General Inpatient Management of Pediatric Diabetes Mellitus at University of Iowa Stead Family Children's Hospital

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Contents

Part III. Unit 3: Creating and Discussing Insulin Regimens

Part IV. Unit 4: Management of Pediatric Diabetes According to Stead Family Children's Hospital Protocols

Introduction

Introduction

This online book is intended to be a self-guided resource for medical students and residents at the University of Iowa Stead Family Children's Hospital caring for hospitalized pediatric patients with diabetes mellitus. This resource was created based on results from a targeted needs assessment of pediatric residents, calling for a more standardized, up-to-date resource about diabetes management. It was also created to meet the perceived needs of the pediatric endocrinology faculty that more standardized education regarding routine inpatient diabetes mellitus management for our learners is needed to ensure that:

1. We are providing an opportunity to learn the management of a complex and chronic endocrine-related illness that will be encountered by all physicians, no matter what future field of medicine they will practice.
2. Our learners provide the highest level of safe, quality care to hospitalized patients with diabetes mellitus according to best practices, standards of care, and our local institutional protocols.

Unfortunately, with the time allotted for pediatric endocrinology for rounds (15 minutes per day) and inconsistent didactic lectures, teaching regarding inpatient pediatric diabetes mellitus has been fragmented. Therefore, this resource is intended to fill gaps in knowledge that may not be fully covered during these intermittent opportunities for education.

All learners who use this resource are encouraged to review

the content in full. At the end of each Chapter, learners are encouraged to complete the end-of-chapter questions to test their understanding and application of the information.

By completing the full contents of this resource, learners should be able to:

1. Differentiate between Type 1 and Type 2 diabetes mellitus and their respective presentations, initial work-up, diagnosis, and initial management.
2. Recognize the most common types of insulin utilized in the inpatient setting.
3. Differentiate between types of insulin based on their pharmacokinetic profiles.
4. Perform basic calculations necessary to generate an initial basal-bolus insulin regimen for new-onset diabetic patients while using appropriate terminology when discussing these insulin regimens.
5. Make appropriate recommendations for adjustment of insulin regimens based on blood glucose trends to work toward achieving goals of treatment.
6. Describe and apply basic nutritional concepts pertinent to inpatient management of diabetes mellitus.
7. Apply knowledge of the University of Iowa Stead Family Children's Hospital's pediatric diabetes protocols for the routine management

of common issues in hospitalized pediatric diabetes patients, including hypoglycemia, hyperglycemia, and ketonuria.

We hope you enjoy using this resource. We welcome any feedback on suggestions on how to improve this resource for you and future learners.

Please send feedback to Dr. Alex Tuttle, alexander-tuttle@uiowa.edu.

PART I

UNIT 1: AN OVERVIEW OF DIABETES MELLITUS

Learning Objectives

1. Given a patient case, be able to:
    - Identify pertinent symptoms necessitating evaluation for diabetes mellitus.
    - Use diagnostic criteria to determine if the patient has diabetes mellitus.
    - List initial diagnostic laboratory tests needed for definitive diagnosis of diabetes mellitus with or without DKA
    - Apply knowledge of diagnostic criteria of diabetic ketoacidosis (DKA) to determine the severity of DKA
        - Apply the same diagnostic criteria to determine the appropriate location of initial hospital care for patients requiring admission

2. Given the patient history, physical exam findings, and laboratory results from the workup of a patient with new-onset diabetes, distinguish between Type 1 and Type 2 diabetes.
3. Discuss differences in pathophysiology between Type 1 and Type 2 diabetes.
4. Describe the corresponding differences in approach to initial treatment of Type 1 and Type 2 diabetes.

Defining and Identifying Diabetes Mellitus:

Defining Diabetes Mellitus:

Diabetes means *siphon* (to pass through) in Greek, while **mellitus** means *sweet* in Latin. The roots of these words allude to the inappropriately high passage of sugar in the urine of a patient who is frequently urinating (**polyuria**).

Diabetes mellitus is a metabolic disease involving inappropriately elevated blood glucose levels (**hyperglycemia**) because of defects in insulin secretion, insulin action, or both. It is a blanket term referring to various causes of hyperglycemia with different pathophysiologic etiologies. We commonly think of Type 1 diabetes and Type 2 diabetes, but *Table 1* lists many other forms of diabetes mellitus.

Table 1: Types of Diabetes mellitus- *American Diabetes (2009), Solis-Herra et al. (2018)*

Type of Diabetes Mellitus	Description of Etiology
Type 1 diabetes	β-cell destruction (mostly immune-mediated but may be idiopathic) leading to absolute insulin deficiency.
Type 2 diabetes	Various degrees of β-cell dysfunction and insulin resistance
Monogenic diabetes (MODY/Neonatal diabetes)	Specific gene mutations leading to defects in β-cell function or defects in insulin action
Diseases of the Exocrine Pancreas (Type 3c diabetes)	Various conditions impacting exocrine pancreatic function (cystic fibrosis, trauma, tumor, pancreatitis, hemochromatosis, infection, etc.)
Drug- or chemical-induced diabetes	Iatrogenic diabetes due to drugs such as glucocorticoids, thiazide diuretics, some HIV/AIDs treatments, atypical antipsychotics, alpha-interferon, etc. that increase the risk of developing diabetes
Gestational diabetes	Diagnosed in the 2nd or 3rd trimester of pregnancy that was not overt diabetes before gestation.
Diabetes secondary to endocrinopathies	Endocrine disorders lead to excess hormone production that antagonizes insulin action (e.g., Cushing's syndrome, GH excess, hyperthyroidism, pheochromocytoma, etc.)
Posttransplant diabetes (PTDM and NODAT)	Hyperglycemia in the post-transplant setting beyond which stress- or steroid-induced hyperglycemia
Uncommon "immune-mediated" forms of diabetes	"Stiff-man" syndrome, anti-insulin receptor antibodies, likely others
Diabetes secondary to infection	Certain viruses have been associated with β-cell dysfunction (e.g., congenital rubella, coxsackievirus B, cytomegalovirus, adenovirus, and mumps)
Genetic syndromes associated with diabetes	Many genetic syndromes are accompanied by an increased incidence of diabetes mellitus, including; Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Wolfram syndrome, Prader-Willi syndrome, porphyria, etc.

The “Polys” and Other Clinical Manifestations:

Children may present with very subtle, or even downplayed, symptoms. It often takes a high degree of suspicion when these children are seen in outpatient settings. Mild hyperglycemia may go unnoticed altogether.

The three “P’s” – polyuria, polydipsia, and polyphagia are classically taught as the common presenting clinical symptoms. However, these “P’s” often do not occur simultaneously or can go unrecognized by the child or their caregiver as “abnormal.”

Click through the following graphic to learn more about how these symptoms may present.

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Other clinical manifestations of persistent hyperglycemia may include:

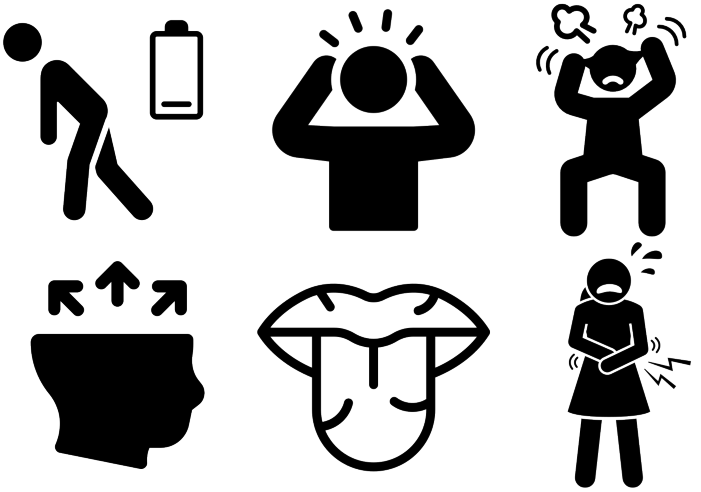

Figure 2 – Fatigue (tired/weak feeling), headache, irritability, trouble concentrating (or declining school performance), changes or irregularities in menses (in pubertal females), dry mouth, recurrent urinary tract infections or candida infections (e.g. oral thrush).

If these initial symptoms of hyperglycemia are ignored long enough, more severe manifestations due to progressive dehydration and the buildup of serum ketones lead to **diabetic ketoacidosis (DKA)**.

These symptoms often drive patients to seek more urgent evaluation at urgent-care clinics, same-day visits with their primary care physician, or emergency departments.

Symptoms of diabetic ketoacidosis (DKA) include:

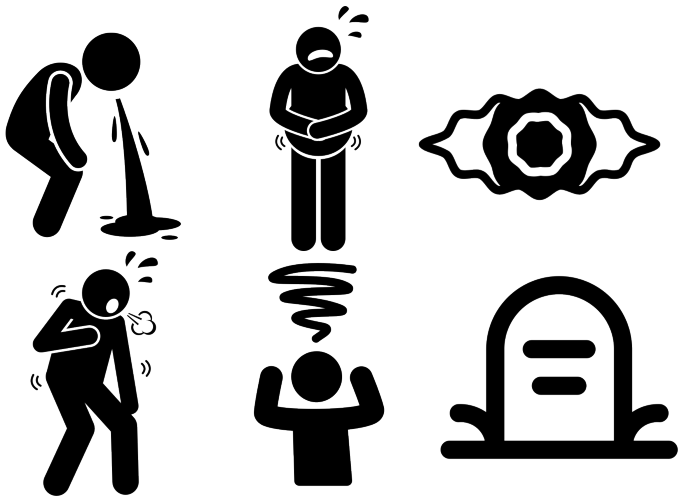

Figure 3 – Nausea, vomiting, abdominal pain, headache, blurry vision, confusion, shortness of breath/respiratory distress (i.e. Kussmaul respirations), Obtunded (e.g. decreased consciousness, altered mental status, and/or slow to respond to stimulation), coma or death.

History and Physical Exam:

A thorough history and physical exam are important when suspecting new-onset diabetes for multiple reasons:

1. Can help determine the etiology and type of diabetes mellitus
2. Evaluates for factors that may cause non-diabetic hyperglycemia
3. Identifies risk factors for developing diabetes mellitus

(such as those in Table 1)

4. Guides clinical decision-making regarding the urgency of work-up and the need for more advanced care

The same applies to a patient with known diabetes mellitus.

Quiz Yourself:

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Figures:

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Diagnostic Criteria

Diabetes Mellitus:

Diagnosis of diabetes mellitus cannot be made based on clinical symptoms alone. It also requires laboratory confirmation of abnormal blood glucose levels.

The diagnostic criteria are listed in *Table 2* below:

Table 2 – Criteria for the diagnosis of diabetes*In the absence of symptoms of hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.Marked discordance between measured A1c and plasma glucose levels should raise the possibility of A1c assay interference due to a variety of factors/conditions such as those that prolong or decrease erythrocyte turnover (e.g. sickle cell disease, hemoglobinopathies, blood transfusions, G6PD deficiency), pregnancy, lead poisoning, certain chronic medication ingestions or vitamin supplements. (Radin, 2014) – in these cases, only plasma blood glucose criteria should be utilized for diagnosis of diabetes**

Unequivocal classic symptoms of hyperglycemia or hyperglycemic crisis with a random plasma glucose of >200mg/dL
OR
Fasting plasma glucose ≥ 126mg/dL, where fasting is defined as no caloric intake for at least 8 hrs*
OR
A1c > 6.5%**, performed in a certified lab and not by point-of-care methodologies*
OR
2-hr plasma glucose ≥ 200mg/dL after a 75g (1.75g/kg) oral glucose load (by oral glucose tolerance test = OGTT) *

There is a spectrum of clinical scenarios along which diabetes may be identified, as seen in *Figure 3* below:

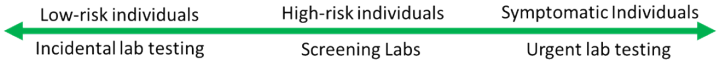

Figure 3 – Spectrum of diagnostic clinical scenarios

Low-risk individuals and high-risk individuals who do not have classic symptoms of hyperglycemia need a second laboratory

method that confirms the presence of *persistent* hyperglycemia.

Isolated or transient periods of hyperglycemia due to stress, surgery, infection, or medications can otherwise lead to the premature or inappropriate diagnosis of diabetes in these individuals.

Prediabetes:

Prediabetes = *individuals with blood glucose too high to be considered normal but not meeting diagnostic diabetes thresholds*

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The diagnostic criteria for prediabetes are demonstrated in *Table 3* below:

Table 3- Diagnostic Criteria of Prediabetes

Fasting plasma glucose of 100 mg/dL to 125mg/dL (*impaired fasting glucose*)
OR
2-hr plasma glucose of 140mg/dL to 199mg/dL after a 75g (1.75g/kg) oral glucose load (by oral glucose tolerance test = OGTT) (*impaired glucose tolerance*)
OR
A1c 5.7 – 6.4%

Diabetic Ketoacidosis (DKA):

If symptoms of diabetic ketoacidosis are present, then additional laboratory evaluation should be urgently pursued to confirm the diagnosis.

This is accomplished by assessing for the presence of severe hyperglycemia (plasma glucose), serum or urine ketones (serum beta-hydroxybutyrate, urine ketone dipstick, or urinalysis), and acidosis (venous blood gas and/or serum bicarbonate level).

Diagnosis of DKA requires the following:

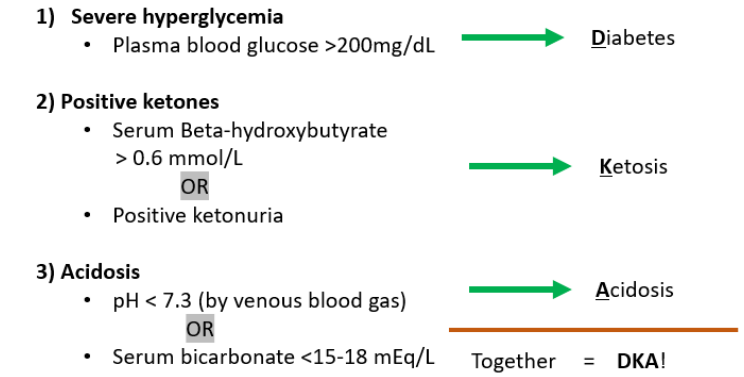

Figure 4 – DKA Diagnostic Criteria

The severity of DKA can be further defined based on the thresholds of pH or serum bicarbonate presented in *Table 4*.

Table 4 – Severity of DKA and Diagnostic Criteria of Hyperosmolar hyperglycemic state (HHS)

	Mild DKA	Moderate DKA	Severe DKA	HHS
Venous pH	7.3 – 7.2	7.1 – 7.19	<7.09	>7.25 (>7.3 arterial)
Serum bicarbonate (CO2)	<15 mEq/L	<10 mEq/L	<5mEq/L	>15 mEq/L
Ketones	Positive	Positive	Positive	Absent to Small
Plasma glucose	>200mg/dL	>200mg/dL	>200mg/dL	>600mg/dL
Effective serum osmolality	Variable	Variable	Variable	>320 mOsm/kg

Ketones may occur without significant acidosis (thus not meeting the criteria for DKA). In diabetic patients with absolute insulin deficiency, the absence of insulin leads to runaway ketone production and eventual pathological acidosis if not addressed quickly.

