CHRONIC CONDITIONS

Management of Type 1 Diabetes in Children in the Outpatient Setting

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EDUCATION GAP

Pediatricians should be aware of diabetes treatment advances, which can lead to optimal control of type I diabetes in the outpatient setting.

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

1. Provide a concise summary of the epidemiology, pathophysiology, and initial presentation of type 1 diabetes in children.
2. Highlight routine diabetes management and screening recommendations.
3. Review the available insulin preparations used in pediatric type 1 diabetes management.
4. Illustrate contemporary diabetes technology and its role in improving diabetes care.

INTRODUCTION

The year 2021 marked the hundredth anniversary of the discovery of insulin by Frederick Banting and Charles Best. (1) This landmark discovery transformed type 1 diabetes from a fatal to a chronic disease. During the past hundred years, type 1 diabetes management has evolved tremendously. Currently, we live in an exciting era of diabetes care that not only provides children with reliable lifesaving insulin but, with recent advancements in insulin delivery and blood glucose monitoring, also promotes a return to normal childhood activities with a hope for reduced long-term complications.

Management of type 1 diabetes in outpatient settings is a complex yet rewarding process. The advancements in diabetes technology and the availability of new preparations of insulin have made optimal control of type 1 diabetes in children a feasible task. In this article, we provide a comprehensive review of the current cutting-edge approaches to children with type 1 diabetes. Furthermore, we explore and discuss the available insulin delivery systems and how they may improve outcomes for children with type 1 diabetes.

ABBREVIATIONS

CGM continuous glucose monitor
DKA diabetic ketoacidosis
FDA Food and Drug Administration
MODY maturity-onset diabetes of the young

EPIDEMIOLOGY OF TYPE 1 DIABETES

The incidence of type 1 diabetes seems to be steadily increasing, (2)(3) with a prevalence among youth in the United States estimated to be 1.54 to 1.93 per 100,000 younger than 20 years. (4)(5) The prevalence of this disease is disproportionately higher among non-Hispanic white individuals compared with all other ethnic groups. Native Americans have the lowest incidence of type 1 diabetes. (4) The peak incidence of diagnosis is bimodal, with a peak between 5 and 9 years of age and another peak between 10 and 14 years of age. (6)(7)

It is essential to differentiate between the different types of diabetes in children. Although type 1 diabetes continues to be the most common form of diabetes in children, there has been an increase in the incidence of type 2 diabetes as well. This increase has been associated with the rise of prevalence of obesity among youth in the United States and worldwide. Note, though, that the presence of obesity in a child with new-onset diabetes is not sufficient to determine the presence of type 2 diabetes over type 1. Therefore, measuring diabetes autoantibodies is frequently necessary to make that differentiation (Table 1).

One form of diabetes mellitus that is often overlooked is monogenic diabetes, or maturity-onset diabetes of the young (MODY), which is a group of genetic forms of diabetes that vary in severity from normal variance with no need for treatment to progressive forms that require insulin treatment similar to type 1 diabetes. In their analysis from the SEARCH for Diabetes in Youth study, Pihoker et al (10) found that 1.2% of children with diabetes have MODY. (11) When a child presents with new-onset diabetes, a clinician should suspect MODY in the presence of negative diabetes antibodies and a strong family history of diabetes mellitus.

PATHOPHYSIOLOGY OF TYPE 1 DIABETES

Type 1 diabetes results from insulin insufficiency due to β-cell destruction from an autoimmune process occurring in genetically susceptible individuals exposed to environmental and immunologic factors. (12) The progression toward overt type 1 diabetes typically goes through 3 consecutive stages: the first stage is manifested by the presence of 2 or more autoantibodies in a presymptomatic and normoglycemic individual; the second stage comprises the presence of autoantibodies with glucose intolerance in a presymptomatic patient; and the third stage begins when the patient starts experiencing the typical symptoms of

Table 1. Comparison between Type 1 and Type 2 Diabetes in Children (5)(6)(8)(9)

VARIABLE	TYPE 1 DIABETES	TYPE 2 DIABETES
Average age at onset	Most commonly <20 y; peaks at 5–9 y and 10–14 y	Postpubertal
Ethnicities with highest prevalence	White, Hispanic, Black	Native American, Black, Hispanic, Asian, Pacific Islander
Physical examination findings	Body habitus tends to be thin or normal; however, some may be overweight	Overweight or obese; signs of insulin resistance present (acanthosis nigricans, hyperpigmentation in the axillary region)
Pathophysiology	Autoimmune destruction of β cells leading to insulin deficiency; genetic susceptibility with exposure to environmental and immunologic factors	Insulin resistance leading to increased insulin secretion; untreated extreme hyperglycemia may impair β cells, leading to ketosis and acidosis
Presentation	Polyuria, polydipsia; weight loss; 30%–40% present in DKA	Polyuria, polydipsia; weight loss; up to 20% of adolescents with type 2 may have DKA
Diagnosis	Glycohemoglobin ≥6.5%; fasting blood glucose >125 mg/dL (>6.9 mmol/L); random blood glucose ≥200 mg/dL (≥11.1 mmol/L); ≥2 positive antibodies: GAD, IA-2, IA-2b, ZnT8	Fasting blood glucose >125 mg/dL (>6.9 mmol/L); random blood glucose >200 mg/dL (>11.1 mmol/L); glycohemoglobin ≥6.5%; antibody negative
Treatment	Subcutaneous insulin	Glycohemoglobin <8.5% or sustained postprandial glucose <240 mg/dL (<13.3 mmol/L): lifestyle modifications; oral medications – metformin; GLP-1 receptor agonist (Liraglutide®) in those aged ≥10 y; glycohemoglobin >8.5% or sustained postprandial glucose >240 mg/dL (>13.3 mmol/L): subcutaneous insulin should be added to the treatment regimen

