.2 mg/kg/d (0.1 mg/kg per dose) depending on BGs. Increase the dose by 0.1 mg/kg. Continue the dose from the previous day.
Last	On the final day and after discharge, continue checking BG at least before every meal/feed, bedtime, and 2 AM to monitor the response. Relative hypoglycemia may necessitate lowering of the glyburide dose in the following weeks to months.	In most SU-responsive cases, insulin can be discontinued in 5–7 d, although mild hyperglycemia may occur. Treat with last titrated short-acting bolus insulin as needed. In some cases, low-dose basal insulin may be needed as well.	By the end of 5–7 d, patients will have either clearly responded to a lower dose or will be on at least 1 mg/kg/d. The dose may continue to be increased after discharge, with some patients requiring up to 2.0–2.5 mg/kg/d (which may be lowered in the following weeks to months).
Notes	If the expected response is uncertain, C-peptide levels before and after (90–120 min after) a meal and glyburide (no insulin) may be done, particularly when the dose is maximized at 1 mg/kg/d. If levels before SU are nearly undetectable but show a significant increment on glyburide, responsiveness is likely. Consider a further increase up to 2.0–2.5 mg/kg/d as needed.	BG ranges and insulin adjustments are only a guideline; the physician should be guided by clinical judgment. If there is any indication that glyburide is helping to control BG levels overall, it is often better to decrease the insulin aggressively so as to avoid hypoglycemia.	Patients with neurodevelopmental disability or those who are older at the time of transition may require higher doses of glyburide. In such cases, the possible benefit of continuing a high dose for the long-term should be carefully considered even if patients still require insulin.

<sup>a</sup> If glyburide was given in last 2 hours or with current BG check, recheck with next feed only; do not give insulin.

## SUMMARY

NDM is caused by a single gene mutation. These patients will most often present within the first 6 months of life but, less commonly, may present at up to 12 months of life. Early clarification of the molecular cause by genetic testing is paramount. Patients with channel mutations, such as *KCNJ11* and *ABCC8*, can be transitioned to SU agents, allowing for simplified administration, decreased treatment costs, and potential neurodevelopmental improvements. Genetic testing may also guide longitudinal monitoring for other associated problems in forms with syndromic features as well as for screening of family members. Patients with 6q24 have a transient hyperglycemia in infancy with the onset of diabetes in adolescence. It is important to distinguish monogenic NDM from other causes of hyperglycemia in the newborn. Insulin-dependent hyperglycemia that persists longer than a week to 10 days, should raise suspicion for an underlying monogenic cause of diabetes and prompt genetic testing.

### Best Practices

- There are more than 20 known monogenic causes of NDM, which may be transient or permanent (see [Table 1](#)).
- Genetic testing should be pursued in any infant with neonatal diabetes, even if hyperglycemia resolves. An underlying monogenic cause can lead to major differences in clinical management and is highly likely when diabetes is diagnosed at less than 6 months of age and less likely but still possible in infants with diabetes between 6 and 12 months of age.
- Hyperglycemia due to stress or illness may occur in neonates, especially in those who are premature or had very low birth weight (see [Fig. 2](#)). Diagnosis of diabetes (and genetic testing) should be considered:
  - Consider the diagnosis when hyperglycemia (glucose >250 mg/dL) persists beyond a few days without alternative explanation.
  - Consider the diagnosis when true serum glucose levels exceed 300 mg/dL, regardless of the time course.
  - Consider the diagnosis in any infant requiring insulin before 6 to 12 months of age.
- In neonates or infants, the authors would recommend using CSII to titrate insulin more precisely and better control blood sugar levels.
- SU responsive mutations are the most common causes of neonatal diabetes, and early treatment with SUs may improve neurocognitive deficits associated with these mutations. A trial of SU (glyburide) may be considered even before the genetic testing results are available (see [Fig. 2](#)).
- Depending on the age of patients and the comfort level of the families, transition insulin therapy to oral glyburide may be done as an inpatient or from home. See [Table 2](#) for guidance on medication transition.

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