The following two conditions may occur in diabetics, but their presentations differ. Click on each to learn more!

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Laboratory Evaluation

Diagnosing diabetes mellitus and determining if there is associated DKA **requires** laboratory evaluation.

Since a patient with suspected new-onset diabetes with clinical symptoms is considered a pediatric medical emergency, prompt laboratory testing is required, even in children who have features more consistent with Type 2 diabetes.

"*Prompt,*" in this case, means labs are performed as soon as possible, on the same day of presentation, with follow-up of these labs on the same day of presentation to ensure the appropriate escalation of care based on the lab results.

Minimum laboratory evaluation for patients with suspected diabetes includes labs that confirm the presence of hyperglycemia and/or the presence of ketones. These labs include:

- Plasma glucose (fasting or random), ideally not by point of care (POC – fingerstick) methods
- Urinalysis or urine dipstick assessing for glucosuria and ketonuria

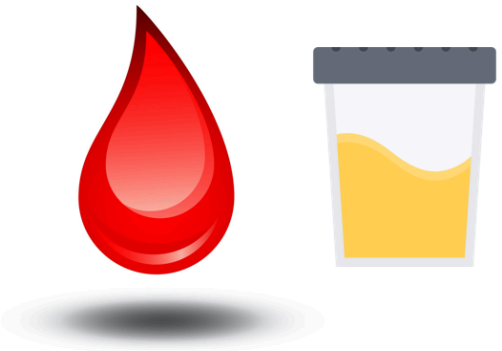

Figure 2: Blood and urine can be utilized to screen and diagnosis diabetes mellitus

The **presence of ketones in the setting of hyperglycemia,** regardless of reported symptoms, should prompt further evaluation for diabetic ketoacidosis by obtaining the following:

- Basic metabolic panel (includes plasma glucose and serum bicarbonate)
- Venous blood gas

Ketosis in Diabetes Mellitus Leads to Shift in Acid-Base Balance

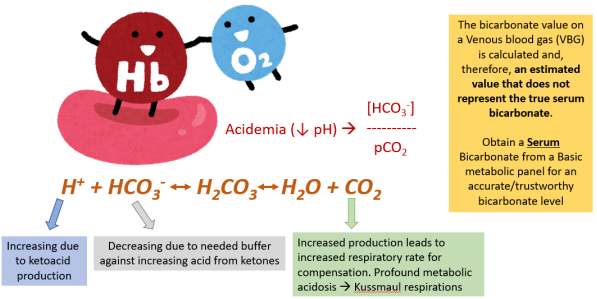

Figure 2 – Ketones formed from the breakdown of fat and protein lead to increased H+ (acid) production, which is buffered by serum bicarbonate (HCO3). This causes the acid-base balance to shift to the right and increases CO2 production. This CO2 must be expelled by the lungs leading to an increased respiratory rate. Eventually, this leads to the classic Kussmaul respirations seen in patients with severe DKA. This respiratory compensation and severe dehydration can lead to

cardiopulmonary arrest if not treated.

For patients presenting to the emergency department with hemodynamic instability, altered mental state, or coma, additional laboratory testing should be obtained to evaluate for other underlying causes of these presenting symptoms, many of which are triggers for DKA.

It is easy to forget that seizures, infections, pancreatitis, intoxication, and ingestions can present in the same way!

Therefore, consider the following additional labs:

- CBC with differential
- +/- blood cultures (especially if presenting with hypotension or other signs of shock)
- Ionized (or total) calcium, phosphorus, and magnesium (to evaluate for other common electrolyte derangements that are common in the setting of DKA)
- Amylase and Lipase (if presenting with nausea/vomiting and abdominal pain symptoms consistent with pancreatitis)
- Drugs of abuse panel (if suspecting intoxication)
- Tylenol/Salicylate levels (if suspecting ingestions)

Lastly, for new-onset diabetes patients, additional laboratory testing is often helpful in further differentiating Type 1 and Type 2 diabetes. **These should be obtained upon inpatient admission if they were not previously obtained**.

These labs include:

- C-peptide
- +/-Total insulin (only if the patient hasn't been started on exogenous insulin)
- Hemoglobin A1c (HbA1c)
- Islet and β-cell pancreatic autoantibodies:
    - o Glutamic acid decarboxylase antibody (GAD Ab)
    - o IA-2 antibody

    - o Insulin antibodies
    - o Islet cell antibody, IGG
    - o +/- Zinc transporter 8 antibody (Zn8Ab)
- TSH with reflex-free T4 (as autoimmune hypothyroidism can be comorbid with T1DM)
- TTG-IgA (as celiac disease can be comorbid with T1DM)

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Images/Figures:

1. *Figure 1 Image Attribution:* "Blood Drop Cliparts #2784471" by https://clipart-library.com and "Clinical Urine Tests Computer Icons Drug Test Urine Collection Device" by kesha0129 at https://imgbin.com/
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My Patient Has Diabetes - Now What?

The patient with positive symptoms but without laboratory diagnosis:

If a pediatric patient with signs/symptoms/history consistent with diabetes is seen in the urgent-care or outpatient clinic setting and has *any signs* of ***hemodynamic instability*** (hypo/hypertension, tachycardia, or tachypnea), the patient should immediately be sent to the local emergency department (ED) for further evaluation.

Figure 1: A patient with symptomatic diabetes with hemodynamic instability should be sent immediately to the emergency department.

Laboratory evaluation should not delay presentation to the ED.

If the *patient is* ***hemodynamically stable,*** prompt, same-day

laboratory evaluation is needed, as discussed in the "Laboratory Evaluation" Chapter.

Based on the laboratory results, a local pediatric endocrinologist or the local tertiary care PICU should be contacted to discuss further patient disposition from ANY setting (urgent care, clinic, or the ED). Disposition may vary depending on your local tertiary care center's practice preferences, as discussed below.

Figure 2: A patient with symptoms of diabetes but stable vital signs should have further lab testing performed. Once labs have returned, the patient should be discussed with a diabetes expert to determine disposition.

It is potential malpractice to send a patient with suspected diabetes home with only a written referral to an endocrinologist. A written or electronic referral can be lost or take several days to be seen. During that time, patients with new-onset diabetes without confirmed etiology can become critically ill from DKA and potentially die.

All new-onset diabetes mellitus is considered a pediatric emergency in which children are assumed to have Type 1

diabetes mellitus until proven otherwise. This is because Type 1 diabetes is statistically the most prevalent type of diabetes in children and adolescents AND can have overlapping symptoms with Type 2 diabetes. Further, Type 1 patients with untreated hyperglycemia may rapidly develop diabetic ketoacidosis in a matter of hours, leading to metabolic decompensation and cardiovascular collapse/death.

The patient with confirmed diabetes mellitus:

What to do with the otherwise well child with new-onset diabetes that is not in DKA can be variable depending on the local Children's hospital system to which the child presents or is transferred. It is important to know your local hospital system's preferences and policies wherever you end up practicing.

When in doubt, contact the local endocrinologist on-call!

Here at the University of Iowa Stead Family Children's Hospital:

We admit:

1. The pediatric endocrinology team coordinates most new-onset pediatric diabetes patients for inpatient diabetes education.

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2. Known diabetic patients with DKA

    - Patients with simple hyperglycemia and ketosis without acidosis (thus not in DKA) can often be managed at home with close communication with the on-call pediatric endocrinologist or in the emergency department

The admission location (PICU vs. the pediatric endocrinology service) depends upon the severity of the patient's presentation. Admission criteria are listed below:

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Bibliography:

Images/Figures:

1. *Figure 1:* Image created by Dr. Alex Tuttle with the following images: *Image Attributions:* "Vitals signs" at https://www.nicepng.com and "Emergency" from https://resources.ourhealthcalifornia.org/er-or-urgent/
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and“Voice On Phone – Voice Call” at https://www.pngkit.com

Differentiating Type 1 From Type 2 Diabetes - The Overview

Following the diagnosis of a child with diabetes mellitus, we must next determine the etiology of their diabetes.

In the past, new-onset diabetes in a child was rarely considered anything other than Type 1 diabetes. However, the incidence of pediatric Type 2 diabetes is rising, and significant overlap in the presentation makes the diagnosis of T1 vs. T2 challenging.

Siller et al. (2020) report the following pitfalls to the current classification of diabetes in children:

1. Depending on age and race/ethnicity, T2DM now accounts for 30-50% of cases in the United States. Elevated BMI, a prior hallmark of T2DM, is now present in 20-40% of children with new-onset T1DM despite the weight loss that often precedes its diagnosis.
2. DKA and markedly elevated HbA1c may also be seen in T2DM at diagnosis. This, in turn, may require immediate initiation of insulin therapy at the time of diagnosis. However, unlike T1DM, sufficient beta-cell function may recover enough to stop insulin therapy and can be further treated with non-insulin agents.
3. Islet autoantibodies may be negative in up to 20% of otherwise classical T1DM, particularly in minority children. Conversely, ~10% of patients with T2DM may have positive autoantibodies (usually GAD or IA-2 antibodies). In these patients, antibody positivity was predictive of later insulin requirements.

Siller et al. also discuss the importance of early and accurate classification of diabetes to mitigate short and long-term complications of diabetes, the psychological impacts, and economic burdens that can result from misclassification.

So how do we distinguish between Type 1 and Type 2 diabetes mellitus?

Figure 1 offers an algorithm that can be used to start thinking about differentiating T1DM from T2DM (if the patient is > six months of age) based on age, obesity, and antibody status.

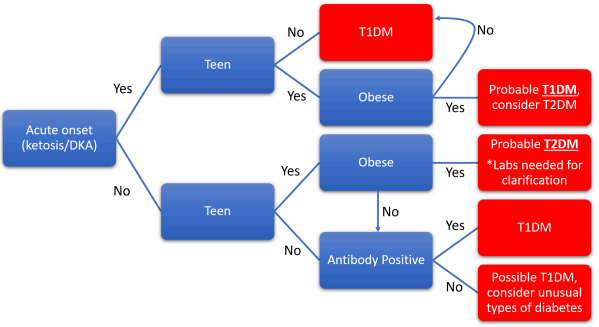

Figure 1 – Simplified diagnostic algorithm when the primary presentation is diabetes mellitus. Figure adapted and modified from Geffner et al., 2014.

Table 1 presents other key differences in clinical and laboratory characteristics that can help further determine the final diagnosis of T1DM vs. T2DM.

	Type 1	Type 2
Age of onset	Throughout childhood to early adulthood	Pubertal children, usually not before age 10 years of age
Sex distribution	F = M	F > M
Ethnic distribution	All (lower frequency in Asian and Native Americans)	All (greater frequency in Hispanic, African American, and Native Americans)
Obesity	Proportionate to the general population	>90%
Onset of symptoms	Usually acute (weeks to a month)	Insidious
Acanthosis nigricans	Rare	Common
Ketosis or DKA at onset	Common	Up to 33%
Islet autoimmunity	Present	Typically absent
Weight loss	Common	Common
Insulin/C-peptide secretion	Low/Low	Variable, more definitive if high/high
Insulin resistance	Normal	Increased
% Probands with 1st or 2nd-degree relatives affected	3-5%	74-100%
Inheritance	Non-mendelian, increased genetic predisposition in those with certain DR/DQ HLA haplotypes	Non-mendelian, strongly familial

Table 1 – Key characteristic differences between Type 1 and Type 2 diabetes mellitus. Table adapted and modified from Geffner et. al, 2014

The remainder of this chapter will explore the differences between Type 1 and 2 diabetes in greater detail regarding epidemiology, pathogenesis, clinical presentations, laboratory findings, and differences in the initial treatment and goals of care.

Quiz Yourself:

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can view it online here:
https://pressbooks.uiowa.edu/pedsendocrinology/?p=89#h5p-29

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Type 1 Diabetes

Epidemiology:

Type 1 diabetes is the most common chronic disease of childhood in the US and accounts for nearly 98% of cases of diabetes in children <10 years of age and over 87% of the cases in children 10-19 years of age.

The incidence of Type 1 diabetes among children <20 years of age in the US is about 2.2 per 1000 children, rising by 1.4% from 2002 to 2015, according to the SEARCH for Diabetes in Youth Study (SEARCH).

The increase in incidence was seen in almost all ages, sex, and race/ethnic groups. Incidence rates also vary substantially but overall are increasing across the globe. The lowest incidence of ~1 per 100,000 person-years is in China and parts of South America. In comparison, rates are much higher at 30 per 100,000 person-years in Caucasian populations of Sweden, Finland, and Sardinia.

Incidence of T1DM in the US is highest in non-Hispanic white children, although the change in incidence rates was higher in non-Hispanic blacks (2.7% per year), Hispanics (4% per year), and Asian/Pacific Islanders (4.4% per year). See *Figure 3* for a comparison of incidence rates between Type 1 and Type 2 diabetes mellitus.

Assuming the current annual increase in incidence continues, the number of T1D and T2D could triple, or even quadruple, to 600, 000 and 85,000 US children, respectively by the year 2050 (Divers et al. 2020 and Lawrence et al., 2021).

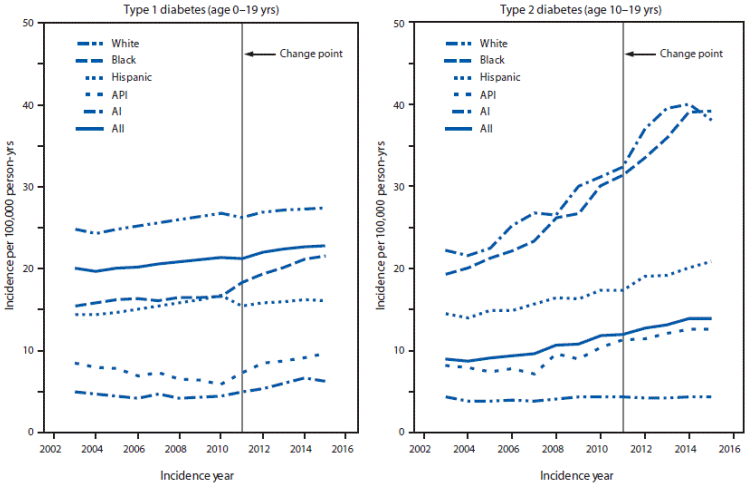

Figure 3 – FIGURE. Model-adjusted incidence of type 1 and type 2 diabetes among youths, overall and by race/ethnicity — SEARCH for Diabetes in Youth Study (SEARCH), United States,† 2002–2015. † SEARCH includes data on youths (<20 years) in Colorado (all 64 counties plus selected Indian reservations in Arizona and New Mexico under the direction of Colorado), Ohio (eight counties), South Carolina (all 46 counties), Washington (five counties), and in California for Kaiser Permanente Southern California health plan enrollees in seven counties. Abbreviations: AI = American Indian; API = Asian/Pacific Islander. * Persons who were AI were primarily from one southwestern tribe.*

Pathogenesis:

In almost all cases, type 1 diabetes is caused by an autoimmune process leading to T-cell mediated destruction of the insulin-producing β-cells of the pancreatic islet cells.