DKA=diabetic ketoacidosis, GAD=glutamic acid decarboxylase, IA-2=tyrosine phosphatase, ZnT8=zinc transporter 8.

diabetes mellitus (polyuria, polydipsia, weight loss, and development of diabetic ketoacidosis [DKA]). (13)(14)

The 4 main autoantibodies found in patients with type 1 diabetes are glutamic acid decarboxylase, tyrosine phosphatase, insulin, and zinc transporter 8 antibodies. The presence of 2 or more of these antibodies in a patient with a genetic propensity for type 1 diabetes places the lifelong risk of developing symptomatic type 1 diabetes close to 100%; the 5- and 10-year risk is approximately 44% and approximately 70%, respectively. (15)

PRESENTATION, DIAGNOSIS, AND INITIAL MANAGEMENT OF NEW-ONSET TYPE 1 DIABETES

Although preventable, approximately one-third of children with new-onset diabetes present with DKA in the United States. (16)(17) This high incidence identifies an area for needed improvement in the identification and management of children with new-onset diabetes. (18)

Presentation

Typical clinical symptoms associated with type 1 diabetes are polyuria, polydipsia, and nocturia. New onset of recurrent bed-wetting is not uncommon in young children with type 1 diabetes. Weight loss is frequently seen at the time of new-onset type 1 diabetes diagnosis. If unrecognized, these symptoms can rapidly progress to abdominal pain, recurrent emesis, dehydration, weakness, and lethargy, (19) which are all symptoms of DKA.

Diagnosis

In the clinic setting, when new-onset diabetes mellitus is suspected in a child, the presence of 1 or more of the following laboratory findings confirms the diagnosis:

- A random plasma glucose level greater than or equal to 200 mg/dL (≥11.1 mmol/L) in the presence of classic symptoms of type 1 diabetes as described previously herein.
- A fasting glucose level greater than or equal to 126 mg/dL (≥7.0 mmol/L).
- A 2-hour glucose level greater than or equal to 200 mg/dL (≥11.1 mmol/L) after a 1.75–g/kg of glucose load (maximum of 75 g).
- A glycohemoglobin level greater than or equal to 6.5%.

If the child presents with symptoms suggestive of DKA, additional laboratory test results should be obtained. Cashen and Petersen (19) detailed the diagnostic criteria and management of DKA in a review article.

Management

Once the diagnosis of new-onset diabetes mellitus is established, insulin therapy should be started. Delay in initiating insulin therapy may lead to progression to DKA.

For non–critically ill children with new-onset type 1 diabetes, there is a debate about whether inpatient diabetes management is required. Many experts argue that inpatient management for new-onset diabetes is not cost-effective and does not lead to better long-term metabolic outcomes. (20)(21) Despite that argument, many countries around the world, and many centers in the United States, opt to admit patients with new-onset diabetes to provide extensive and multidisciplinary diabetes education, to monitor for adverse reactions to treatment, and to ensure that the patients and their families are comfortable with starting the diabetes management journey at home.

Regardless of the setting of initial diabetes education, the diabetes treatment team should include an expert in pediatric diabetes (pediatrician or endocrinologist), a diabetes educator with expertise in pediatric-onset diabetes, a dietitian, a social worker, and a mental health specialist to help the child and the family cope with the psychological burden of this chronic disease.

INSULIN

At this time, due to the nature of the disease, intensive insulin therapy is the only treatment for patients with type 1 diabetes. This is established through a daily multiple-injection regimen or via a continuous subcutaneous insulin infusion device (insulin pump).

Although common practice is to use insulin in the form of basal (insulin that is administered regardless of the patient's feeding status) and prandial (ie, administered before or around meals/snacks) insulin for the management of type 1 diabetes in children, note that insulin therapy should be individualized and titrated based on the need of the child, the child's lifestyle, and the child's blood glucose patterns throughout the day. (22)

Throughout the past century, insulin preparations have advanced tremendously from purified extract from the pancreas in 1921 to modified insulin analogues using recombinant DNA technology today. (23)

Exogenous insulin preparations are broadly divided into 2 categories: rapid-acting/short-acting insulin analogues and basal insulin analogues. In each of these categories, the advancements in genetic engineering and recombinant

Table 2. Comparison of the Different FDA-Approved Insulin Products for Children with Type 1 Diabetes (24)(25)(26)(27)

INSULIN TYPE		ONSET	DURATION (h)	PEAK (h)
Ultra-long acting	Degludec	30–90 min	>24	None
Long acting	Glargine	1–3 h	24	None
	Determir	1–2 h	24	6–8
Intermediate acting	NPH	1.5–4 h	Up to 24	2.8–13
Short acting	Regular	0.5–1 h	5–8	2–4
	Aspart	10–20 min	3–5	1–3
	Glulisine	10–20 min	6	1
	Lispro	15 min	2–5	0.5–1.0
Ultra-rapid acting	Ultra-rapid aspart (Fiasp®)	5 min	3–4	23 min

FDA=Food and Drug Administration, NPH=neutral protamine Hagedorn.

