CPQ Women and Child Health (2019) 1:4
Review Article

Updates in Pediatric Endocrinology and Diabetes in 2018

Kaitlyn Shank[1], B.S. & Kanika Shanker[1,2*], M.B.B.S., M.D.

[1]*Penn State College of Medicine, Penn State Health, Milton S. Hershey Medical Center, Hershey, Pennsylvania*

[2]*Clinical Assistant Professor of Pediatrics, Summit Endocrinology, Summit Physician Services, Summit Health, Chambersburg*

[*]**Correspondence to:** Dr. Kanika Shanker, Clinical Assistant Professor of Pediatrics, Summit Health, USA.

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Received: 19 February 2019

Published: 07 March 2019

Keywords: *Updates; Diabetes; Endocrinology; Insulin; FDA*

Abstract

Pediatric endocrinology deals largely with the very common diseases of childhood and adolescence such as diabetes, rickets and obesity along with more rare and nuanced diseases such as congenital adrenal hyperplasia and disorders of sexual differentiation. Technology rapidly advances the treatment of diabetes and guidelines are constantly changing for the treatment of many common endocrine conditions. In this succinct review, we present the most updated recommendations and guidelines provided by the nationally and internationally recognized regulatory bodies such as The Endocrine Society, The Pediatric Endocrine Society and the USA Food and Drug Administration. Through this mini review, we hope to provide important updates and knowledge to the providers taking care of neonates, young children and adolescents worldwide.

Background

In this ever-changing world, it is sometimes difficult to keep up with the recent advances in the field of pediatric endocrinology and diabetes. In this review article, we briefly discuss clinical guideline updates in pediatric endocrinology followed by a succinct overview of the advancements in diabetes technology and medication. We have tried to provide concise and accurate developments in the field in the year 2018.

Methods

References for this review were identified through searches of PubMed, Medline, and Embase for articles published until December 2018 using the terms "updates, diabetes, endocrinology" [MeSH Terms] OR "insulin" [All Fields] OR "continuous glucose monitors, FDA" [All Fields]. The reference lists of the articles thus identified were also searched. The search was not restricted to English-language literature.

I. Updates in Pediatric Endocrinology

1) Updates in the Treatment of X-linked Hypophosphatemia [1]

The U.S. Food and Drug Administration (FDA) in April 2018, approved Crysvita (burosumab-twza). It is the first drug approved to treat adults and children ages 1 year and older with X-linked hypophosphatemia (XLH). XLH, a rare inherited form of rickets, with biochemical presentation of low levels of phosphorus in the blood. It leads to impaired bone growth and development along with problems in bone mineralization for children and adolescents. Burosumab-twza is a monoclonal antibody against the phosphaturic hormone-fibroblast growth factor-23. The peak plasma effect comes at 8-11 days.

2) Updates in Hirsutism:

Defined as excessive hair growth in women in a male-pattern hair distribution. It is a common disorder in females and affects 5%-10% of the females. The polycystic ovarian syndrome, the most common cause [2].

Evaluation and Treatment of Hirsutism in Premenopausal Women:

An Endocrine Society Clinical Practice guideline came out in April 2018. Prior to that guidelines came in 2008, the 2018 guidelines has widened the evaluation guidelines. The 2018 guideline suggests:

i) Testing for elevated androgen levels in all women with an abnormal hirsutism score. The androgen levels include total and free testosterone levels and other sex hormones such as dehydroepiandrostenedione levels. The hirsutism score, also known as the Ferriman-Gallwey Hirsutism score, is an assigned number with progressive increases in the score depending on the intensity of hair growth in nine body parts.

ii) Added the recommendation to screen women for nonclassic congenital adrenal hyperplasia (NCCAH) due to 21-hydroxylase deficiency by measuring early morning 17-hydroxyprogesterone levels in the follicular phase or on a random day for those with amenorrhea or infrequent menses.

iii) Against testing for elevated androgen levels in females with normal menstrual periods and normal hirsutism score.

iv) Recommended against solo antiandrogen monotherapy with medications such as spironolactone unless adequate contraception is used due to the potential risk of teratogenicity.

v) Against using insulin-lowering drugs such as metformin for the sole indication of hirsutism unless metabolic indications are there.

