Neonatal diabetes mellitus (NDM) is a rare genetic condition with an incidence of 1 in 100,000 (1) that presents before 1 year of age (2). There are two main clinical forms of NDM: permanent NDM (PNDM), which requires lifelong treatment with insulin, and transient NDM (TNDM), which may spontaneously remit and sometimes recurs in the second to third decade of life. In most cases, TNDM and PNDM cannot be distinguished clinically at the time of diagnosis, and genetic analysis needs to be performed.

The genetic origin for >90% of TNDM cases has been established. In TNDM, 68% of the cases have abnormalities in an imprinted region on chromosome 6q24; 10% have KCNJ11 gene mutations; and 13% have an ABCC8 gene mutation (3). Multiple genes involved in pancreatic development, β-cell apoptosis, or dysfunction cause PNDM (4). The most common mutations are in the $K_{ATP}$ channel genes KCNJ11 (30%) and ABCC8 (11%) or the insulin (INS) gene (13%) (3).

Insulin is acutely required in most infants to establish metabolic control in NDM (5). Early initiation of sulfonylurea treatment is also recommended (6) as a treatment option in selected cases of NDM caused by ABCC8 and KCNJ11 mutations, and, in responsive cases, sulfonylurea therapy provides better long-term metabolic control (7,8) and could even improve neurodevelopmental outcomes (9).

The MiniMed 530G (Medtronic, Inc., Northridge, CA) is a first-generation artificial pancreas system approved by the U.S. Food and Drug Administration (FDA) on 26 September 2013 for the management of diabetes in people ≥16 years of age. The system includes an external glucose sensor and insulin pump, transmitter, glucose meter, and therapy management software. Sensor signals are transmitted to the MiniMed 530G insulin pump and converted into glucose values every 5 minutes. Fingerstick blood glucose testing is still required for both device calibration and management decisions. The unique feature of this system is that it can be programmed to automatically suspend delivery of insulin when sensor glucose values fall below a predefined threshold between 60 and 90 mg/dL. The system is not designed to treat hypoglycemia, but rather to detect severe hypoglycemia, alerting the user to immediately check blood glucose to determine appropriate treatment. The ASPIRE (CArfilzomib, Lenalidomide, and Dexamethasone versus Lenalidomide and Dexamethasone for the treatment of Patients with Relapsed Multiple Myeloma) study showed reduced nocturnal hypoglycemia without significant differences in A1C when using sensor-augmented insulin pump therapy (SAPT) with a threshold-suspend feature compared to SAPT without threshold suspend (10).
Case Report
A 3-month-old girl with no significant medical history presented to the emergency room with irritability, lethargy, emesis, and difficulty breathing. On initial physical examination, the patient appeared severely dehydrated and tachycardic, with labored breathing consistent with Kussmaul breathing. Initial laboratory evaluation revealed hyperglycemia (serum glucose 605 mg/dL), an A1C of 13.3%, severe metabolic acidosis (pH 6.87, bicarbonate 3 mEq/L), hypernatremia (153 mEq/L), and a potassium level of 4.2 mEq/L. She was admitted to the pediatric intensive care unit (PICU) and started on an intravenous insulin infusion with a total daily requirement of 1 unit/kg/day. Additional testing included islet cell and glutamic acid decarboxylase antibodies, which were negative; C-peptide (1.6 ng/mL [reference 0.9–7.1]); an abdominal ultrasound, which showed no evidence of pancreatic agenesis or hypoplasia; and genetic testing to evaluate for the most common gene mutations implicated in NDM. Genetic testing revealed a missense point mutation involving the INS gene (c.323A>G, p.Tyr108Cys).

Medtronic, Inc., was contacted, and a MiniMed 530G with the Enlite sensor system and supplies were provided to the center to allow for immediate use during the patient’s hospital stay. Initial system placement occurred in the PICU 2 days after diagnosis, when the patient was clinically stable and ready to be transitioned to a subcutaneous insulin regimen. The insulin infusion set used was the Medtronic Sure-T 6 mm, inserted into the subcutaneous tissue and recommended for site change every 2 days. Enlite sensors were used to measure glucose values in the interstitial fluid and recommended for site change every 6 days. These sensors are currently approved for use on the abdomen, but the patient’s size limited abdominal use, and sensor locations included the outer legs and arms.

Although the patient was sent home with the SAPT system meter, hospital policy required fingerstick glucose values to be obtained using the Nova Biomedical Point-of-Care Connectivity and Xpress Analyzer with StatStrip Xpress glucose strips. These glucose values were also used to provide two to four sensor calibrations daily during inpatient management. Simple but necessary accommodations for pump use in such a small infant included limiting patient access to the pump and tubing to avoid unintentional disconnection.