DNA technology have allowed for the invention of different types of insulin products that vary in onset of action, peak, and length of effect (Table 2). (23)

Rapid-Acting/Short-Acting Insulin Analogues

These forms of insulin differ from each other by small alterations in the amino acid structure of the insulin molecule. In 1982, regular recombinant human insulin (Humulin®; Eli Lilly and Co, Indianapolis, IN) was the first genetically engineered medication ever approved by the Food and Drug Administration (FDA). (22) This was followed by Novolin® R (Novo Nordisk Inc, Plainsboro, NJ) in 1991. To improve the insulin absorption process when administered subcutaneously, newer insulin analogues were produced: lispro (Humalog®; Eli Lilly and Co) was approved by the FDA in 1996, aspart (NovoLog®; Novo Nordisk Inc) in 2000, and glulisine (Apidra®; sanofi-aventis US, Bridgewater, NJ) in 2004. (1) These analogues are more rapidly absorbed, metabolized, and excreted than human regular insulin, providing a more ideal way to dose insulin with meals for patients with diabetes. Recently, ultra-rapid-acting insulin preparations were introduced to the market. In January 2020, Fiasp® (Novo Nordisk Inc), an ultra-rapid-acting insulin aspart, was approved by the FDA for use in children as young as 2 years old. The intent of the ultra-rapid-acting insulin is to make it easier for patients with diabetes to administer insulin for carbohydrate coverage right before, while, or even within 20 minutes after eating. (23)

Long-Acting Insulin

These forms of insulin are designed to be administered once a day to maintain steady glucose levels throughout the day. Similar to short-acting insulin, forms of long-acting insulin differ in their amino acid structures. In the United States, glargine (Lantus® [sanofi-aventis US] and Basaglar® [Eli Lilly and Co]) and determir (Levemir®; Novo Nordisk Inc) are long-acting insulin forms approved for use in children for diabetes management. In 2016, the FDA approved use of the ultra-long-acting insulin degludec (Tresiba®; Novo Nordisk Inc) in children.

DIABETES MANAGEMENT AT HOME

Before embarking on the different ways to manage type 1 diabetes in children at home, it is critical to mention the tremendous social and psychological impact of this disease on children and their families on starting the journey of self-management.

The optimal method to manage type 1 diabetes at home differs significantly among patients based on their age, eating habits, lifestyles, parental level of education, socioeconomic status, and many other factors. However, it is established that the constant gold standard is to deliver an intensive insulin regimen via multiple daily injections or a continuous insulin infusion device (insulin pump). (22)

To determine the total daily dose of insulin, the patient's age, weight, and pubertal status are considered. The usual initial total daily insulin dose is 0.5 to 1.0 U/kg.

Multiple Daily Injections

To maintain insulin replacement as close to physiologic as possible, a combination of long- and short-acting insulin preparations is usually needed. A ratio of 40% to 50% of long-acting insulin and 50% to 60% of short-acting insulin is widely acceptable as an initial dosing regimen. In most scenarios, long-acting insulin is administered once a day. Short- or rapid-acting insulin preparations are typically administered preprandially to prevent hyperglycemia after eating. The timing of insulin administration is adjusted based on the child's eating habits and the pattern of their glucose trends associated with food. In certain situations, rapid-acting insulin is given between meals in patients with significant hyperglycemia or an illness. The dose of short-acting insulin is calculated based on insulin-

to-carbohydrate ratios, or fixed insulin doses based on the amount of carbohydrates the child eats with every meal. To provide flexibility, insulin doses are tailored to the child's carbohydrate intake with every meal, hence carbohydrate counting with insulin-to-carbohydrate ratios is generally the preferred method when the patient and/or the family can apply these skills after inpatient or outpatient education. Preprandial or between-meal hyperglycemia is treated with correction doses of short-acting insulin. This is usually calculated based on a glucose target and correction factor or on a sliding scale.

Insulin doses are adjusted frequently after diagnosis depending on glucose level patterns. Many diabetes centers invest time and effort to educate patients and families on monitoring patterns of hypoglycemia and hyperglycemia and on self-adjusting insulin doses. Avenues of communication with the diabetes management teams are open for questions and concerns from families of children with diabetes.

To clarify the process outlined previously herein, we provide a practical example. A 10-year-old boy presents with a 2-week history of polyuria, polydipsia, and weight loss. At presentation he is found to have a random glucose level of 285 mg/dL (15.8 mmol/L) and a glycohemoglobin level of 8.9%. The remainder of his evaluation ruled out DKA. After discussing the diagnosis of diabetes mellitus with the child and his family, the diabetes team, in coordination with the child's family and primary care provider, decided to admit him to the hospital for diabetes management and education. The child's weight is 32 kg and he is prepubertal. The diabetes treatment team decided to start him on a daily multiple-injection insulin regimen.