3) Updates in the Treatment of Endocrine Disorders in Childhood Cancer Survivors [3]

Hypothalamic-pituitary and growth disorders in survivors of childhood cancer: An Endocrine Society Clinical Practice guideline was released in August 2018. The guideline outlined the following:

i) Radiation-induced hypothalamic-pituitary dysfunction is both dose- and time-dependent; doses to the hypothalamus-pituitary <30 Gy are associated primarily with growth hormone deficiency and precocious puberty whereas deficits of luteinizing hormone/follicle stimulating hormone, thyroid stimulating hormone and adrenocorticotropic hormone are seen following hypothalamic-pituitary doses >30 Gy, often years after the completion of cancer therapy.

ii) Impaired linear growth and short adult height are most commonly seen in survivors exposed at a young age to central nervous system, spinal or total body irradiation.

iii) Hypothalamic-pituitary dysfunction is frequently observed in childhood cancer survivors, especially in those with tumors involving the hypothalamic-pituitary region or those previously exposed to radiation to the central nervous system.

iv) Key differences and unique features that are specific to cancer survivors such as not relying solely on serum IGF-I levels in childhood cancer survivors exposed to HP axis radiotherapy to make the diagnosis of growth hormone deficiency.

v) Recommend against using testicular volume as the primary or sole indicator of degree of sexual development in male childhood cancer survivors previously treated with gonadotoxic agents, such as alkylating agents or testicular radiotherapy.

4) Updates in the Evaluation and Management of Congenital Adrenal Hyperplasia (CAH)

Congenital Adrenal Hyperplasia occurs due to Steroid 21-Hydroxylase Deficiency. The clinical presentation of CAH depends on the degree of the genetic mutations mediating the conversion of 17 hydroxyprogesterone to 11 deoxycortisol [4]. An Endocrine Society Clinical Practice guideline was released in November 2018, highlighting the following. Prior to these guidelines, it was published in 2010.

1. Shared decision making among congenital adrenal hyperplasia patients, their families, and healthcare professionals in regard to the medical, surgical, and psychological management of the disorder is emphasized.

2. Detailed protocols for adults, especially pregnant women, are included.

3. Advice against using experimental treatment approaches outside of formally approved clinical trials, categorized as an upgraded "Good Practice Statement", is provided.

5) Updates in the Evaluation and Management of Obesity in Children

Food Labelling [5]

i) In 2018, menu labeling provisions of the Affordable Care Act took effect, covering approximately 300,000 food retail establishments nationwide; FDA estimates this will save approximately $8 billion in health costs over the next two decades.

ii) The vending machine rule, an effort to promote calorie labeling of articles of food in vending machines, came into effect in 2016, but for some products sold in glass-front vending machines, the rule was delayed until July 2018.

Wearables

iii) The year 2018 proved to be productive in further developing market space for wearables measuring physical activity: Besides step tracking, the newer devices can monitor heart rate, sense an impending fall and even conduct an electrocardiogram. So far we do not have randomized control trials to prove which device is best for collecting data points from the user. The utility of these devices is certainly based on the user's motivation and provides objectivity to the user.

Glucagon-Like Peptide-1 Receptor Agonist (GLP-1) [6]

iv) GLP-1 agonists are widely used for the management of type 2 diabetes in the adult population. This class of medication has demonstrated an effect in suppressing appetite by working at the level of the hypothalamus, hence decreasing caloric intake. Two large adolescent clinical trials evaluating GLP-1 receptor agonists are projected to conclude before the end of 2019, which are expected to shed light on the safety and efficacy of this drug in the pediatric population.

Physical Activity [7]

The physical activity guidelines for Americans in 2018 were published by the US federal government. It provided the first physical activity standards for children ages 3-5 years. The recommended target is at least three hours of varied physical activity per day, consistent with the existing guidelines in Australia, Canada and the United Kingdom.

II. Technological Advances in the Management of Diabetes Mellitus

The prominent advantages and disadvantages of this section are illustrated in Table 1.