Some degree of anticipated variability did occur between blood glucose and sensor glucose readings. However, overall, sensor data provided valuable trend information for dose considerations.

Figure 1 provides an overview of daily hospital use of the sensor. As shown, subcutaneous insulin infusion was started initially at a low rate and titrated upward based on both the sensor data and point-of-care fingerstick blood glucose levels.

The patient received only basal insulin during hospitalization with the expectation that use of carbohydrate ratios and correction factors would be started in the outpatient environment after improved assessment of basal needs and insulin sensitivity. She was initially started with a basal rate of 0.025 units/hour, with fingerstick glucose checks every hour. If two readings were >400 mg/dL, the basal rate was titrated up by 0.025 units. High and low alarms were set at 400 and 200 mg/dL, respectively, and the threshold suspend was calibrated at a sensor value of 90 mg/dL. Conservative insulin doses and elevated blood glucose targets between 200 and 400 mg/dL were chosen to avoid hypoglycemia in such a young patient.

In the course of 3 days, using both sensor data and fingerstick glucose checks, the insulin dose was titrated up rapidly to almost eight times the initial dose. Figure 1 illustrates how sensor and fingerstick glucose data...
helped providers rapidly increase the insulin dose during the first day of transition. Fingerstick glucose values were obtained every hour on the first day of transition and every 2 hours on day 2; ultimately, these were decreased to only four times per day and as needed for calibration. Sensor data were checked every hour by the nurses and, if outside the target range, were cross-checked with fingerstick values. The fingerstick readings were used to help determine insulin dose changes.

There were no incidences of sensor failure, nor was the low glucose sensor threshold reached at any time during the initial hospitalization. However, the pump was manually suspended once when the sensor value was persistently below the 200 mg/dL target to prevent hypoglycemia. Later, the patient was also provided with multiple daily basal rates to account for decreased feedings between midnight to 6:00 a.m.

Although genetic test results were pending, the patient on hospital day 7 was started on glyburide because some cases of NDM will respond favorably to this treatment (2). Although glyburide was increased to the maximum recommended dose of 0.8 mg/kg/day and she required a dramatic reduction in her insulin infusion rate, she did not achieve insulin independence. She was discharged with a daily insulin requirement of 0.3 units/kg/day, including basal rates of 0.025 units/hour from midnight to 6:00 a.m. and 0.1 units/hour from 6:00 a.m. to midnight, for a total of 1.95 units of aspart insulin daily.

Gliburide was discontinued when the results of the genetic testing returned, and the daily insulin requirement remained ~0.3 units/kg/day. Subsequently, on an outpatient basis, the target range was decreased to 80–180 mg/dL, and, as the patient started feeding less frequently and began eating solid food, she started to receive insulin boluses for meals. Her A1C progressively improved to 7.7% (estimated average glucose 174 mg/dL). To date, the patient has not experienced any severe hypoglycemia, has had appropriate growth and weight gain, and has achieved age-appropriate milestones.

**Discussion**

The patient in this case has a mutation previously described and known to cause PNDM (11). The uniqueness of this case is the management of NDM right after diagnosis using a recently introduced first-generation artificial pancreas system. Although not FDA approved for use in patients <16 years of age, using the MiniMed 530G with Enlite sensor device was optimal in this case, allowing for delivery of the very small doses of insulin necessary to treat this infant. Using multiple daily injections (basal/bolus therapy) typical for pediatric patients, precise delivery of insulin would have been challenging, and such a regimen would have greatly increased the risk of hypoglycemia. Before the first-generation artificial pancreas system became available, the use of diluted insulin might have been considered to minimize the risk. Using this system, we were able to rapidly increase the insulin doses as needed without the patient experiencing significant hypoglycemia.

We noticed a significant decrease in the patient’s required insulin dose after starting glyburide. Since our patient has a mutation in the *INS* gene rather than in the *ABCC8* or *KCNN1* gene, the insulin dose reduction could not be attributed to sulfonylurea. This reduction was most likely caused by recovery of endogenous insulin secretion after the glucotoxic effect on the pancreas decreased.