Because the boy is prepubertal and appeared well-hydrated, his initial total daily dose of insulin is calculated based on 0.7 U/kg (a value of 0.5–1.0 U/kg per day); the decision to choose the initial dose depends on the setting (whether the child is observed in the hospital or at home), the age of the child, and pubertal status. Typically, lower doses are chosen in younger, lean, and prepubertal children.

- Total daily dose = 32 × 0.7 = 22.4 U per day (rounded to 22 U daily)
- Dose of long-acting insulin = 22 × 50% = 11 U to be administered at bedtime daily
- For short-acting insulin dose, the team decided to calculate based on a carbohydrate ratio and correction factors as follows:
  - To estimate the insulin-to-carbohydrate ratio, the "500 rule" was used; this is a widely accepted rule to calculate the carbohydrate ratio by dividing 500 by the total daily dose of insulin. Insulin-to-carbohydrate ratio = 500/22=22.7 (rounded to 23). This means that the patient will receive 1 U of short-acting insulin for every 23 g of carbohydrates consumed.
  - To establish the correction doses of insulin for elevated glucose levels before meals, the team chooses a target glucose level of 120 mg/dL (6.7 mmol/L). They used the "1,800 rule," which is another widely accepted rule to calculate correction factor by dividing 1,800 by the total daily dose of insulin. Correction factor = 1,800/22=81.8 (rounded to 80). This means that 1 U of insulin is estimated to lower the glucose level by 80 mg/dL (4.4 mmol/L). So, the patient, his family, and the hospital staff will be using the following formula to calculate insulin dose in the case of hyperglycemia: (blood glucose – 120)/80. (22)

During the hospital stay, the child and his family receive education on using a glucometer to check glucose level, carbohydrate counting, insulin dose calculations, insulin dose administration, management of hypoglycemia, management of diabetes during illnesses, management of diabetes during exercise, and when to contact the diabetes team. While in the hospital, minor adjustments to insulin doses were needed due to high or low glucose values.

After being discharged from the hospital, the child's family contacts the diabetes team on a regular basis for updates and frequent insulin dose adjustments.

Using Advanced Diabetes Technology

The complexity of diabetes management at home, the need to frequently check glucose levels, and the importance of accurately calculating and delivering the insulin doses make using continuous subcutaneous insulin infusion devices (or insulin pumps) and/or continuous glucose monitoring devices a necessity for some children with diabetes.

Insulin Pumps. Insulin pumps are being used effectively and safely in children with type 1 diabetes. Advancements in technology have made them portable and user-friendly. Although using insulin pumps eliminates the need for complex math knowledge and frequent insulin injections, children with diabetes are still required to count their carbohydrate intake with every meal and snack to receive accurate doses of insulin. Only rapid-acting insulin preparations are delivered via insulin pumps in continuous and bolus patterns. When a child with diabetes is started on an insulin pump, the diabetes team assists with programming multiple settings into the pump, as follows:

1. Basal rates: To cover the need for basal insulin, insulin pumps deliver rapid-acting insulin in a continuous fashion. The diabetes team sets up the hourly rate of insulin delivery. The advantage of this is the ability to deliver different doses of basal insulin throughout the day. For example, some children have an increase in their glucose levels in the early stages of the morning due to secretion of multiple hormones. In these children, a higher basal rate in the morning, but not at night, is helpful to prevent hyperglycemia.
2. Insulin-to-carbohydrate ratios: The concept of insulin-to-carbohydrate ratios is similar to that of multiple daily injections, which is to provide insulin coverage for the amount of carbohydrates the child is consuming. The diabetes team can set different carbohydrate ratios for different times of the day based on the child's need. Before eating, the child dials the amount of carbohydrate he or she is planning on eating, and the pump calculates the insulin dose recommended using the programmed carbohydrate ratio.
3. Correction factor and blood glucose target: These are similar to what is used in multiple daily injections. The child or a family member dials the glucose level, and the pump recommends the insulin dose calculated based on the correction dose, blood glucose target, and active insulin time.
4. Active insulin or insulin action time: To avoid hypoglycemia from repetitive insulin corrections or "insulin stacking," the diabetes team programs the active insulin time setting in the pump, which is the estimated amount of time insulin is active for in the body after an insulin bolus administration. This is usually set at 3 to 5 hours. The pump takes into consideration the length of time since the last dose of insulin when calculating a new correction dose of insulin. It does that by using the active insulin time setting.