The autoimmune process is thought to be due to an unknown environmental trigger in those with a concomitant genetic susceptibility conferred by specific major histocompatibility complex (MHC) HLA-subtypes (DR/DQ

haplotypes) on chromosome 6. While there is a genetic component to T1DM risk, only 10-20% of individuals diagnosed with T1DM have a family member with T1DM. The environmental component is suggested by the results of monozygotic twin concordance studies in which only 30-40% of initially unaffected twins develop diabetes when followed to 20 or 30 years of age.

Studies conducted through TrialNet are aimed at the prevention of Type 1 diabetes. These studies have pushed for a further distinction of Type 1 diabetes by "stages" by where an individual is identified on the spectrum of disease progression (Chiang et al., 2018 and Besser et al., 2022). Explore *Figure 1* for more information!

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Figure 1 – Shows the progression and stages of Type 1 diabetes. This figure and the associated information are adapted from https://www.trialnet.org/t1d-facts.

Clinical Presentation:

Symptoms of diabetes mellitus were discussed previously and include polyuria, polydipsia, polyphagia, and weight loss.

In Type 1 diabetes, these symptoms usually present on acute (days) to subacute (weeks to a few months) timeframes.

Up to 40% of children with Type 1 diabetes present with varying degrees of DKA severity.

Physical exam finds are usually limited to complications of progressive dehydration and acidosis.

- While acanthosis nigricans (AN) is more likely to be absent in those with Type 1 diabetes, Calcaterra et al. (2021) show that the prevalence of acanthosis nigricans is greater in children with Type 1 diabetes compared to healthy controls and is associated with older age and presence of obesity. Yet another factor complicating the clinical differentiation of T1DM from T2DM.

Laboratory Findings:

The diagnostic criteria for diabetes were discussed previously. Additional second-tier laboratory testing should be obtained to further distinguish between Type 1 and Type 2 diabetes.

Laboratory results that help define the diagnosis of Type 1 diabetes include:

- ***Positive islet/β-cell autoimmune antibodies*** include:
    - Glutamic acid decarboxylase antibodies (GAD Ab)
    - IA-2 Antibodies
    - Insulin antibodies
    - Islet cell antibodies
    - +/- Zinc transporter antibodies
- ***Low or inappropriately normal levels*** of:
    - o C-peptide (the endogenous cleavage product of pro-insulin, secreted in a 1:1 ratio upon insulin release)
    - o Total insulin (a measure of endogenous insulin)
        - *Note: Total insulin levels should not be obtained in individuals who have already been started on exogenous insulin via injections or continuous infusion (i.e. an insulin drip).*

An Overview of Initial Treatment:

Optimal management of Type 1 diabetes requires:

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As Type 1 diabetics have insulin deficiency, the mainstay of treatment is ***insulin replacement therapy*** by using basal/bolus insulin regimens AND close monitoring of glucose. The overall goal of treatment is to mimic the physiologic production of insulin by the pancreas.

Basal/Bolus insulin regimens:

Discussed in greater detail in Unit 2.

Different routes of insulin administration can be achieved by these regimens:

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In the following matching game, match the pictures of the diabetes devices at the periphery with the correct label:

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Whichever route of insulin administration is chosen, it is then combined with a method of glucose monitoring which can be achieved by:

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As seen in the table below, each insulin delivery method can be combined with various glucose monitoring methods. This allows endocrinologists to customize insulin therapy and glucose monitoring to the needs of the individual patient and their family in a way that optimizes their ability to attain the goals of insulin therapy.

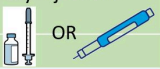
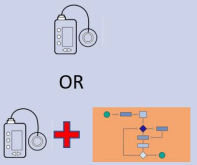
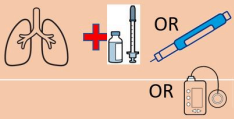
Insulin Therapy Methods:	Routes of insulin delivery available:	Method of Glucose Monitoring:
Multiple Daily Injections (MDI) 	Vial and Syringe	BGM, isCGM, or rtCGM
	Insulin Pens	BGM, isCGM, or rtCGM
Continuous Subcutaneous Insulin Infusion (CSII)	Insulin pump alone	BGM, isCGM, or rtCGM
	Sensor-augmented insulin pump with automatic insulin suspension only for prevention of hypoglycemia	rtCGM + BGM as needed
	**Hybrid Close Loop insulin pump systems** (uses FDA approved proprietary algorithms in certain pump models/brands OR non-FDA approved Do-it-yourself "looping" allowing for automated insulin delivery for prevention of hypo- AND hyperglycemia)	rtCGM + BGM as needed
Inhaled + Injected Basal Insulin (in clinical trials)	Vial and Syringe (for basal insulin only) + inhaled (for rapid-acting insulin)	BMG, isCGM, or rtCGM
	Insulin pen (for basal insulin only) + inhaled (for rapid-acting insulin)	BGM, isCGM, or rtCGM
	Insulin pump (for basal delivery only) + inhaled (for rapid-acting insulin)	BGM, isCGM, or rtCGM

Table 1 – Each insulin therapy method (left column) has one or more available routes of insulin delivery (middle column). Each of these routes of insulin delivery, in turn, can be paired with certain glucose monitoring methods (right column). Abbreviations: BMG = fingerstick blood glucose monitoring, isCGM = intermittently scanned continuous glucose monitor (CGM), rtCGM = real-time CGM.

Glucose monitoring methods are discussed in greater detail in Unit 6.

Quiz Yourself:

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Type 2 Diabetes

Epidemiology:

The incidence of Type 2 diabetes in youth in the US is rising, disproportionately more so in certain minority populations. Data also indicates a slight female predominance.

Note that the overall incidence of T2DM is lower than T1DM, so it is still more likely that a pediatric patient <20 years old with new-onset diabetes has T1DM.

- According to the SEARCH trial, the incidence of Type 2 diabetes from 2002 to 2012 increased by 7.1% overall = 9 per 100,000 in 2002-2003 to 13.8 per 100,000 in 2014-2015.
    - An increase in incidence rate was seen in all age, sex, and race/ethnicity groups except the non-Hispanic white population
    - The highest rate of change in incidence rates (AKA annual percent change) was observed in Asians or Pacific Islanders (7.7%) followed by Hispanics (6.5%), and non-Hispanic Blacks.
        - Patients of American Indian ethnicity are more likely to present with Type 2 diabetes rather than Type 1 diabetes.

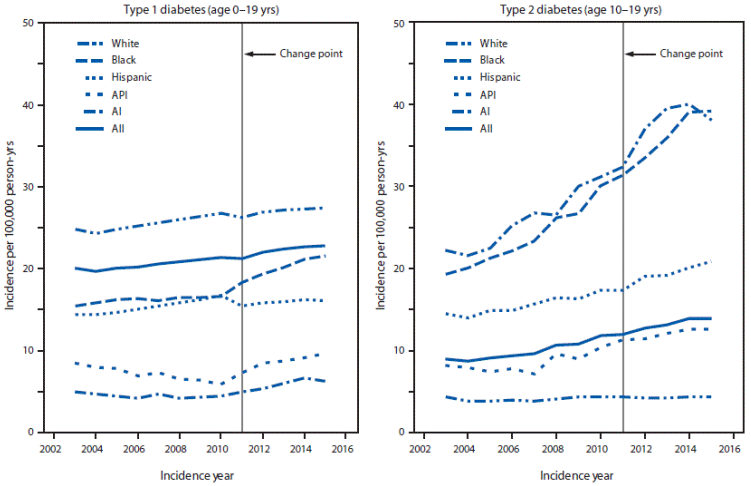

Figure 1 – Model-adjusted incidence of type 1 and type 2 diabetes among youths, overall and by race/ethnicity — SEARCH for Diabetes in Youth Study (SEARCH), United States,† 2002–2015. † SEARCH includes data on youths (<20 years) in Colorado (all 64 counties plus selected Indian reservations in Arizona and New Mexico under the direction of Colorado), Ohio (eight counties), South Carolina (all 46 counties), Washington (five counties), and in California for Kaiser Permanente Southern California health plan enrollees in seven counties. Abbreviations: AI = American Indian; API = Asian/Pacific Islander. * Persons who were AI were primarily from one southwestern tribe.*

- A recent cross-sectional, multicenter prevalence study by Lawrence et al. (2021) showed that the prevalence of Type 2 diabetes has almost doubled in 10–19-year-olds from 0.34 to 0.67 per 1000 youths in 2001 and 2017 respectively.
    - The greatest change in prevalence was again seen in non-Hispanic blacks and Hispanic youths.

While obesity prevalence rates have been associated with increased rates of Type 2 diabetes in all population groups, it is likely not the only explanation for the changes in incidence and prevalence seen in minority populations. Rather, this may

represent genetic susceptibility toward insulin resistance. This is likely why a strong family history of T2DM is often seen among affected youths.

- 45-80% have at least one parent with DM and 74-100% have a first- or second-degree relative with T2DM.

Risk factors contributing to T2DM include:

- Increasing weight, rate of weight gain, BMI, waist-to-hip ratio, and central fat distribution
- Genetic background (ethnicity/race and other family genetics)
- Sedentary lifestyle
- Being small OR large for gestational age
- Being an infant of a diabetic mother
- Lack of (or shortened duration) of exclusive breastfeeding as an infant

Pathogenesis:

Type 2 diabetes is caused by a combination of insulin resistance and the inability of the pancreatic β-cells to compensate with sufficient insulin secretion.

Type 2 diabetes is rarely seen in pre-pubertal children under ten years of age.

- Pubertal children have a natural, intrinsic increase in insulin resistance due to increased sex steroid production. Most children can compensate for this increased resistance by increasing β-cell insulin production.
- For those who are unable to compensate, a relative insulin deficiency develops.

- The addition of obesity, other risk factors, and genetic background can tip the scales even further and lead to the eventual emergence of clinical Type 2 diabetes.

Insulin resistance occurs mostly at the liver, muscle, and adipose tissue level, leading to metabolic derangements in glucose, protein, and lipid metabolism. This, in turn, causes vascular endothelial dysfunction leading to micro-and macro-vascular complications that occur earlier than in Type 1 diabetes.

The Figure below shows the relationship between how insulin secretion changes as insulin resistance increases, leading to Type 2 diabetes. Explore the graph below for further information!

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In some cases, patients who have an initial response to non-insulin medications that improve insulin secretion and/or insulin sensitivity may develop irreversible β-cell insulin secretory failure. These patients then become dependent on exogenous insulin replacement.

Clinical Presentation:

Children with Type 2 diabetes can present on a spectrum

ranging from acute manifestations of symptoms overlapping with Type 1 diabetes (the polys and weight loss) to mild hyperglycemia noted incidentally.

- Up to 50% may be asymptomatic.
- While presentation in DKA is less common in Type 2 diabetes, it does occur in up to 10% of children with new-onset T2DM.
- Over 90% of children with Type 2 diabetes are overweight (BMI greater than the 85th percentile) or obese (BMI greater than the 95th percentile).
- Hypertension, skin infections, yeast infections, and acanthosis nigricans may be present on the exam
    - Acanthosis nigricans is common (60-95% of patients), but not always present.

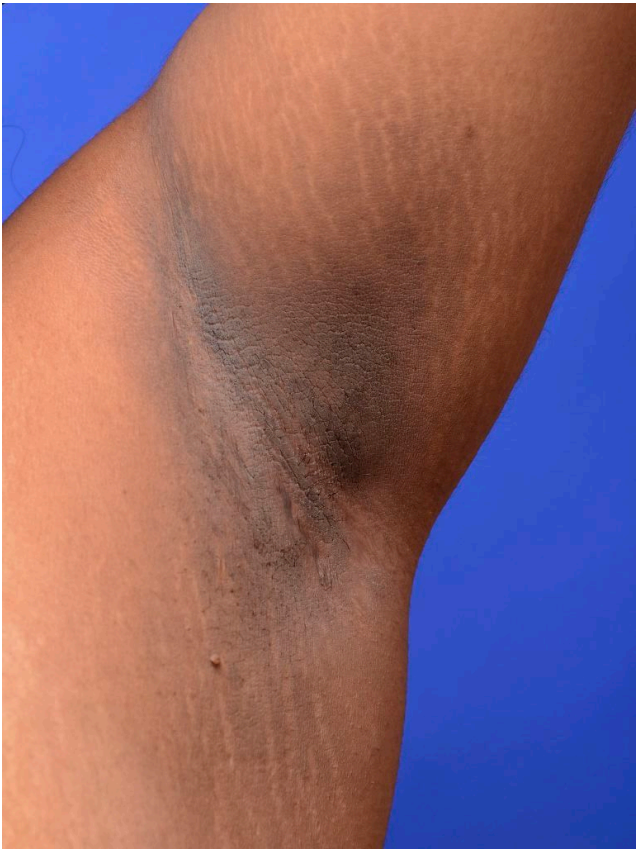


Figure 2 – Acanthosis nigricans of the axilla. The overlying hyperpigmented skin has a thickened, "velvet-like" texture. Also seen here are light, vertical striae (stretch marks). Acanthosis nigricans usually appears in flexural creases of the axilla, neck, and groin. Image Attribution: " Acanthosis nigricans on axilla" by Mark F. Brady; Prashanth Rawla CC By-SA 4.0

Laboratory Findings:

After meeting the diagnostic criteria for diabetes, second-tier laboratory testing should be obtained to further distinguish between Type 1 and Type 2 diabetes.

Children with Type 2 diabetes are more likely to present with earlier and severe complications of obesity and diabetes at the time of diagnosis when compared with Type 1 diabetes.

Therefore, screening for retinopathy, dyslipidemia, hypertension, microalbuminuria, and non-alcoholic fatty liver disease (NASH) is necessary at the time of (or soon after) diagnosis.

Laboratory results that help define the diagnosis of Type 2 diabetes include:

- ***Elevated levels*** of:
  - C-peptide (the endogenous cleavage product of pro-insulin, secreted in a 1:1 ratio upon insulin release)
  - Total insulin (a measure of endogenous insulin)
  - AST/ALT (if persistently elevated, these may be due to the presence of NASH)
  - Cholesterol and/or Triglycerides (dyslipidemia)
  - Urine microalbumin (persistently elevated levels may indicate early nephropathy)

- ***Negative (or few) Islet/β-cell autoimmune antibodies***:
  - At the University of Iowa, we often send GAD, IA-2, anti-Insulin, and anti-Islet cell autoantibodies for almost all patients with new-onset diabetes if there is any doubt about the diagnosis between Type 1 and Type 2 diabetes. However, as discussed previously, the following autoantibodies may be present in T2DM and also portend the future need for exogenous insulin therapy:
    - Glutamic acid decarboxylase antibodies (GAD Ab)

- IA-2 Antibodies

While laboratory tests can be helpful, they sometimes do not provide a definitive diagnosis of Type 1 vs. Type 2 diabetes mellitus. Often the definitive diagnosis becomes clearer over time, and if it does not, may prompt endocrinologists to consider other forms of diabetes mellitus.