Table 1: *Key advantages and disadvantages of the various pumps, continuous glucose monitors and insulin advances in 2018*

	Description	Advantages	Disadvantages	FDA approved age group	Durability
T:Slim X2 Insulin Pump with Basal-IQ Technology	Predictive low-glucose suspend insulin pump	Predicts low glucose 30 min in advance and suspends insulin delivery, restarting when glucose rate stabilizes Touch screen pump with free software upgrades Uses only CGM FDA-approved for clinical decision making without daily finger stick calibrations Fewer alarms than Medtronic	Not a fully closed-loop system (cannot automatically adjust basal in real time response to CGM)	Age 6 and older	Watertight up to 3 feet for 30 min Shatter resistant glass Contraindicated with MRI
Medtronic MiniMed 670G	Hybrid closed loop insulin pump	Operates in automode - automatically adjusts basal insulin every 5 min based on CGM Predicts low glucose 30 min in advance and suspends insulin delivery, restarting when glucose rate stabilizes	Frequent alarms Uses Guardian 3 CGM which requires daily finger stick calibrations	Age 7 and older	Waterproof up to 12 feet for up to 24 hours Can withstand air pressure from 10.2 psi to 15.4 psi Contraindicated with MRI
Dexcom G6 CGM	Continuous glucose monitor	Does not require any finger stick calibrations Sensors FDA approved for 10-day wear Data can be shared with 5 Smart devices Not contraindicated with acetaminophen as with Dexcom G4 and G5 Simpler auto-applicator with one-button insertion Small, user-friendly transmitter	After 7 days adhesive begins to wear off 7-10 min delay between blood and interstitial fluid glucose changes	Age 2 and older	Water resistant sensor Contraindicated with MRI

Eversense CGM	Subcutaneously implanted CGM sensor with externally attached Smart Transmitter	Up to 90 day use of sensor before replacement No weekly sensor insertions No sensor showing through skin Provides on-body vibe-alerts when low or high even when mobile device is not near	Has only been FDA approved for use in upper arm Tetracycline antibiotics can interfere with glucose readings Must be implanted by healthcare professional Requires twice daily calibrations	Ages 18 and older	MRI conditional (sensor can go through MRI but transmitter must be removed) Water resistant submerged in 1 meter up to 30 min
Guardian Connect CGM	First Smart CGM system for MDI	Alerts users 10-60 min before a hypoglycemic episode Approved to help guide insulin management decisions for patients on multiple daily injections	Not FDA approved for clinical decision making, does not replace finger sticks, only used to follow trends Can only be worn for up to 7 days Contraindicated with Tylenol, NSAIDs, cold medicine or paracetamol	Ages 14 and older	Contraindicated with MRI Water proof up to 2.5 meters up to 30 min
Fiasp by Novo Nordisk	Ultra-fast acting aspart insulin (containing niacinamide for faster absorption)	Enters the blood stream from interstitial fluid in 2.5 minutes Inject at the start of a meal or 20 minutes into meal Available in 10-mL vial or 3-mL FlexTouch pen	Cannot drink alcohol while using Fiasp Not approved for use in insulin pumps Same side effect profile of NovoLog (allergic reaction, weight gain, hypokalemia, risk of heart failure in conjunction with certain diabetic oral agents)	Ages 18 and older	<u>Unopened:</u> -Stable at Room Temp for 28 days -Stable refrigerated until expiration date <u>Opened:</u> -Stable for 28 days both at room temp and refrigerated

*CGM = Continuous Glucose Monitor
*MDI = Multiple Daily Injections

1) T:slim X2 Insulin Pump with Basal-IQ Technology

a) On June 27, 2018, the FDA approved the t:slim X2 Insulin Pump with Basal-IQ, a predictive low-glucose suspend feature that stops insulin delivery when the anticipated glucose falls into the hypoglycemic range and automatically resumes when levels begin to rise, predicting 30 minutes in advance. This was the first integrated CGM-pump system by Tandem (with Dexcom G6) and is approved for use in type 1 diabetics ages 6 years through adulthood. The PROLOG trial (a 6-week randomized crossover trial) showed a 31% reduction in hypoglycemia in this integrated system compared to sensor-augmented therapy alone [8]. Basal-IQ technology was officially launched in August 2018.