Before prescribing insulin pumps to a child with type 1 diabetes, the diabetes team assesses the need and readiness for insulin pumps. The advantages and disadvantages of insulin pumps over multiple daily injections should be clearly disclosed to the child and his or her family. The advantages of insulin pumps include their ease of use, increased flexibility, accurate dose calculation, ability to use multiple basal rates, ability to temporarily adjust basal rates up or down in case of activity or illness (temporary basal insulin, or “temp basal”), decrease or eliminate the need for insulin injections, lower the risk of hypoglycemia, and slightly improves overall diabetes control. (28) The disadvantages include the need to carry a device at all times, cost, risk of skin infection, and risk of pump malfunction or insertion site occlusion or dysfunction that can quickly lead to severe hyperglycemia and DKA if not timely recognized and addressed. (28)

Multiple brands of insulin pumps are commercially available in the United States. All these brands share the same basic concepts as detailed previously. Technology for type 1 diabetes is continually evolving. Table 3 highlights the current FDA-approved pumps and systems in the United States at this time.

Stand-alone Continuous Glucose Monitoring Devices. To achieve optimal diabetes control, it is necessary for children with diabetes to frequently monitor their glucose levels. This used to be typically achieved by self-monitoring of blood glucose using glucometers. It entails obtaining a capillary blood sample using a small needle multiple times per day (before meals and snacks, before and during exercise, at bedtime, during the night, etc). Monitoring glucose levels using a glucometer provides multiple snapshots of where the blood glucose level is at the time of checking. (33) However, this method of testing is not sufficient to give a full picture of whether these levels are on their way down or up.

With their ability to provide the wearer with a new interstitial glucose concentration reading every 5 to 15 minutes, continuous glucose monitors (CGMs) have become desirable and are more widely used. There has been a remarkable advancement in the technology of CGMs that led to accurate and user-friendly information. (34) Recent personal CGMs can deliver real-time information regarding current glucose concentrations and their trends, in addition to alarming the user if glucose levels are out of the preset target range. They also provide data regarding average glucose levels, percentage of time in the hypoglycemia or hyperglycemia range, percentage of time in the target range, and how variable these levels are over time. (35) Persons with diabetes can automatically share their data with multiple people of their choosing. Several versions/brands of CGMs are approved for use in children with diabetes in the United States. Note that CGMs can be used in patients administering insulin via multiple daily injections or continuous subcutaneous insulin infusion devices.

Sensor-Augmented Pumps and Closed-Loop Systems. Using diabetes technology in the form of insulin pumps and CGMs has been shown to be associated with overall improved diabetes control, lower risk of hypoglycemia, improvement in patients' and families' well-being, and reduction of fear of hypoglycemia. (34)(35)(36)(37)

Sensor-augmented insulin pumps refer to a system in which the CGM data are automatically transmitted to the

Table 3. Summary of the Available (and Future) Advanced Diabetes Technology for Children with Diabetes in the United States (29)(30)(31)(32)

VARIABLE	CGMs	STAND-ALONE CONTINUOUS INSULIN INFUSION DEVICES	PREDICTIVE LOW-INSULIN PUMP SYSTEMS	HYBRID CLOSED-LOOP INSULIN PUMP SYSTEMS	ARTIFICIAL PANCREAS
Device description	Electrodes sit under the skin, monitoring glucose levels in the interstitial fluid	Manual insulin pump uses preset data; does not react or interact with CGM data	The pump and CGM are connected; the pump relies on CGM readings; if blood glucose is predicted to be low in the next 20 min, the pump suspends basal insulin delivery	Uses a CGM to adjust basal insulin; adjusts basal insulin for high and low glucose levels; may administer small insulin boluses for elevated glucose values; may have additional exercise and sleep modes	Glucagon and insulin delivery; automatic adjustments of insulin doses
Current commercially available brand names that are FDA approved in the United States	FreeStyle Libre 2; Dexcom G5 and G6; Medtronic Guardian Connect	Tandem t:slim; Medtronic MiniMed Series; Insulet Omnipod	Tandem t:slim + Dexcom CGM Basal-IQ system; Medtronic MiniMed 630G + Guardian Sensor 3 CGM system	Medtronic MiniMed 670G + Guardian 3 CGM system; Tandem t:slim + Dexcom G6 CGM systems	Not yet available
FDA-approved specifications by age	FreeStyle Libre, ≥4 y; Dexcom G6, ≥2 y; Guardian Connect, ≥14 y	Medtronic, varies by pump; OmniPod, all ages; t:slim, ≥6 y	Tandem t:slim Basal-IQ, ≥6 y; Medtronic MiniMed Series + Guardian CGM 2, ≥2 y	Medtronic 670, ≥7 y; Medtronic 770G + Guardian Connect, ≥2 y; Tandem t:slim, ≥6 y, ≥55 lb, ≥10 U of insulin per day	
Seeking FDA approval				OmniPod 5 + Dexcom G6 system; Tidepool Looping App, may combine older sensors and pumps	

CGM=continuous glucose monitor, FDA=Food and Drug Administration.

pump. Similar to insulin pumps and CGMs, sensor-augmented pumps have gone through a significant degree of development during the recent 2 decades. The first step was to use the sensor data in the pump to suspend insulin delivery when the person with diabetes experiences hypoglycemia. The application of this new system led to a decrease in total time in hypoglycemia and in fear of hypoglycemia that people with diabetes experience. (38)(39) The next generation of this technology aimed to suspend basal insulin delivery when the patient is predicted to become hypoglycemic soon. Application of this system was again associated with lowering the risk of hypoglycemia, particularly at night. (40)(41)