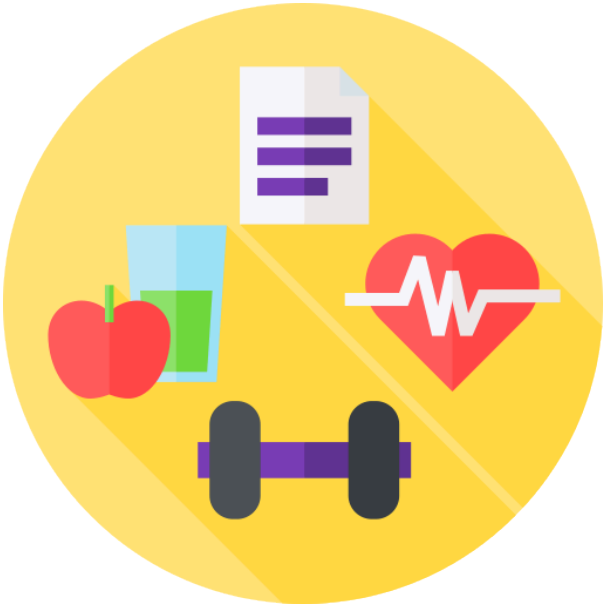
Overview of Treatment:

The same multidisciplinary team of healthcare providers for patients with Type 1 diabetes (*link*) is necessary for the treatment of children with T2DM.

The goals of treatment for T2DM differ from T1DM and involve:

1. Normalizing glycemia with target HbA1c of less than 6.5% without excessive hypoglycemia
2. Education about healthy lifestyle changes in diet and activity aimed at promoting healthy weight loss.
3. Prevention or control of associated comorbidities (dyslipidemia, hypertension, nephropathy, hepatic steatosis, sleep apnea, and mental health concerns)

The cornerstone of T2DM therapy is behavioral and lifestyle modification.



Emphasis on including the entire family in these lifestyle changes is essential, as many of these children come from home environments where other family members often struggle with similar issues of obesity or even diabetes. Motivational interviewing techniques and setting small, achievable goals are needed to optimize success in adherence of the patient and family members to these long-term changes. Image Attribution: "Lifestyle Icon" by Freepik CCBY3.0

Pharmacotherapy:

Initial pharmacotherapy is guided by the presenting severity of the patient's metabolic status as seen in *Figure 3*.

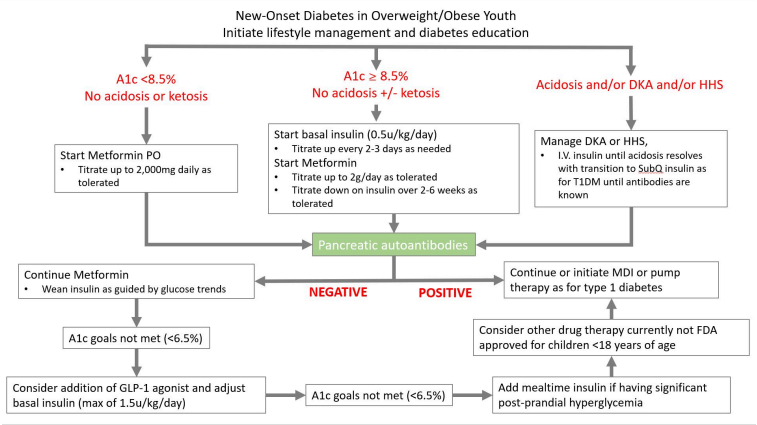


Figure 3 – Modified from the American Diabetes Association (ADA) 2018 position statement for the evaluation and management of Youth-onset T2DM (Arslanian et al., 2018).

- Until 2018, the only medications approved for treating type 2 diabetes in children included metformin and insulin.
    - There are other oral and injectable anti-diabetes medications approved for treating Type 2 diabetes in adults, but as with all pediatric pharmacologic trials, approval of these medications for use in children is generally significantly delayed.
- In the last few years (2019 – 2023), GLP-1 agonist therapies have become FDA-approved for treating Type 2 diabetes in children. These include:
    - Liraglutide (Victoza)
    - Extended-release Exenatide

Pramlintide, SGLT2 inhibitors, DPP-4 inhibitors, and some other adult-FDA-approved antidiabetes medications can be considered if there is a failure to achieve sufficient glycemic control with metformin and GLP-1 agonist therapy. The selection of these additional therapies in adults is guided by

the presence of other complications of diabetes and cardiovascular disease.

Quiz Yourself:

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PART II

UNIT 2: INSULIN BASICS

Learning Objectives

1. Provided information about different classes of insulin, trainees will be able to identify the four most utilized insulins in the inpatient setting here at University of Iowa Stead Family Children's Hospital
2. Using knowledge of the pharmacokinetic profiles of each of these four insulins, learners will be able to identify the intended effects of these insulins on a patient's blood glucose profile
3. Using information about the pharmacokinetics of different types of insulins, learners will be able to:
    1. Identify the timing of administration of the four most used insulins
    2. Identify the frequency of administration of the four most used insulins
4. Provided information about basal/bolus insulin regimens, learners will demonstrate the use of correct terminology when discussing insulin

regimens

Endogenous vs. Exogenous Insulin

Endogenous Insulin:

Insulin is a peptide hormone produced by β-cells of the pancreatic islets of Langerhans that comprise the endocrine pancreas.

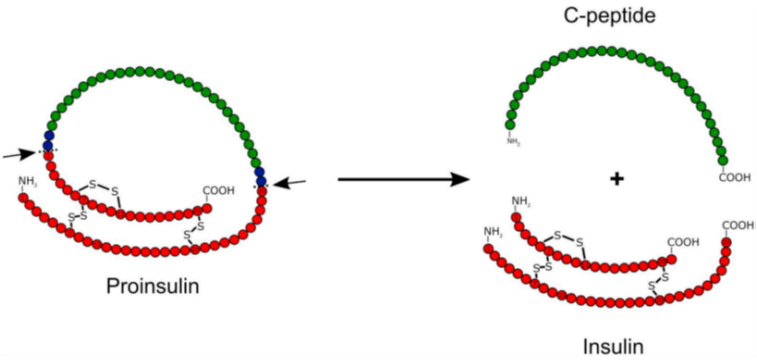

Figure 1 – Prior to exocytosis from the β-cells, proinsulin is cleaved into the mature insulin and C-peptide, resulting in a 1:1 ratio of active insulin to c-peptide upon systemic release. Photo Attribution: "Schematic illustration of insulin synthesis" by Hörber, Achenbach, Schleicher, & Peter, 2020 CC BY-NC-ND 4.0

C-peptide has a longer half-life than the mature insulin cleavage product. The detection of this C-peptide (especially in

the fasting state) is a useful indicator of the insulin secretory capacity of the β-cells.

Thus, C-peptide is useful for determining if a patient has insulin deficiency (as with diabetes) or insulin excess (as with hyperinsulinism leading to recurrent hypoglycemia).

Insulin acts upon insulin receptors in various target organs leading to its overall anabolic effects related to carbohydrate, lipid, and protein metabolism as summarized in Table 1.

Metabolic Effect:	Insulin Stimulates:	Insulin Inhibits:
Carbohydrate Metabolism	-Glucose transport and rate of glycolysis in fat and muscle tissue -Glycogen synthesis in fat, muscle and liver	-Glycogen breakdown in muscle and liver -Rate of glycogenolysis and gluconeogenesis in the liver
Lipid Metabolism	-Fatty acid and Triacylglycerol synthesis in tissues -Uptake of triglycerides (blood → fat/muscle) -Cholesterol synthesis in liver	-Lipolysis in fat → decreased plasma free fatty acids -Fatty acid oxidation in muscle and liver (and thus ketogenesis)
Protein Metabolism	-Amino acid transport into tissues -Protein synthesis	-Protein degradation in muscle and thus urea formation

Table 1 – Physiologic Effects of Insulin. Adapted from Molina, 2013

Exogenous Insulin:

Exogenous insulin used in insulin-replacement therapy is synthetic insulin that is mass-produced using recombinant DNA technology and is based upon the amino acid sequence of mature human insulin.

As C-peptide is not produced in the manufacturing process of insulin analogs, a patient with recurrent hypoglycemia with **detectable insulin levels and absent C-peptide** should raise suspicion of surreptitious self-insulin administration in children without diabetes.

Quiz Yourself:

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Insulin Concentration and Types of Insulin

Insulin Concentrations:

Regardless of the type of insulin used, **the standard concentration of insulin is U-100**.

U-100 = 100 units of insulin per 1 mL of solution

- Most insulin syringes are calibrated to be U-100 syringes in which each 1 unit marking represents 1 unit of insulin.
    - It is important at discharge to ensure the correct types of insulin syringes (size and needle caliber) are supplied.
    - At Stead Family Children's Hospital, this is done by the discharging endocrinologist or one of the diabetes educators. It is not usually the responsibility of the discharging resident team unless they are specifically asked to place these discharge orders.

When reconciling patient medications during inpatient admissions, it is important to verify that a patient is not using diluted (sometimes used in children < 1-2 years of age) or more concentrated insulins (often used in patients with significant insulin resistance, as seen in some teenagers or those with Type 2 diabetes).

The most common concentrated insulins include U-200, U-300, or U-500 insulins, which are 200, 300 or 500 units of insulin per mL of solution, respectively.

Verifying the insulin concentration is imperative for safety and the avoidance of medical error.

Delivery of U-100 insulin to a patient who usually takes concentrated insulin can lead to iatrogenic hyperglycemia due to underdosing.

Conversely, if a patient on dilute insulin (e.g., U-10, U-20, U-50) receives standard U-100 or more concentrated insulin, it can lead to iatrogenic and potentially deadly hypoglycemia.

Types of Insulins:

There are many different types of exogenous insulin used in insulin-replacement therapy and each can be categorized by its duration of action. These categories are broken down in *Table 2* produced by the Centers for Disease Control and Prevention.

Insulin Type	Onset	Peak Time	Duration	Method
Rapid acting	15 minutes	1 hour	2 to 4 hours	Usually taken right before a meal. Often used with longer-acting insulin.
Rapid-acting inhaled	10 to 15 minutes	30 minutes	3 hours	Usually taken right before a meal. Often used with injectable long-acting insulin.
Regular/short acting	30 minutes	2 to 3 hours	3 to 6 hours	Usually taken 30 to 60 minutes before a meal.
Intermediate acting	2 to 4 hours	4 to 12 hours	12 to 18 hours	Covers insulin needs for half a day or overnight. Often used with rapid- or short-acting insulin.
Long acting	2 hours	Does not peak	Up to 24 hours	Covers insulin needs for about a full day. Often used, when needed, with rapid- or short-acting insulin.
Ultra-long acting	6 hours	Does not peak	36 hours or longer	Provides steady insulin for long periods.
Premixed	5 to 60 minutes	Peaks vary	10 to 16 hours	Combines intermediate- and short-acting insulin. Usually taken 10 to 30 minutes before breakfast and dinner.

Table 2 – Types of insulin categorized by the duration of action. Onset is defined as the amount of time it takes from subcutaneous injection to absorption and initial systemic action of this insulin. Peak time is the time of the most potent glucose-lowering effect of the injected insulin. Duration is the total amount of the insulin's glucose-lowering effect present after the initial injection.

In the matching game below, drag the correct insulin class/types (found on the right) to their correct pharmacokinetic profile (the colored lines on the left). Then, drag the brand-name insulins (Lantus, NPH, Tresiba, Levemir, Humalog, Regular) to their corresponding pharmacokinetic profile and insulin type pairing.

Hint: You may need to read the remainder of Unit 2 to learn more about the brands of insulins.

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https://pressbooks.uiowa.edu/pedsendocrinology/?p=194#h5p-15

The types of insulin chosen for the treatment of diabetes are dependent upon various factors, including:

- Goals of insulin therapy
- The method of insulin delivery
- Insurance coverage
- The individual needs of the patient

It is beyond the scope of this book to review each type of insulin; however, the most common types of insulin used in the inpatient setting at Stead Family Children's Hospital will be reviewed along with the role each insulin plays in a basal/bolus insulin regimen.

Quiz Yourself:

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can view it online here:
https://pressbooks.uiowa.edu/pedsendocrinology/?p=194#h5p-32

Bibliography:

1. Centers for Disease Control and Prevention. (2022, December 30). *Types of insulin*. Centers for Disease Control and Prevention. https://www.cdc.gov/diabetes/basics/type-1-types-of-insulin.html

The Basal/Bolus Insulin Regimen

As previously discussed in Unit 1: "Type 1 Diabetes", the goal of insulin therapy in Type 1 diabetes mellitus is to mimic the physiologic production of insulin by the pancreas. This can be approximated using a **basal/bolus insulin regimen,** as depicted in *Figure 2*.

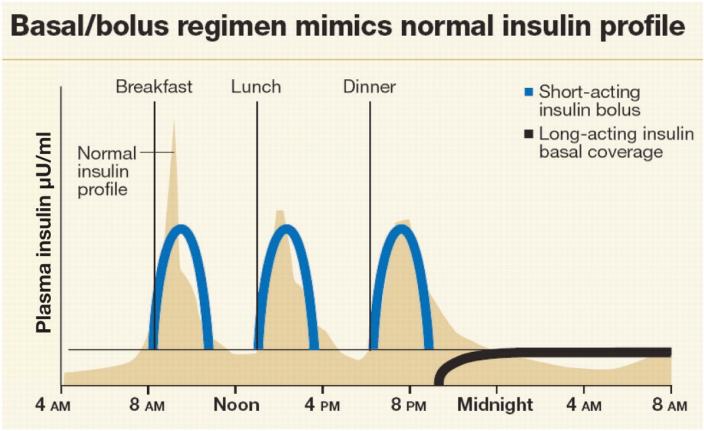


Figure 2 – The dark yellow represents a normal physiologic insulin profile throughout the day with post-prandial insulin spikes at 10 am, 2 pm, and 8 pm due to carbohydrate ingestion at mealtimes (breakfast, lunch, and dinner). A rapid-acting insulin is strategically administered as a bolus (represented by the bold, blue lines) 15 minutes before meals to achieve paired timing of insulin action with the absorption of carbohydrates (discussed further in "Rapid-acting insulins"). Additional rapid-acting insulin may also be administered at these times to correct for pre-prandial hyperglycemia to bring post-prandial blood sugars down into the goal glycemic range (most often 70-150mg/dL) within 2 hours after a meal. Note that overnight, while sleeping and fasting between meals, glucose production still occurs due to the release of glucose from glycogen stores in the liver. Thus, basal insulin is also needed (represented by the bold, black line). Image Attribution: "Basal/bolus regimen mimics normal insulin profile" by Magaji and Johnston (2011) BY License for non-commercial reuse, Version 1.0

Basal insulin covers background/basal glucose release from the liver. This hepatic glucose production usually occurs to maintain normal blood glucose during fasting. Pancreatic insulin production never drops to zero, so in patients who are insulin deficient, basal insulin administration mimics the basal insulin production from the pancreas to maintain control over hepatic glycogenolysis.