Detectable C-peptide at the time of diagnosis in cases of PNDM caused by *INS* gene mutation has been pre-
viously reported (12,13). Similar to what was previously reported in the literature (12), at 1 year after diagnosis, the patient’s fasting C-peptide was low (0.3 ng/mL [reference 1.1–4.4]). Given the unique circumstances of the situation, PICU and floor nursing staff had to be specifically educated on this new form of SAPT with threshold suspend. One-on-one teaching, along with the provision of pump instruction manuals and 24 hour/day access to both the endocrinologists and a CDE helped the nursing staff with this new technology. Since this event, hospital policies have been updated to incorporate this new technology and to support nursing staff in their roles related to pump therapy, especially when parents have not yet been trained on pump technology, as occurred in this case.

For this patient, the pump order was initiated 2 days after diagnosis. However, in our state at the time of this event, Medicaid did not approve CGM. The new pump system presented a significant barrier in insurance approval and timely shipment of the patient’s MiniMed 530G system. Ongoing team efforts with Medtronic and the state regulatory office proved successful in obtaining approval ~1 month after the initial request. This required additional clinical review, as well as direct communication with the chief medical officer at the Oklahoma Health Care authority and the senior nurse within the hospital’s medical authorization unit. Additional investigation was necessary to determine a local supplier able to accept state Medicaid payment. After several unsuccessful attempts, Medtronic was able to develop a local process. The patient’s personal product was received 5 months after the initial medical order.

This new, first-generation artificial pancreas system not only provided optimal pharmacological doses of insulin, but also allowed the diabetes team to make precise dose adjustments. It also allowed continuous monitoring of glucose values with threshold suspend technology, assisting in the prevention of hypoglycemia. Furthermore, this novel use of new technology allowed a safe transition from the PICU to the hospital medical-surgical unit and, ultimately, to the home environment.

Duality of Interest
No potential conflicts of interest relevant to this article were reported.

References
1. Grulich-Henn J, Wagner V, Thon A, et al. Entities and frequency of neonatal diabetes: data from the diabetes documentation and quality management system (DPV). Diabet Med 2010;27:709–712
2. Karges B, Meissner T, Icks A, Kapellen T, Holl RW. Management of diabetes mellitus in infants. Nat Rev Endocrinol 2011;8:201–211
3. Stoy J, Greeley SA, Paz VP, et al. Diagnosis and treatment of neonatal diabetes: a United States experience. Pediatr Diabetes 2008;9:450–459
4. Rubio-Cabezas O, Ellard S. Diabetes mellitus in neonates and infants: genetic heterogeneity, clinical approach to diagnosis, and therapeutic options. Horm Res Paediatr 2013;80:137–146
5. Greeley SA, Naylor RN, Philipson LH, Bell GI. Neonatal diabetes: an expanding list of genes allows for improved diagnosis and treatment. Curr Diab Rep 2011;11:519–532
6. Thurber BW, Carmody D, Tadie EC, et al. Age at the time of sulfonylurea initiation influences treatment outcomes in KCNJ11-related neonatal diabetes. Diabetologia 2015;58:1430–1435
7. Philla KQ, Bauer AJ, Vogt KS, Greeley SA. Successful transition from insulin to sulfonylurea therapy in a patient with monogenic neonatal diabetes owing to a KCNJ11 P333L mutation. Diabetes Care 2013;36:e201
8. Wagner VM, Kremke B, Hiort O, Flanagan SE, Pearson ER. Transition from insulin to sulfonylurea in a child with diabetes due to a mutation in KCNJ11 encoding Kir6.2: initial and long-term response to sulfonylurea therapy. Eur J Pediatr 2009;168:359–361
9. Shah RP, Spruyt K, Kragie BC, Greeley SA, Mualil ME. Visuomotor performance in KCNJ11-related neonatal diabetes is impaired in children with DEND-associated mutations and may be improved by early treatment with sulfonylureas. Diabetes Care 2012;35:2086–2088
10. Bergenstal RM, Klonoff DC, Garg SK, et al. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med 2013;369:224–232
11. Edghill EL, Flanagan SE, Patch AM, et al. Insulin mutation screening in 1,044 patients with diabetes: mutations in the INS gene linked to permanent neonatal/infancy-onset diabetes mellitus. J Clin Invest 2008;118:2148–2156
12. Colombo C, Porzio O, Liu M, et al. Seven mutations in the human insulin gene linked to permanent neonatal/infancy-onset diabetes mellitus. J Clin Invest 2008;118:2148–2156
13. Polak M, Dechaume A, Cave H, et al. Heterozygous missense mutations in the insulin gene are linked to permanent diabetes appearing in the neonatal period or in early infancy: a report from the French ND (Neonatal Diabetes) Study Group. Diabetes 2008;57:1115–1119

M R A I N E T A L .