2) The Dexcom G6 Continuous Glucose Monitor (CGM)

a) The Dexcom G6 was the first FDA-permitted CGM approved for making treatment decisions without confirmatory finger sticks or calibrations. The sensors are approved for 10-day wear and data from the device can be shared with 5 smart devices. It has been shown to reduce night time hypoglycemic events by 79% in clinical studies. The G6 is approved for children ages two years and older and is not contraindicated with acetaminophen use, as with the G5 transmitters.

3) Fiasp by Novo Nordisk

a) Fiasp was first approved by the FDA for adults with diabetes on September 29, 2017, as an injectable ultrafast acting insulin. It is a formulation of Aspart insulin with the addition of Niacinamide (vitamin B3) which augments its absorption into the bloodstream from the subcutaneous tissue in only 2.5 minutes. It can be dosed at the beginning of a meal or 20 minutes in and has proven to show greater glucose-lowering ability (and lower A1c) than the fast-acting insulins, though there is still limited data for its clinical utility in insulin pumps. It is offered as a FlexTouch prefilled delivery pen and a 10 mL vial. Currently, it is not FDA-approved for use in insulin pumps in the US, but it has been approved for pump use in several European countries.

4) The Eversense Continuous Glucose Monitoring System

a) Eversense was FDA-approved on June 21, 2018, as the first CGM sensor permitted for up to three months use, with no weekly sensor self-insertions. A fluorescence-based sensor is implanted into the arm of the patient and responds to interstitial glucose with fluorescent light that is measured and translated into a blood glucose value. The sensor must be calibrated at least twice daily and is approved for ages 18 and older. The device is contraindicated with use of dexamethasone, mannitol, sorbitol and tetracycline. The 2018 PRECISE II trial demonstrated that the Eversense CGM system provided accurate glucose readings through the 90-day sensor with favorable safety outcomes [9,10].

5) Guardian Connect Continuous Glucose Monitor

a) The Guardian Connect by Medtronic Minimed was FDA approved on March 8th, 2018 for ages 14 and older. The sensor readings are not intended to directly inform blood glucose management, but rather to provide an indication of when a finger stick may be required. It alerts users 10-60 minutes in advance of a hypoglycemic event. The Sugar.IQ assist software offers in-depth analysis of blood glucose trends from data acquired through the sensor. This is the first Smart CGM system for people on insulin injections and it uses the guardian sensor 3 from Medtronic. It can be worn up to 7 days and is contraindicated with Tylenol, many NSAIDs, cold medicine or paracetamol.

6) Medtronic MiniMed 670G Pediatric Indication

a) The Medtronic MiniMed 670G hybrid closed loop system using the SmartGuard automated insulin delivery insulin pump and integrated guardian 3 sensor was FDA approved in July 2018 for use in pediatric

patients ages 7-13. In a 3-month in-home study on the closed loop system, clinical trials showed time in glycemic range for pediatric patients increased from 56.2 to 65.0% with an A1c reduction from 7.9 to 7.5% compared to management on traditional pump therapy alone. Additional clinical trials are currently underway to assess safety in pediatric patients ages 2-6 for the Medtronic MiniMed 670G.

7) Updates from American Diabetes Association [11]

a) The American Diabetes Association publishes standards of medical care in diabetes every year. The new standards that came out in January 2019 highlight the following points:

i) Screening for eating disorders in children with diabetes starting between the ages of 10-12 years.

ii) The target hemoglobin A1c should be individualized depending on the needs of the child and the family.

iii) The importance of screening high risk children for type 2 diabetes, including associated comorbidities, and maintaining awareness for rapid progression and severity of this diagnosis.

Conclusion

There were a myriad of advancements and updates in the realm of pediatric endocrinology and diabetes in the year 2018. We have highlighted the latest monoclonal antibody targeted therapy for X-linked hypophosphatemia as well as the updated clinical guidelines for the diagnosis and treatment of hirsutism, the treatment of endocrine disorders in childhood cancer survivors, and the evaluation and management of congenital adrenal hyperplasia. We have elucidated both the medical and technological advancements as well as guidelines improved to better address childhood obesity. Finally, we have discussed the latest advancements in pump, continuous glucose monitor and insulin therapy for type 1 diabetic pediatric patients in addition to advantages and contraindications for each.

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