- The ***method*** of basal insulin delivery dictates what type of insulin is used as the "basal insulin." Basal insulin delivery is accomplished either by:

    1. The administration of long-acting injectable insulin when using multiple daily injections
    2. Through the programmed delivery of a continuous, low-rate infusion of rapid-acting insulin when using insulin pump [CSII] therapy.

A **bolus** is the administration of a single, usually larger dose of short- or rapid-acting insulin.

Bolus insulin is used:

1. Cover spikes in blood glucose due to ingestion of carbohydrates/glucose from food
2. As needed to:
    1. Bring high blood sugars back into a normal range
    2. Treatment of ketonemia (or ketonuria)

Administration of bolus insulin occurs by giving:

1. A single injection of rapid-acting insulin is given via syringe or insulin pen when using multiple daily injections.
2. Alternatively, boluses can be delivered by an insulin pump when the user directs the pump to "push" the desired amount of rapid-acting insulin over a short time (seconds to minutes).

Other insulin regimens exist that involve combinations of other types of insulin (aside from rapid-acting and basal insulin), but these go beyond the scope of this book.

Also, remember that the classic basal/bolus regimen may not be necessary for treating Type 2 diabetes depending on the

initial severity of their presentation and ability to achieve A1c goals over time.

Quiz Yourself:

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.uiowa.edu/pedsendocrinology/?p=241#h5p-33

Bibliography:

1. Vasudev Magaji, Jann M. Johnston; Inpatient Management of Hyperglycemia and Diabetes. *Clin Diabetes* 1 January 2011; 29 (1): 3–9. https://doi.org/10.2337/diaclin.29.1.3

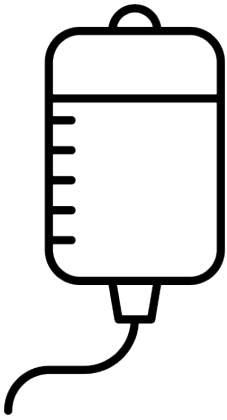
Short-Acting Insulin

Regular (aka Human) **insulin** is synthetically produced by DNA recombinant technology and is an exact copy of human insulin without amino-acid substitutions.

Brand name examples: Humulin-R or Novolin-R

Administration:

1. Subcutaneous injection:
    - Regular insulin can be used as a bolus insulin as part of a basal/bolus insulin regimen.
    - Its use has largely been supplanted by rapid-acting insulins (discussed in the next chapter)



2. Intravenous (IV) infusion
    - Regular insulin by continuous IV infusion is most

commonly used in the inpatient setting to treat diabetic ketoacidosis (DKA) or persistent hyperglycemia not due to diabetes mellitus.
    - Once DKA has resolved, patients are transitioned from a Regular insulin IV drip to a subcutaneous insulin regimen using a combination of long-acting and rapid-acting insulins (if using multiple daily injections) or just rapid-acting insulin (if using an insulin pump).

Pharmacokinetics:

1. Subcutaneous Injection:
    - Onset of Action: 30 minutes
    - Peak Action: 2-3 hours
    - Duration of Action: 3-6 hours
2. Intravenous (IV) Infusion:
    - Elimination half-life: ~3-7 minutes
        - Due to this short half-life, stopping an insulin drip will lead to >75% of the Regular insulin being eliminated from the body within 15 minutes of stopping the drip. For insulin-deficient diabetes patients, this means rebound hyperglycemia and rapid re-development of ketosis can occur if a plan for transition for IV to subcutaneous insulin is not in place.
            - Rapid-acting insulin's onset of action starts around 10-15 minutes but does not peak until at least 2 hours after administration. Therefore, the continuation of the IV regular insulin drip

for 30 minutes AFTER administration of rapid-acting insulin for carbohydrate coverage allows for a sufficient “bridge period” to help ensure rebound hyperglycemia and ketosis does not recur.

- Here at the Stead Family Children’s Hospital, we usually give long-acting insulin while a patient is on the insulin drip, which helps decrease the risk of rebound hyperglycemia and allows for a shorter bridging period (30 minutes instead of 1-2 hours) before shutting off the IV regular insulin drip.

Quiz Yourself:

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Rapid-Acting Insulins

Lispro (brand name: Humalog) is the rapid-acting insulin currently used on the inpatient Stead Family Children's Hospital formulary.

Humalog is a synthetic form of human insulin modified at positions 28 (Lysine to Proline) and 29 (Proline to Lysine) in the B-chain as seen in *Figure 1*.

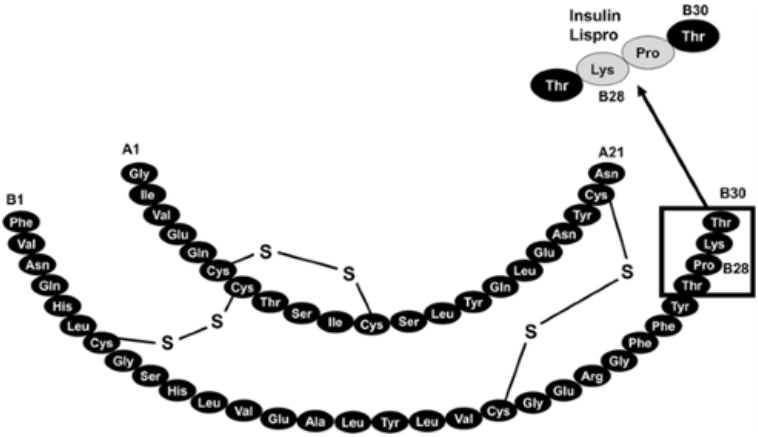

Figure 1 – Structure of insulin lispro. Ala alanine, Arg arginine, Asn asparagine, Cys cysteine, Gln glutamine, Glu glutamic acid, Gly glycine, His histidine, Ile isoleucine, Leu leucine, Lys lysine, Phe phenylalanine, Pro proline, Ser serine, Thr threonine, Tyr tyrosine, Val valine. Image Attribution: "Structure of insulin lispro" by Candido at al, 2018 CC BY-NC 4.0

While these substitutions appear minor, they cause a significant increase in the absorption rate of this analog insulin into the blood after subcutaneous injection (or infusion) compared to Regular insulin (short-acting) insulin.

This increased absorption rate accounts for the quicker onset of action (10-15 minutes), leading to early peak action (by 1 hour)

and a shorter duration of action (cleared from the system by 2 to 4 hours after injection).

Rapid-acting insulin is now the most common type of insulin utilized in basal/bolus regimens for subcutaneous injection and subcutaneous infusion.

Administration:

Rapid-acting insulin boluses are ideally given 15 minutes **BEFORE** anticipated meals, as this is how long it takes for the insulin to move from the subcutaneous space into the bloodstream and start having action at its insulin receptors.

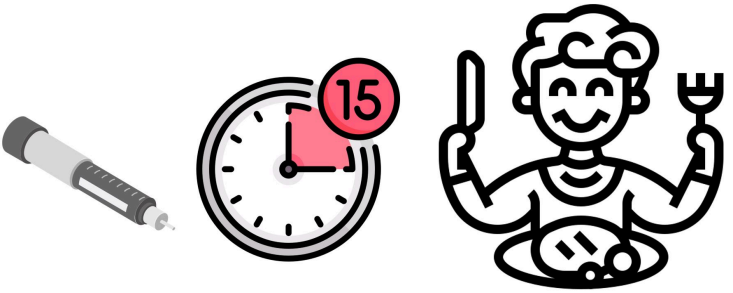

Figure 2 – Rapid-acting insulin is best dosed 15 minutes (or sometimes sooner) before a carbohydrate-containing meal.

Coincidentally, this is also about how long the initial carbohydrates are absorbed from ingested food at a meal.

This paired timing of insulin action with ingestion of food allows for ideal post-prandial blood glucose in the target range, as discussed in *Figure 3*.

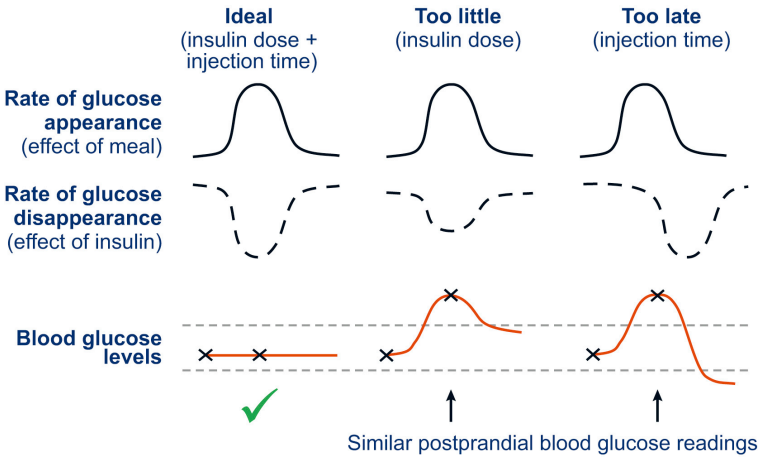

Figure 3 – "Ideal postprandial blood glucose levels = right insulin dose + right injection time. Ideal postprandial BG control requires an appropriate dose of insulin given at the right time so that the rate of BG appearance after a meal is matched by the rate of BG disappearance. If the insulin dose is too low, the glucose disappearance rate will not match the rate of glucose appearance, resulting in postprandial hyperglycemia. If the insulin dose is administered too late, the rate of BG disappearance will also not match the rate of BG appearance, resulting in postprandial hyperglycemia and late postprandial hypoglycemia. Patient education often focuses on postprandial BG levels and assumes that high BG levels are due to the insulin doses being too low, but they may also reflect that insulin action is too late. Horizontal dashed lines represent the glycemic target range. BG, blood glucose." Image Attribution: by Senior and Hramiak (2019) CC BY-NC-ND 4.0

For young or very sick children who are unpredictable eaters, rapid-acting insulin can be given right after allowing 20-30 minutes to eat the carb-containing foods that they are able to eat. The delivered dose of insulin is determined by the amount of ingested carbohydrates eaten during the 20-30 minutes timeframe. This is not ideal and often leads to more significant post-prandial blood glucose spikes and more difficulties getting post-prandial blood glucose to remain in the target range.

Rapid-acting insulin is the only type of insulin used in insulin pumps. The continuous low rate of rapid-acting insulin infusion via a pump replaces the need for a subcutaneous injectable long-acting insulin. Boluses for carbohydrate coverage should still be given at least 15 minutes before eating.

Many different brands of rapid-acting insulin used in the outpatient setting are unavailable on the inpatient formulary. These include:

- Lispro (Admelog, Lyumjev),
- Apidra (Glulisine)
- Aspart (Novolog, Fiasp)
    - Fiasp is an *ultra-rapid-acting* insulin with a quicker onset of action of 5-10 minutes compared to Novolog and the other rapid-acting insulins listed here.

Conversion from one rapid-acting insulin to another rapid-acting insulin is a 1:1 conversion and, therefore, does not require any specific dose adjustment.

Quiz Yourself:

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can view it online here:
https://pressbooks.uiowa.edu/pedsendocrinology/?p=222#h5p-35

Bibliography:

1. Candido R, Wyne K, Romoli E. A Review of Basal-Bolus Therapy Using Insulin Glargine and Insulin Lispro in the Management of Diabetes Mellitus. Diabetes Ther. 2018 Jun;9(3):927-949. doi: 10.1007/s13300-018-0422-4. Epub 2018 Apr 13. PMID: 29654514; PMCID: PMC5984925.
2. Senior P, Hramiak I. Fast-Acting Insulin Aspart and the Need for New Mealtime Insulin Analogues in Adults With Type 1 and Type 2 Diabetes: A Canadian Perspective. Can J Diabetes. 2019 Oct;43(7):515-523. doi: 10.1016/j.jcjd.2019.01.004. Epub 2019 Jan 24. PMID: 30872107.

Figures:

Figure 2: Image Attribution: Created by Alex Tuttle by compilation of the following images from left to right: “Insulin icons” by vectorsmarket15, “15 minutes icon” by Freepik, and “Eat icons” by Eucalyp from Flaticon.com

Long-Acting Insulins

Lantus (glargine) is a recombinant human insulin analog.

It is preferred long-acting insulin on the Stead Family Children's Hospital's inpatient formulary.

Lantus works as a long-acting insulin because after its injection into the subcutaneous tissue, the acidic solution (pH 4) in which the insulin is dissolved is rapidly neutralized. This leads to the formation of microprecipitates from which small amounts of insulin monomers are slowly released (*Figure 1*), resulting in a relatively constant concentration/time profile over 24 hours with no pronounced peak.

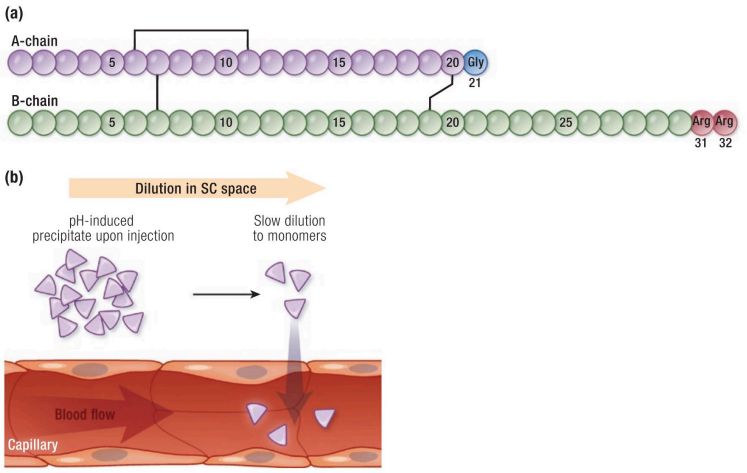

Figure 1 – "Insulin glargine. A: Amino acid structure of insulin glargine. B: Mechanism of protraction of insulin glargine: pH-induced precipitation at the SC space." Image attribution: Hirsch et al., 2020 (Endocrine Reviews 41(5):1-23) CC BY 4.0

Long-acting insulins are usually dosed once in the morning or before bedtime and given around the same time each day.

Most long-acting insulins are considered “peakless” insulins as they have a gradual onset, usually within a few hours after administration, and have a long duration of action. They are ideal when used as part of a basal/bolus insulin regimen involving multiple daily injections or with inhaled insulin.

A Common Mistake:

As long-acting insulin comprises about 50% of the total daily insulin needs, **there is almost never a reason that long-acting insulin doses should be held or not administered.**

- Dose reductions may need to be considered prior to planned major surgical procedures.

A common mistake made by less experienced providers or patients is holding long-acting insulin if:

1. A patient is sick and has a significantly decreased appetite
2. The blood glucose is low around the time the long-acting insulin is usually given.

Patients who are ill produce stress hormones and have increased sympathetic tone. This, more often than not, leads to hyperglycemia and an increased risk of ketosis. By not giving the long-acting insulin, the relative insulin deficiency makes

hyperglycemia worse and can make the patient enter into DKA.

Acute hypoglycemia is usually due to an error in the dosing of the rapid-acting insulin or recent exercise. Patients should treat their hypoglycemia and then take their long-acting insulin if it is due. A decrease in the long-acting insulin dose may need to be considered if a patient is struggling with recurrent hypoglycemia throughout the day, however, even then, the dose should never be held entirely.