The previously mentioned advancements in insulin delivery technology paved the road toward hybrid closed-loop insulin delivery systems as a step closer to a completely automated closed-loop insulin delivery system. At the time of writing this review article, 2 hybrid closed-loop systems are authorized for use in children with diabetes in the United States: MiniMed™ 670G (Medtronic, Minneapolis, MN) and t:slim X2™ insulin pump with Control-IQ™ technology (Tandem Diabetes Care, San Diego, CA). (42)(43) Both systems operate based on algorithms that incorporate real-time sensor data to adjust basal insulins to avoid hypoglycemia or hyperglycemia (Guardian™ CGM [Medtronic] for the MiniMed system and Dexcom G6 [Dexcom Inc, San Diego] for the Tandem system). The user of both systems is still required to inform the system of the amount of carbohydrates consumed for meals and snacks to calculate insulin boluses. To prevent hypoglycemia with exercise, the systems target higher glucose levels at the time of exercise.

THE CLINIC VISIT

Although many children with new-onset diabetes receive their initial training in the hospital, most of the type 1 diabetes education and management is performed in the outpatient setting. The structure of the clinic visit flow varies greatly among centers. This expands from a single provider with a clinic nurse to a multidisciplinary visit with a diabetes educator, a dietitian to assess and determine the need to further educate the patient and the caregivers about how to read labels and count carbohydrates, a social worker, and a mental health specialist. Each member of the multidisciplinary team plays an important role in the care of children with type 1 diabetes.

Children with type 1 diabetes are recommended to have routine visits for their diabetes at least every 3 months. During each of these visits, the diabetes team reviews the child's glucose values, assesses for educational gaps, and evaluates the child's barriers to optimal diabetes control (social, financial, psychological, etc). In addition, the team evaluates growth pattern, development, and the child's overall health, mental health, and well-being. Physical examination must include measuring blood pressure, inspection of injection or pump insertion sites to check for signs of lipodystrophy, and examining glucose monitoring sites (fingertips and/or CGM insertion locations). (44) Inquiring about tobacco use or exposure status is recommended at every visit.

The child and the caregiver's knowledge of symptoms and signs of hypoglycemia, sick day management plans, and management of diabetes at school and during exercise should be evaluated on a regular basis. The diabetes team should follow an age-appropriate approach to ensure involving the child in her or his own diabetes care and decision making without placing the child under too much pressure.

The following laboratory tests are recommended for children with diabetes (44)(45):

- Glycohemoglobin every 3 months
- Thyroid function at the time of diagnosis (after the child is clinically stable) and every 1 to 2 years if thyroid function is normal
- Tissue transglutaminase IgA (if IgA sufficient) at the time of diagnosis. If normal, repeat in 2 years and then every 5 years.
- Fasting lipid profile when the child is older than 10 years. Repeat every 3 to 5 years if the low-density lipoprotein cholesterol level is less than 100 mg/dL (<2.6 mmol/L).
- Urine albumin-to-creatinine ratio after 5 years of diagnosis and the child is in puberty or older than 10 years (whichever comes first).

Dilated eye exam should be done every 2-4 years starting 3-5 years after diagnosis or when puberty is started. Comprehensive foot examination is recommended annually after age 10 or at time of puberty, starting 5 years after diagnosis. Evaluation and testing for other autoimmune diseases (Addison disease, autoimmune hepatitis, autoimmune gastritis, etc) should be considered when clinically indicated. (45) A mental health assessment should be obtained on a regular basis. Table 4 highlights a recommended screening schedule for children with type 1 diabetes.

MANAGEMENT OF HYPOGLYCEMIA

Hypoglycemia is the most common acute complication of type 1 diabetes treatment in children (and in adults). Understandably, the fear of hypoglycemia plays a significant role as a barrier to optimal diabetes control in children with diabetes. Many factors can lead to mild to severe hypoglycemia in children: excessive insulin, inaccurate carbohydrate counting, physical activities, alcohol consumption, concurrent illnesses, and the presence of other chronic diseases, such as celiac disease or Addison disease. (47) Children, particularly young ones, may not experience the typical symptoms of hypoglycemia, such as shakiness, sweating, irritability, hunger, palpitations, etc. Any change in the child's mood or behavior can be an indication of hypoglycemia. Young children's inability to communicate their symptoms poses an added difficulty to recognize hypoglycemia. (48)

Educating children with diabetes and their caregivers about hypoglycemia should not only focus on treatment of low glucose levels but also emphasize recognizing signs and symptoms of hypoglycemia. Management of hypoglycemia depends on the degree of hypoglycemia, the severity of symptoms, and the child's ability to consume carbohydrates by mouth.