Potential for Error:

In the outpatient setting, there are many other types of long-acting insulin that patients may be using.

It is important to recognize when patients are on these other types of long-acting insulin, as:

1. **Different concentrations of long-acting insulins exist**
2. **Conversion to Lantus may not be a "one to one" conversion**

    - Biosimilar/analogs of Lantus including Basaglar and Semglee are a 1:1 conversion.
    - Examples of Long-acting insulins that are not always a 1:1 conversion include:

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the text. You can view it online here: https://pressbooks.uiowa.edu/pedsendocrinology/?p=229#h5p-17

Quiz Yourself:

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Bibliography:

1. Hirsch IB, Juneja R, Beals JM, Antalis CJ, Wright EE. The Evolution of Insulin and How it Informs Therapy and Treatment Choices. Endocr Rev. 2020 Oct 1;41(5):733–55.

doi: 10.1210/endrev/bnaa015. PMID: 32396624; PMCID: PMC7366348.

PART III

UNIT 3: CREATING AND DISCUSSING INSULIN REGIMENS

Learning Objectives

1. Given the equations needed to calculate an initial insulin regimen for a patient with new-onset diabetes mellitus, trainees will generate an initial basal-bolus insulin regimen.
2. Given the definitions of the terms “hyperglycemia correction”, “carbohydrate coverage”, and “ketone correction”, trainees will utilize these terms correctly when discussing rapid-acting insulin administration
3. Provided the concepts of insulin sensitivity factor (ISF), sliding scale, and insulin to carbohydrate ratios (I:C), trainees will demonstrate the correct application of these concepts when discussing rapid-acting insulin administration.

Calculating Total Daily Dose

For every patient admitted with new-onset diabetes mellitus, regardless of whether they present with DKA, they will eventually need to be started on an initial basal/bolus insulin regimen consisting of multiple daily injections (MDI therapy).

Figure 1 summarizes the basic steps needed to calculate such a regimen.

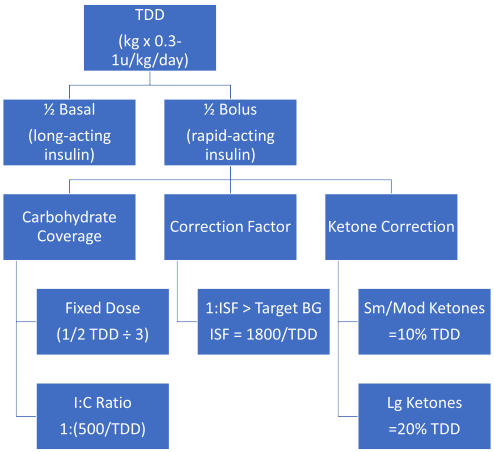

Figure 1 – Algorithm used for calculation of an initial basal/bolus insulin regimen

The remainder of this unit discusses the details and considerations that go into each of these calculations so that the regimen can be further optimized for the individual patient. Overall, the initial regimen is an "educated guess" with the goal of preventing excessive hypoglycemia and hyperglycemia.

Further adjustments are made to the individual components of the insulin regimen (e.g. the insulin-to-carbohydrate ratios, hyperglycemia correction, etc.) based on the evaluation of daily glucose trends in the outpatient setting. Hence, a new insulin regimen does not need to be "re-calculated" for patients with known diabetes who already have an established insulin regimen. Adjustments to the insulin regimen are discussed further in Unit 5.

Calculating Total Daily Dose for New-Onset Diabetes:

The first step in calculating the insulin regimen is determining how to calculate the **total daily dose** (TDD). TDD represents the total amount of daily insulin (basal and bolus insulin) needed by an individual during a 24-hour period.

This initial calculation is an educated guess guided by various factors used to estimate how "insulin sensitive" a patient will be. These factors include:

- Patient age
- Weight
- Stage of puberty
- The severity of the patient's initial presentation

In general, a young, non-obese, pre-pubertal child will be more insulin sensitive than an older, obese, pubertal child.

For children, **initial TDD is calculated based on a range of 0.5 units/kg/day to 1 unit/kg/day.**

Each endocrinologist may arrive at a slightly different initial TDD for each patient; however, the following algorithm in *Figure 2* can help guide your decision about where to start on this TDD spectrum:

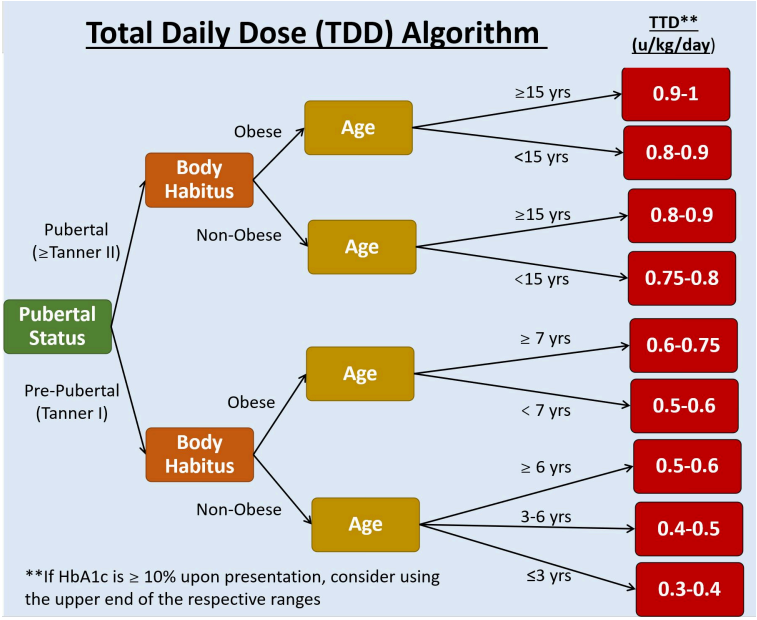

Figure 2 – Proposed algorithm to guide decision about what TDD to use based on multiple factors influencing insulin sensitivity.

Some physicians will also consider the severity of the patient's diabetes presentation. For example, a patient who does not present in DKA and has a lower HbA1c (<9-10%) is likely more insulin sensitive when compared to a patient who presents in DKA or has a more elevated HbA1c. This is because the later patient is likely to have more significant glucotoxicity causing their remaining functional beta-cells to be "stunned" and unable to produce endogenous insulin.

This glucotoxicity resolves when glucose levels are maintained in a more normal range, and the remaining functional beta-cells "wake up" and start reproducing endogenous insulin. This leads to a period of time, called "**the honeymoon period**" during which patients rely on less exogenous insulin to maintain normal blood glucose *(Figure* 3).

As the autoimmune process in Type 1 diabetes continues, this remaining functional beta-cell mass eventually succumbs to autoimmune destruction and the patient's insulin requirements increase. The honeymoon period is variable and unpredictable from one patient to the next, and may last weeks, months, or even up to a few years.

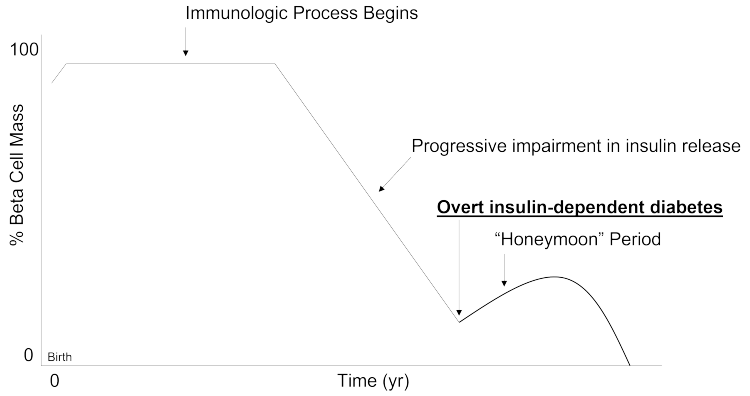

Figure 3 – The proposed natural history of beta-cell dysfunction in Type 1 diabetes. Note the honeymoon period occurs after diagnosis with the overt onset of diabetes requiring exogenous insulin administration. Improvement of initial glucotoxicity leads to a transient period of mild to moderate improvement in beta-cell mass function. This period eventually ends due to the continued autoimmune process.

Once you have determined where your patient falls on the TDD spectrum, use your selected total daily dose and multiply by the patient's weight to determine the total number of units of insulin the patient needs in a 24-hour period.

Examples: Calculating TDD for new-onset T1DM MDI Basal/Bolus Insulin Regimen

1. A 6-year-old, non-obese (17kg), prepubertal male presents in moderate DKA with an initial HbA1c of 11%.
    - If we use the algorithm in *Figure 2* we find TDD range should be 0.5-0.6 u/kg/day
    - As he is presenting in DKA and has HbA1c >10%, we will assume he is a bit more insulin resistant, so we will use the upper end of this range, thus TDD of 0.6 u/kg/day
        - TDD * weight (in kg) = total units of insulin per day
        - 0.6 u/kg/day * 17 kg **= 10.2 units/day**
2. A 14-year-old, non-obese (59 kg), pubertal female presents with hyperglycemia, HbA1c 9%, and has suspected T1DM based on second-tier laboratory testing.
    - Using *Figure 2*, TDD range is 0.75-0.8 u/kg/day
    - The patient is not presenting with DKA and does not have a very elevated HbA1c, so the lower end of this range is used.

- TDD * weight (in kg) = total units of insulin per day
- 0.75 u/kg/day * 59kg = **44.3 units/day**

Calculating TDD for Patients with Known Diabetes:

It is also important to know how to determine an average TDD for patients with known DM who are already on insulin, as this is often used to determine how much rapid-acting insulin is needed for the ketone corrections.

In these cases, TDD is determined by adding up all of the rapid-acting insulin from mealtime doses and the long-acting insulin doses taken over an average 24-hour period.

Example: Calculating TDD for known T1D on MDI Therapy

1. Ask the patient to review, on average, the doses they take for a standard breakfast, lunch, and dinner. Add these together and include the long-acting insulin dose.

Breakfast dose: 8 units

Lunch dose: 5 units

Dinner dose: 7 units

Long-acting dose: 20 units

Total daily dose: 40 units

2. Alternatively, if you know the I:C ratios for meals and know approximately how many carbs they eat per meal, you can estimate TDD by calculating their meals doses and then adding the long-acting insulin dose.

Breakfast: I:C is 1:10, usually eating ~50g CHO = 5 units

Lunch: I:C is 1:15, usually eating 45g CHO = 3 units

Dinner: I:C is 1:8, usually eating 60g CHO = 7.5 units

Long-acting dose: 25 units

Total Daily Dose: 40.5 units

Average TDD is easy to find for patients who are on insulin pumps, as the pumps keep track of delivered insulin and will report an average TDD over the last 7 days (you can ask patients to find this in their pump settings).

Example: Finding TDD for known T1D on an Insulin Pump

The patient or family should be able to find this information on their own, however, if they cannot, you can use the following instructions to help them find this within their pump.

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Quiz Yourself:

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Recommended Additional Reading:

More comprehensive information about insulin treatment in Type 1 diabetes can be found at:

Cengiz E, Danne T, Ahmad T, Ayyavoo A, Beran D, Ehtisham S, Fairchild J, Jarosz-Chobot P, Ng SM, Paterson M, Codner E. ISPAD Clinical Practice Consensus Guidelines 2022: Insulin treatment in children and adolescents with diabetes. Pediatr Diabetes. 2022 Dec;23(8):1277-1296. doi: 10.1111/pedi.13442. PMID: 36537533.

Calculating Basal and Bolus Insulin Needs

Calculating Basal Insulin Needs:

- For children >3 years of age, basal insulin needs are 50% of the TDD.
- Children <3 years of age are generally very insulin sensitive and often require more bolus than basal insulin. Therefore, discuss using 20-40% of the TDD for the initial basal insulin dose.

Example: Calculating Basal Insulin Dose

1. For the 6-year-old from our previous example with a TDD of 10.2 units/day
    - Basal insulin = 0.5 x TDD
    - Basal insulin = 0.5 x 10.2 units/day
    - Basal insulin = 5.1 units/day
        - Round to the nearest 0.5 units (if using vial/syringe) **OR** the nearest

whole unit (if using insulin pens)

- Thus, this patient needs **5 units of long-acting insulin**

2. For the 14-year-old from our previous example with a TDD of 44.3 units/day
    - Basal insulin = 0.5 x TDD
    - Basal insulin = 0.5 x 44.3 units/day
    - Basal insulin = 22.2 units/day
        - After rounding (per the above example), this patient needs **22 units of long-acting insulin**

Calculating Bolus Insulin Needs:

For children > 3 years old, 50% of the patient's total daily insulin needs come from basal insulin; the other 50% comes from bolus insulin. This bolus insulin is usually divided across three meals per day (breakfast, lunch, and dinner) and thus represents the initial insulin needed for **carbohydrate coverage**.

Keep in mind that families are educated on one of two methods for carbohydrate coverage:

1. Constant Carb Diet
2. Insulin to Carbohydrate Ratios

Each method has its advantages and disadvantages and is discussed in further detail below.

Constant Carb Diet:

This method involves giving a fixed dose of insulin for a fixed amount of carbohydrates per meal.

Each patient with new-onset diabetes will meet with a dietician; however, the chart in *Figure 4* is a good place to start when estimating the number of carbohydrates per meal based on a patient's sex, age, and weight.

Boys

Age	Avg Wt	Carbs/Meal	Carbs/Snack
1-3	13 kg	35-40 gm	10 gm AM, PM, HS
4-6	18 kg	40-45 gm	10 gm AM, PM, HS
7-10	27 kg	50-55 gm	10-15 gm PM, HS
11-14	43 kg	65-70 gm	10-15 gm PM, HS
15-18	63 kg	85-90 gm	10-15 gm PM, HS

Girls

Age	Avg Wt	Carbs/Meal	Carbs/Snack
1-3	13 kg	35-40 gm	10 gm AM, PM, HS
4-6	17 kg	40-45 gm	10 gm AM, PM, HS
7-10	26 kg	50-55 gm	10-15 gm PM, HS
11-14	44 kg	55-60 gm	10-15 gm PM, HS
15-18	57 kg	65-70 gm	10-15 gm PM, HS

Figure 4 – This chart can estimate the number of carbs per meal needed for a child using a constant-carb meal plan based on age, sex, and weight.

The amount of insulin per meal is determined by splitting 50% of the TDD among (typically) three meals per day. Children who are bolus or G-tube dependent may need additional boluses or use of different types of insulin.

Example A: Calculating Units of Insulin Needed per Meal for a Constant Carb Meal Plan

1. Using the 17kg, 6-year-old, male patient from our prior example with a TDD of 10.2 units/day:
    - 50% of the TDD/ 3 meals per day = units of insulin per meal
    - (10.2 u/day x 0.5)/ 3 = 1.7 units per meal
    - *Round to the nearest half-unit*, as this is the most accurate dose that can be delivered by an insulin syringe or an insulin pen. Thus, = 1.5 units per meal
    - Using the chart in *Figure 2* we find that our patient would need **1.5 units of insulin per meal consisting of a target of 40-45g of carbohydrate (CHO) per meal.**
2. Using the 59kg, 14-year-old, female patient from our prior example with a TDD of 44.3 units/day:
    - 50% of the TDD/3 meals per day = units of insulin per meal
    - (44.3 u/day x 0.5)/3 = 7.4 units per meal
    - Rounds to 7.5 units per meal (per rounding rules above)
    - Using the chart in *Figure 2,* our patient would need **7.5 units of insulin per meal**

consisting of a target of 60-65g CHO per meal

The constant carb diet method is advantageous for families that may have difficulty with the calculations needed for the insulin to carbohydrate method.

The disadvantage of this method of carbohydrate coverage is its inflexibility, as patients must eat around the same number of carbs for all meals of the day. Too many or too few carbs for this dose could lead to hyper- or hypoglycemia respectively.

Insulin to Carbohydrate Ratio (I:C) Method:

The insulin to carbohydrate ratio method involves a mathematical calculation to determine the amount of rapid-acting insulin needed for coverage of the anticipated carbohydrates to be eaten at a given meal.

I:C ratio of 1:10 means 1 unit of rapid-acting insulin will theoretically cover 10 grams (g) carbohydrates (CHO).

Example B: Using I:C ratio to determine the amount of rapid-acting insulin for a meal

1. A patient uses an I:C of 1:25 for Breakfast and anticipates they will be eating a bowl of cereal with milk at breakfast consisting of a total of 42g of carbs (12g from 8oz of milk and 30g from 1/2 cup of cereal). How much rapid-acting insulin is needed for carbohydrate coverage for this patient's breakfast?
    - 42 grams of carbs for breakfast using a 1:25 ratio
    - Units of insulin for carb coverage =42g /25g per 1 unit of insulin
    - = 1.7 units of rapid-acting insulin needed to cover 42 g of carbs for breakfast
    - Round to nearest 1/2 unit increment **= 1.5 units**
2. A patient uses an I:C of 1:5 for Dinner and anticipates they will be eating a total of 62g of carbohydrate at dinner. How much insulin is needed for carbohydrate coverage for this patient's dinner?
    - 62 g of cab for dinner using a 1:5 ratio
    - Units of insulin for carb coverage = 62g /

5g per 1 unit of insulin

- =12.4 units of rapid-acting insulin needed to cover 62g of carbs for dinner
- Round to nearest 1/2 unit increment = **12.5 units**

Note: I:C ratios are inversely proportional to their strength. In other words, a smaller ratio (e.g. 1:5) is stronger (i.e. provides more insulin per carb) than a larger ratio (e.g. 1:25, which provides less insulin per carb). This is important when adjusting the insulin to carbohydrate ratios for patients as discussed further in Unit 5.

I:C ratios can also give you an idea of how "insulin sensitive" patients are, as patients who require smaller ratios are generally more insulin resistant (requiring more insulin) than patients who use larger ratios.

The I:C ratio method is advantageous over the constant carb diet method, as it allows for increased flexibility for patients who may have a varied diet and eat varying amounts of carbohydrates with meals throughout the day.

The insulin to carbohydrate ratio itself can be determined in two ways:

1. **The "500-rule"**

Example C: Calculating I:C Ratio using the "500-Rule"

1. For our 6-year-old in our prior example with TDD of 10.2 u/day, we want to calculate his I:C ratio using the 500-rule and find out how much insulin he needs for his Lunch consisting of an anticipated 35g of carbohydrates.
    - Take 500 divided by the TDD
    - 500/TDD = 1 unit of insulin for "X" grams (g) of carbohydrates (CHO)
    - 500/10.2 = 49 –> means 1 unit of insulin theoretically covers 49g of carbohydrates = 1:49
        - Round to **1:50** (as this makes the math easier!)
    - To cover 35g of carbohydrates, the patient would need:
        - 35g / 50g per 1 unit of insulin
        - = **0.7 units of insulin.** As this cannot be delivered accurately by a standard syringe or insulin pen:
            - **Round down to 0.5 units** if the patient is going to be sedentary (e.g. most kids in the hospital

setting)

- **Round up to 1 unit** if the patient is going to be <u>active</u> and running around

2. For our 14-year-old in our prior example with TDD of 44.3 u/day, we want to calculate her I:C ratio using the 500-rule and find out how much insulin she needs for her Dinner consisting of an anticipated 73g of carbohydrates.

- 500/TDD = 1 unit of insulin for "X" g of CHO
- 500/44.3 = 11.3 –> means 1 unit of insulin theoretically covers ~11g of carbohydrates = **1:11**
- To cover 73 g of CHO for dinner, the patient would need:
  - 73g / 11g per 1 unit of insulin
  - = **6.6 units of insulin** –> Rounded to **6.5 units** which can be accurately delivered by insulin syringe or insulin pen

This method tends to be the most conservative calculation when determining the I:C for a patient with new-onset diabetes mellitus in that it usually leads to ratios that give <50% of the TDD as bolus insulin. This method is good to use in patients who are predicted to be very insulin sensitive.

2. Based on the constant carb calculation:

An I:C ratio can also be derived from the calculations used in the Constant Carb Method discussed above. However, this I:C ratio is generally stronger than the ratios derived from the

500-rule calculation. Therefore, I:C ratios using this method may increase the risk for iatrogenic hypoglycemia.

Neither method is incorrect, however, some faculty will prefer to use one method over the other. Others will calculate I:C ratios using both methods and use a ratio that "splits the difference".

Example D: Calculating the I:C ratio from the Constant Carb Method

1. Using our answer from Example B for our 6-year-old patient who we found needed 1.5 units of insulin per meal consisting of a target of 40-45g of carbohydrate (CHO) per meal on a Constant Carb Diet. What is this patient's equivalent I:C ratio?
    - As 1.5 units of rapid-acting insulin is used to cover 40-45g of CHO, we can see that:
        - 40g CHO/1.5 units = 26.7
        - 45g CHO/1.5 units = 30
        - So this patient's actual I:C ranges between 1 unit for every 25 g CHO (1:25) and 1 unit for every 30 g CHO (1:30).
            - Compared to our I:C ratio calculated using the 500-rule in Example C (1:50), we see that

these ratios derived from the Constant Carb Method are stronger.

- Thus, **a conservative approach would be to "split the difference" and use a ratio of 1:35 or 1:40**

2. Using our answer from Example B for our 14-year-old who we found needed 12.5 units of insulin per meal consisting of a target of 60-65 g of CHO per meal on a Constant Carb Diet. What is this patient's equivalent I:C ratio?

    - As 12.5 units of rapid-acting insulin is used to cover 60-65 g of CHO, we can see that:

        - 60 g CHO/12.5 units = 4.8
        - 65 g CHO/ 12.5 units = 5.2
        - So this patient's actual I:C is about 1 unit for every 5 grams of CHO (1:5)

            - Compared to our I:C ratio calculated using the 500-rule in Example C (1:11), a ratio of 1:5 is 2 x stronger!
            - Therefore, **a conservative approach would be to "split the difference" and use a ratio of 1:8 or 1:9**

Quiz Yourself:

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.uiowa.edu/pedsendocrinology/?p=258#h5p-38

Calculating Correction Factors and Ketone Corrections

The calculations completed for basal insulin needs and bolus insulin needs for carbohydrate coverage represent 100% of the total daily dose (TDD). Despite this, additional calculations are needed to determine how much rapid-acting insulin should be given for the correction of hyperglycemia (the **correction factor**) and the correction for the presence of ketones (**ketone correction**). These calculations for "correction insulin" are discussed below.

The Correction Factor:

More rapid-acting insulin is given in addition to the insulin needed for carbohydrate coverage when there is pre-prandial hyperglycemia in an effort to "correct" the post-prandial blood glucose (2-3 hours after injection) to within the normal target blood glucose range. The extra insulin needed for this correction of hyperglycemia is called the **correction factor**. The importance of this correction factor is demonstrated in *Figure 1.*

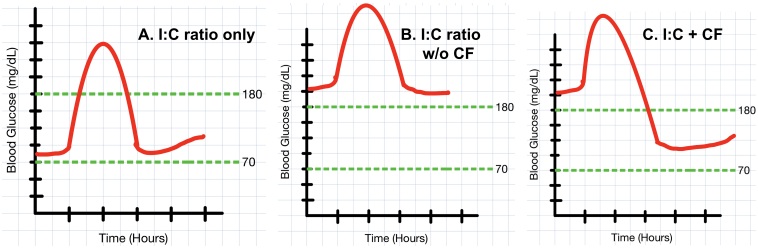


Figure 1- The effect of a correction factor (CF) on blood glucose. A. The return of post-prandial blood glucose (BG) within 2-3 hours to pre-prandial BG levels indicates an appropriate amount of carb coverage (I:C ratio) was provided. B. Pre-prandial hyperglycemia will persist even if appropriate carb coverage is provided. C. The additional CF insulin given in addition to the I:C ratio allows for post-prandial BG to return to the normal range (70-180mg/dL).

The first step in deriving a patient's correction factor is determining their **insulin sensitivity factor** (ISF). ISF is an estimate of insulin sensitivity and represents the theoretical total number of points that a patient's blood glucose is lowered after administering a single (1) unit of insulin. For example, an ISF of 50 means that 1 unit of insulin will lower a patient's blood glucose by 50 points (e.g. from 200mg/dL to 150mg/dL).

ISF is calculated using the "1800-rule":

Example: Calculating ISF from the 1800-Rule:

1. Using our 6-year-old patient from prior

examples with TDD of 10.2 u/day, what is the patient's ISF?

- ISF = 1800/TDD
- ISF = 1800/10.2
- **ISF = 176**
  - Thus, 1 unit of insulin will theoretically drop this patient's blood sugar by 176 points, and thus, 0.5 units of insulin will drop it by half of this (176/2) = ~90 points.

2. Using our 14-year-old patient from prior examples with TDD of 44.3 u/day, what is the patient's ISF?

- ISF = 1800/TDD
- ISF = 1800/44.3
- **ISF = 41**
  - Thus, 1 unit of insulin will theoretically drop this patient's blood sugar by 41 points.

Once the ISF is determined, this is combined with the desired blood glucose above which to start correcting for hyperglycemia so that blood glucose can return to a normal range. The resulting combination is the **correction factor**.

Correction Factor = 1 unit for every [ISF] over [target blood glucose]

As a general rule of thumb:

- ISF is generally rounded to the nearest 25 to 50-point

increment
- Target blood glucose is adjusted in increments of 50 (starting from 150)

The correction factor is then utilized to generate a **correction factor scale,** which allows for easy use and visualization of the additional amount of insulin needed to be added to carbohydrate coverage at meals.

Example: Defining the Correction Factor

1. From our prior examples, our 6-year-old was found to have an ISF of 176. What is his correction factor and corresponding correction factor scale?
    - 1 unit of insulin will drop his BG by 176 points (indicating he is very sensitive to insulin)
    - 0.5 units of insulin will drop his BG by ~90 points, which can be rounded to 100 (per our rule of thumb)
        - As the normal glycemic range is 70-150mg/dL, starting to correct BG > 150mg/dL with this patient's ISF would potentially cause hypoglycemia (as 151mg/dL – 100 = 51mg/dL). Therefore, this patient's target blood glucose should be set to 200, so that the

patient receives his first 0.5 unit correction when BG is 201 – 300.

- This way, if he is given 0.5 units at a BG of 201, his lowest predicted BG would be 101mg/dL

- Therefore his correction factor is: **0.5 units for every 100 over 200**
- His corresponding correction factor scale would be written as:

  - **201 – 300, give + 0.5 unit**
  - **301 – 400, give +1 unit**
  - **401 – 500, give +1.5 units**
  - **>500, call house officer**

2. From our prior examples, our 14-year-old was found to have an ISF of 41. What is her correction factor and corresponding correction factor scale?

   - 1 unit of insulin will drop BG by 41 points (indicating average to mild insulin resistance)

     - Can be rounded to 50 points (per our rule of thumb)

   - Correcting for BG starting > 150mg/dL would result in correction of most BG back into target range of 70-150mg/dL
   - Therefore, her correction factor is: **1 unit for every 50 > 150mg/dL**
   - Her corresponding correction factor scale is:

- **151 – 200, give + 1 unit**
- **201 – 250, give +2 units**
- **251 – 300, give +3 units**
- **301 – 350, give +4 units**
- **351 – 400, give +5 units**
- **401 – 450, give +6 units**
- **451 – 500, give +7 units**
- **>500, call house officer**

At other institutions, families may be taught a different method for hyperglycemia correction that allows for a more precise determination of the amount of insulin needed for hyperglycemia correction. However, this method requires higher math skills, which may be difficult for many families. This correction factor is calculated as follows:

Hyperglycemia correction dose (in units) = [Current BG – Target BG]/ISF

Additional information about the protocol for the management of hyperglycemia here at the University of Iowa Stead Family Children's Hospital is discussed further in Unit 4.

Ketone Corrections:

The last step in generating a basal/bolus insulin regimen is the calculation of the **ketone corrections**, which is needed if a patient develops ketonemia or ketonuria.

Management of ketones will vary from one institution to another. Here at the Stead Family Children's Hospital, a ketone correction consists of giving:

10% of TDD for small or moderate ketones

20% of TDD for large ketones

Example: Calculating Ketone Corrections

1. What would the ketone corrections be for our 6-year-old from our prior examples with TDD of 10.2 u/day?
    - For small to moderate ketones:
        - 10% of TDD
        - 0.1 x 10.2 u/day
        - **=1 unit for small/moderate ketone correction**
    - For large ketones:
        - 20% TDD
        - 0.2 x 10.2u/day (or 2 x the small/moderate ketone correction)
        - **=2 units for large ketone correction**
2. What would the ketone corrections be for our 14-year-old from our prior examples with a TDD of 44.3u/day?
    1. Small/Mod ketone correction = 10% TDD = 0.1 x 44.3 = 4.4 units -> rounded to nearst 1/2 unit **= 4.5 units**
    2. Large ketone correction = 20% TDD = 0.2 x 44.3 = 8.8 units -> round to **9 units**

Our institution's specific protocol for treating ketones is discussed further in Unit 4: "Ketone Management".

Quiz Yourself:

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.uiowa.edu/pedsendocrinology/?p=260#h5p-39

Consistency of Terminology

When patients are admitted to the hospital, we attempt to emulate the same management principles that we teach our patients and their families to do at home.

When possible, we try to use the same carbohydrate coverage method (e.g. I:C ratio vs. Constant Carb method), provide the appropriate hyperglycemia correction with their correction factor, and check for/provide ketone corrections as they would be instructed to do at home. Protocols related to this management are discussed further in Unit 4.