In mild hypoglycemia when the child is awake, the amount of carbohydrates needed to raise the glucose level to greater than 70 mg/dL (>3.9 mmol/L) varies based on the child's age, size, cause of hypoglycemia, and whether the child uses a CGM or a sensor-augmented pump. Just 0.3 g/kg of rapidly absorbed carbohydrates (such as juice or glucose tablets) is usually sufficient to resolve hypoglycemia. (49) When treatment is administered, a glucose level should be rechecked in 10 to 20 minutes, or closely monitored using the CGM to watch for an uptrend of the

Table 4. Recommended Screening Schedule for Children with Type 1 Diabetes (34)(35)(46)

SCREENING		FREQUENCY
Laboratory		
Diabetes control	Glycohemoglobin every 3 mo	—
Autoimmune disease	Autoimmune thyroid disease	Thyroid function testing every 1–2 y
	Celiac disease	Celiac screen around diagnosis, 2 y after diagnosis if normal, then every 5 y
Cardiovascular disease	Fasting lipid profile	Start at age >10 y Repeat every 3–5 y if LDL cholesterol <100 mg/dL (2.6 mmol/L)
Nephropathy	Urine albumin-to-creatinine ratio	Obtain after 5 y of diagnosis and child is in puberty or >10 y (whichever comes first), then yearly
Clinical		
Growth	Height, weight, and BMI% calculation	Every office visit
Physical examination	Lipohypertrophy	Foot examination annually starting at puberty or age >10 y if the patient has had diabetes for 5 y
	Hypertension screen	
	Foot examination	
Retinopathy	Dilated eye examination	3–5 y after diagnosis (if age >11 y) or puberty has started; then every 2 y or every 4 y if glycohemoglobin <8%
Mental health		
Depression screening	Diabetes Distress Scale	Initiate at age 7–8 y
	Patient Health Questionnaire-9	Separate interviews at age 12 y
Disordered eating	Diabetes Eating Problems Survey	Ages 10 and 12 y

BMI=body mass index, LDL=low-density lipoprotein.

glucose level direction. If the glucose level is still low (or not trending up), repeated treatment is indicated. The use of sensor-augmented pumps with the capability to suspend insulin delivery on or before a low glucose level decreases the risk of severe hypoglycemia and the need for repeated treatment. (47)

Severe hypoglycemia in which a child is not conscious or not able to take carbohydrates by mouth should be treated urgently with glucagon. Until recently, glucagon was available as a powder that requires reconstitution in sterile water before being administered intramuscularly or subcutaneously. In 2019, the FDA approved a prefilled, ready-to-use glucagon injection for the treatment of severe hypoglycemia in children. (50)(51) Furthermore, in the same year, the FDA approved intranasal glucagon for use in children older than 4 years with severe hypoglycemia. (52)

MANAGEMENT OF TYPE 1 DIABETES IN SCHOOL

Children spend an average of more than 6 hours a day at school. (53) Children with diabetes are covered under Section 504 of the Rehabilitation Act of 1973. This means that many state laws necessitate that school districts provide a medically safe environment to children with diabetes without discrimination. (54) Based on that, most schools are required to make some adjustments to facilitate the opportunity for good medical care for children with diabetes. The diabetes management regimens for kids with type 1 diabetes should be tailored to provide their needs at school while not compromising their school performance. Blood glucose level targets do not differ at school from at home. Plans should be in place with coordination with the child's caregiver(s) for when to check glucose values, who and when to administer insulin for meals, and what to do in case of illness, exercise, hypoglycemia, or hyperglycemia. (55) A person with knowledge on when and how to administer glucagon treatment in case of severe hypoglycemia should be available at all times in school. Students' involvement in their diabetes management at school depends on their age and maturity level.

MANAGEMENT OF TYPE 1 DIABETES IN EXERCISE AND SPORTS

Carrying a diagnosis of type 1 diabetes should not be a reason to prevent a child from achieving exercise goals, whether the activity is strictly for leisure or for competitive purposes. (56) However, it is important to educate children with diabetes and their families about the effect of exercise on the child's glucose metabolism and the risks of hypoglycemia or hyperglycemia associated with it. Multiple factors affect glucose levels during exercise, including length of exercise, type of sport, time and

amount of last dose of insulin, amount of and time since carbohydrates consumed before exercise, glucose level before exercise, etc.

The diabetes team should create an individualized plan for the child with diabetes and the caregiver(s) regarding management of diabetes during exercise. Children with diabetes should check their glucose levels frequently when exercising (before, during, and after). A reduction of insulin dose before exercise, or a plan to consume a specified amount of carbohydrates before exercise, should be considered. Carbohydrate-containing snacks should always be available to treat episodes of hypoglycemia. The effect of physical activities on glucose levels may last for hours after exercising and varies among children and the types and length of the physical activities.

The advancement of diabetes technology and the emergence of sensor-augmented pumps and hybrid closed-loop systems have lowered the risks and frequency of hypoglycemia in children with diabetes during and after exercise. (57) The ability of CGMs to share glucose data and trends to multiple caregivers decreases the burden on the child and allows others to assist with monitoring. In addition, the pumps' capability of adjusting basal insulin based on real-time sensor data plays a protective role from hypoglycemia and hyperglycemia. Furthermore, current hybrid closed-loop systems are equipped with an exercise mode that, if used, allows the pump to target higher glucose values while the child is active.

MANAGEMENT OF TYPE 1 DIABETES DURING ILLNESS

Caregivers of children with type 1 diabetes should be provided with clear plans regarding managing type 1 diabetes during an illness because children with type 1 diabetes are at risk for hypoglycemia, hyperglycemia, severe dehydration, and DKA when sick. These plans need to explicitly state that children with diabetes still need insulin even if they are not eating. Their insulin dose may need to be adjusted based on the type of illness, presence of ketones, ability to consume carbohydrates, presence of fever, etc. Caregivers should always be encouraged to contact their diabetes team as needed to get advice.

At-home measurement of serum or urine ketones is a common tool used as a marker to help the family and the health-care team to determine the severity of illness and insulin insufficiency for the child.

Frequent glucose level checks using a glucometer or a CGM are an essential step in managing diabetes during an illness. In the case of hypoglycemia, families should treat instantly (as discussed previously herein). Hyperglycemia is treated with insulin dose corrections as instructed by the diabetes care team. If a child uses an insulin pump, caregivers should assess pump malfunction or a problem in the delivery system in the case of unexplained hyperglycemia. It is always a good idea to change the infusion set immediately if hyperglycemia does not improve after a correction dose of insulin using the pump.

Recurrent emesis or the presence of large amounts of serum or urine ketones are signs of DKA and require immediate medical attention. (58)(59)

MENTAL HEALTH INVOLVEMENT IN DIABETES MANAGEMENT

The complex, chronic, and "never-ending" tasks of managing type 1 diabetes bear a substantial amount of emotional and physical stress on children with diabetes and their families. Numerous studies have shown increased incidence of depression, anxiety, and posttraumatic stress disorder–like symptoms in young children and adolescents with type 1 diabetes and their caregivers. (60)(61)(62)(63)

Adolescents with type 1 diabetes are particularly prone to high-risk behaviors such as smoking, underage drinking, and unprotected sexual activities compared with other teenagers without diabetes. (64)(65)(66) Mental health screening should be a routine part of the diabetes clinic assessment. Many screening tools are available and have been used. Some examples of these screening tools are the Generalized Anxiety Disorder 7 screening tool, the Patient Health Questionnaire-9, and the Children's Depression Inventory. (67)(68) A plan should be in place for when/if a child has a positive screening test, has signs of a mental health struggle, or has significant risk factors. The diabetes team should always have access to a mental health expert. Many children with diabetes need continued evaluation and counseling for years after their diabetes diagnosis.

FAMILY AND PATIENT SUPPORT

A new diagnosis of type 1 diabetes in the pediatric population introduces a new dynamic for both the family and the child. At times, this creates a feeling of isolation when dealing with a chronic illness that they will carry for the rest of their lives. Some may be the only one in the school with type 1 diabetes.

The diabetes team can play an important role in assisting children with diabetes and their families in connecting with peers who have similar experiences while complying with confidentiality standards for their patients. In

addition, the Juvenile Diabetes Research Foundation and the American Diabetes Association have resources and access to many events available for patients and families on their websites. (69)(70) Furthermore, diabetes camps have been outlets for many children with diabetes to meet others, learn from their knowledge, and have mentoring experiences. Moreover, when used properly, social media can provide quick and readily available access to communities and support from other users with type 1 diabetes.

CONCLUSION

Type 1 diabetes management in children is a complex task for children, caregivers, and health-care teams. This task requires a team approach, good communication, and continued education. The advancement in insulin products and diabetes technology has made achieving optimal diabetes control much more feasible.

Summary

- According to level A evidence, type 1 diabetes results from insulin insufficiency caused by β-cell destruction from an autoimmune process in genetically susceptible individuals with exposure to environmental and immunologic factors.
- According to level A evidence, once the diagnosis of type 1 diabetes is established, intensive insulin therapy should be initiated promptly.
- According to level D evidence, the setting in which to initiate type 1 diabetes management (inpatient or outpatient) is still debatable and depends on the expertise of the diabetes team, the availability of resources, and the patient's and the family's comfort level with and ease of access to health-care.
- According to level A evidence, the advancements in insulin products and diabetes management technologies (in the form of insulin pumps, continuous glucose monitors, closed-loop and hybrid closed-loop systems) have improved diabetes care in children and adults with type 1 diabetes.
- According to level D evidence, outpatient diabetes management teams should have readily available access to a diabetologist, diabetes educator, dietitian, social worker, and mental health specialist.
- According to level D evidence, children with type 1 diabetes and their families should receive frequent assessment and education regarding management of type 1 diabetes during illnesses, at school, during exercise, and at the time of hypoglycemia or hyperglycemia. They should have access to their diabetes team in cases of urgent needs.

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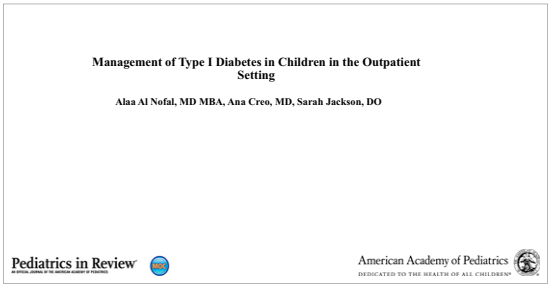

References for this article can be found at doi.org/10.1542/pir.2020-001388.