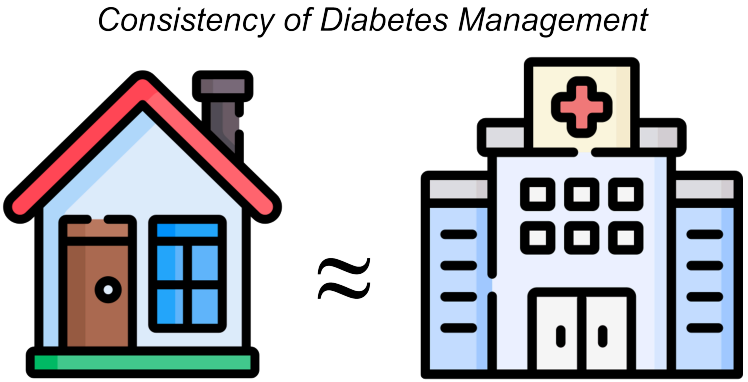
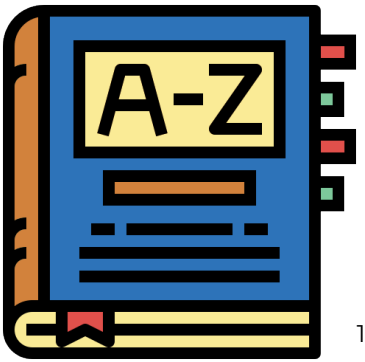


Figure 1

Consistency with how we manage diabetes in the hospital setting and at home is just as important as using the correct terminology when discussing insulin regimens between providers and families. This helps to eliminate confusion about

an already complex medical condition that may occur when incorrect terms are used.



When discussing insulin regimens (i.e. during rounds), it is particularly important to clarify what rapid-acting insulin was given for, as the same insulin is utilized to accomplish up to three different tasks:

1. Carbohydrate coverage
2. Hyperglycemia correction
3. Ketone corrections

When discussing the total amount of pre-prandial rapid-acting insulin, one should specifically state:
"'W' units of insulin were given for 'X' grams of carbohydrate coverage and an additional 'Y' units of insulin were given for hyperglycemia correction for a total of 'Z' units of pre-prandial rapid-acting insulin."

A common mistake is to misuse the word "correction" when talking about rapid-acting insulin for carbohydrate coverage.

It would be incorrect to say, "8 units of correction was given at Breakfast", as this statement implies that the entire 8 units of rapid-acting insulin was given for correction of hyperglycemia and that no insulin was provided for carbohydrate coverage at breakfast.

It would be correct to say "6 units of insulin was given for 40 grams of carbohydrate coverage and an additional 2 units of insulin given for hyperglycemia correction for a total of 8 units of insulin given before breakfast."

Lastly, it is important to remember the difference between hyperglycemia corrections and ketone corrections. Both

involve the use of rapid-acting insulin. **Neither of them should ever be given at the same time** (as discussed in Unit 4).

Bibliography:

Figures:

All images in this Chapter are from Flaticon.com; Figure 1, “Consistency of Diabetes Management” was generated by Dr. Alex Tuttle using “home icons” by Freepik and “hospital icons” by Freepik. “English icons” was created by smalllikeart.

PART IV

UNIT 4: MANAGEMENT OF PEDIATRIC DIABETES ACCORDING TO STEAD FAMILY CHILDREN'S HOSPITAL PROTOCOLS

Learning Objectives

1. Given a summary of the University of Iowa's SFCH's pediatric diabetes protocol, trainees will demonstrate proper management of carbohydrate coverage, hypoglycemia, hyperglycemia, and ketosis
2. Given our SFCH pediatric diabetes protocols and the American Diabetes Association guidelines, trainees will be able to identify age-based glucose target goals for the following: normoglycemia, pre- and post-prandial glucose, hemoglobin A1c, hyperglycemia, and

hypoglycemia.

3. Using the SFCH's pediatric diabetes protocols, trainees will be able to:
    1. Recall the correct monitoring of blood glucoses during inpatient admissions
    2. Recite the correct timing of routine administration of insulin
4. Given three treatment options for the management of hypoglycemia, trainees will be able to identify the two best options for the emergency treatment of hypoglycemia in the inpatient setting
5. Given a ketosis simulator, trainees will be able to demonstrate their ability to manage ketones using a computer-simulated patient and insulin dosing options
6. Given example scenarios, trainees will demonstrate:
    1. Application of correct glucose monitoring when insulin is given at non-protocolized times according to the University of Iowa SFCH's pediatric diabetes protocol.
    2. Recognize when deviation from protocol is necessary to maintain glycemic control and/or patient safety

The Pediatric Diabetes Protocol at Stead Family Children's Hospital

The various rules and established target blood glucose target ranges lend themselves well to the protocolization of diabetes mellitus management in the inpatient setting.

The University of Iowa Stead Family Children's Hospital has established nursing policies for the inpatient management of pediatric diabetes mellitus. These policies are based upon the Division of Pediatric Endocrinology's agreed-upon set of rules that are used at this institution. **Such policies may be slightly different at other institutions, so it is important to take the time to familiarize yourself with our institution-specific protocols.**

The diabetes-specific nursing protocols at UIHC can be found on the UIHC Policy Resources website (https://thepoint.healthcare.uiowa.edu/sites/UIHCPolicyResources) and searched for under the "Policy Tech" link. These include:

- Bedside Blood Glucose Monitoring in the Acute Care Units – DN.P.CWS.03.050
- Glucagon – DN.P.CWS.10.130
- Hypoglycemia Treatment in Patients with Diabetes – DN.P.CSW.13.030
- Insulin Administration – DN.P.CSW.10.200

While nursing protocols are in place for routine pediatric

diabetes mellitus management, **there are times when non-protocolized blood glucose checks or insulin administration is necessary.** This is especially true for ill or unstable patients with diabetes who are at increased risk for more unpredictable changes in their glycemic control.

General Tips For Success:

1. **Maintain close communication with your bedside nurse for the entirety of the patient's inpatient course.**
    - You may consider asking the nurse to tell you each blood sugar at the time it is obtained
        - This keeps you up-to-date in real-time about what your patient's blood sugar is doing even when you may be busy doing other things or away from the computer without easy access to these numbers
        - It allows you to quickly react to hypoglycemia or severe hyperglycemia
        - You easily ask questions to the nurse about preceding events leading up to an unexpected blood glucose value.
            - For any blood sugar that is not

in the target range, ask yourself, "What caused this blood sugar to be out of range? Is there a pattern that is recurring where a specific change in the insulin regimen should be made?"

2. **Determine what should be done for each blood sugar that is obtained.**
    - Repeat the blood sugar? Do Nothing? Give carb coverage? Give Correction?
        - If insulin is needed, calculate how much insulin should be given and double-check this with the nurse
        - Does a correction dose of insulin need to be given for hyperglycemia at a non-protocolized time?
        - Is the patient eating a 2nd dinner and therefore needs extra Carb coverage?
3. **Always confirm when the next blood sugar check should take place.**
    - Is it per protocol or does it need to be a non-protocolized blood glucose check?

Blood Glucose Monitoring

Routine glucose monitoring:

Routine blood glucose monitoring with a bedside point-of-care (POC) glucometer is needed for all patients admitted to the hospital with insulin-dependent diabetes mellitus (e.g. T1DM, T2DM, CF-related DM, etc.).

Routine blood glucose monitoring is performed 9 times per day at the following "protocolized" times:

1. Within 15-30 minutes before meals (3 x per day)
    - These are ***preprandial blood sugars***
2. Two hours after each meal (3 x per day)
    - These are ***postprandial blood sugars***
3. "Bedtime" (~2100)
4. Midnight (0000)
5. 3 AM (0300)

The timing of routine blood glucose monitoring and insulin administration within the hospital is demonstrated in *Figure 1*.

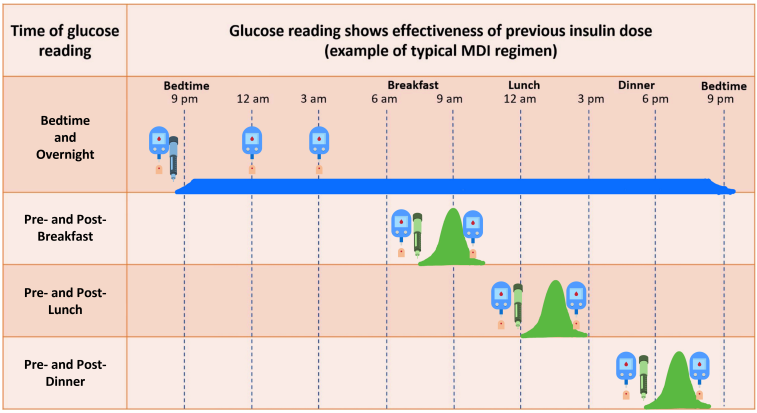


Figure 1 – Routine blood glucose monitoring occurs a minimum of 9 times per day in the hospital. A basal/bolus insulin regimen with MDI therapy is depicted in which long-acting insulin (blue) has action overnight. Rapid-acting insulin (green) has action in the 2-4 hours after injection and affects the pre-prandial blood sugars of the next meal.

Inpatient blood glucose monitoring for patients with non-insulin-dependent Type 2 diabetes usually includes:

1. Fasting AM blood glucose prior to breakfast
2. A 2-hour postprandial blood glucose after lunch or dinner

A Note on CGMs:

- **CGMs are not currently FDA approved for**

inpatient use as the accuracy of these devices may be drastically impacted by acute illness (patients are in a state of disequilibrium) and various medications.

- If a patient is allowed to continue wearing their CGM:
  - POC blood glucose must also be obtained and logged by nursing during their admission as CGM readings may not be reliable.
  - Additional POC blood glucose checks are needed to confirm alarms/ alerts by the device.

- CGMs must be removed prior to MRIs and prior to x-ray radiation (CT or X-rays)

Blood Glucose Monitoring in Special Circumstances:

The frequency of bedside blood glucose monitoring by POC blood glucose checks changes under the following conditions:

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https://pressbooks.uiowa.edu/pedsendocrinology/?p=313#h5p-19

Plasma glucose	BAG A *NS + lytes **or** ½NS +lytes* *Given as ratio*	BAG B *D10 NS +lytes **or** D10 ½NS +lytes* *Given as ratio*	Final dextrose concentration
> 250	1	0	0%
200-249	1	1	5%
150-199	1	3	7.5%
100-149	0	1	10%

< 100 mg/dl – Call the endocrinologist on call

Table 1 – Two-bag system titration chart. The ratio of the two-bag system used for patients on an insulin drip is titrated based on hourly blood glucose to maintain blood glucose in a range of 100-250 mg/dL.

Additional blood glucose checks may be needed **outside of the routine checks** that were discussed above.

Keep the following rules of thumb in mind and you will never go wrong:

Blood Glucose Checks at "Non-protocolized" times:

1. **When in doubt, check a blood sugar**
    - It is always safer to check blood sugar more often (or sooner than the next scheduled check) if you have clinical doubts or concerns about a patient
2. **Before ANY rapid-acting insulin**

administration

- This includes any non-protocolized insulin administration
- It is always safer to determine where the blood sugar is starting from as it may help guide how much insulin is to be given and the timing of the follow-up blood glucose check

3. **2-3 Hours AFTER any rapid-acting insulin administration**

   - This includes insulin delivered at non-protocolized times or insulin given for ketone corrections
   - Why?

     - Rapid-acting insulin's peak action time is 1-2 hours and the duration of action is 3-4 hours after administration. Checking a blood sugar 2-3 hours after insulin administration allows you to see how the patient's blood sugar "responds" to the dose that was given and monitors for the development of hypoglycemia.

4. **For any symptoms of hypoglycemia or severe hyperglycemia or ketosis**

   - Hypoglycemia should be treated immediately if present
   - Hyperglycemia, if causing significant

symptoms should be addressed and the patient should check for the presence of ketones

Quiz Yourself:

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Blood Glucose Goals

Glycemic targets aimed at the prevention of long-term microvascular and macrovascular complications have been defined by multiple organizations (*Table 2*).

Goals	NICE	ISPAD	ADA
A1c	<6.5%	<7%	<7%
Premeal	70-126 mg/dL	70-130 mg/dL	90-130 mg/dL
Postmeal	90-162 mg/dL	90-180 mg/dL	
Prebed	70-126 mg/dL	80-140 mg/dL	90-150 mg/dL

Table 2 – Glycemic targets as defined by three different organizations. Adapted from ISPAD Clinical Practice Consensus Guidelines 2022: Glycemic control targets and glucose monitoring for children, adolescents, and young adults with diabetes by de Bock et al.

Here at Stead Family Children's Hospital, we use a combination of the ISPAD and ADA glycemic goals. Goals are individualized to the patient's condition and age.

Glycemic Goals at Stead Family Children's Hospital:

Age 6 and Older:

- Before meals: **70** – 150 mg/dL
- Bedtime and during the night: 90 – 150 mg/dL

Age 1 to 5:

- Before meals: **80** – 150 mg/dL
- Bedtime and during the night: 90 – 150mg/dL

We adjust insulin regimens with the goal of keeping the majority of blood glucose values in these goal ranges, but we know that keeping 100% of blood sugars in this range is not (yet) always achievable. Highs and lows happen, even for diabetics with tight glycemic control.

The increased use of continuous glucose monitors (CGMs) in the outpatient setting has recently led to a consensus that the aim is to keep greater than 70% of blood sugars within a target range of 70mg/dL to 180mg/dL.

Hemoglobin A1c (HbA1c) is the most commonly used blood test used to track compliance with insulin therapy and glycemic control over time.

- **Goal HbA1c in children < 18 years of age is <7%**
    - Less stringent goals (<7.5-8%) may be appropriate in children who cannot articulate symptoms of hypoglycemia, have hypoglycemia unawareness, have limited life expectancy, or where the harms of treatment are greater than the benefits.

HbA1c is formed due to non-enzymatic glycosylation of Hemoglobin A and higher proportions of glycated hemoglobin occur with higher concentrations of blood glucose.

Since the majority of hemoglobin is contained within red blood cells and red blood cells have an average lifespan of

120 days, **HbA1c is a representation of average blood glucose concentration over the preceding 2-3 months.**

Table 3 demonstrates the approximate conversion of A1c to average blood glucose.

A1c (%)	mg/dL
5	97 (76-120)
6	126 (100-152)
7	154 (123-185)
8	183 (147-217)
9	212 (170-249)
10	240 (193-282)
11	269 (217-314)
12	298 (240-347)

Table 3 – A1c to blood glucose conversion table where data in parentheses are the 95% CI. This data was derived from ADAG data of ~2,700 glucose measurements over 3 months per A1c measurement in 507 adults with T1, T2, or no diabetes. The correlation between A1c and average glucose was 0.92. Adapted from Nathan, Kuenen et al. (2008).

There are many conditions that may lead to falsely elevated or lowered HbA1c values due to changes in the typical erythrocyte lifespan (e.g. asplenia, splenomegaly, pregnancy, various causes of anemia), changes in glycosylation (e.g. Vitamin E ingestion, chronic alcohol consumption, blood transfusions), and assay interferences (e.g. Vitamin C ingestions). (*Radin, 2013*)

Alternative methods of glycemic control may be necessary such as fructosamine (which reflects blood glucose control over the preceding 2-3 weeks).

Quiz Yourself:

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References and Recommended Readings:

1. de Bock M, Codner E, Craig ME, Huynh T, Maahs DM, Mahmud FH, Marcovecchio L, DiMeglio LA. ISPAD Clinical Practice Consensus Guidelines 2022: Glycemic targets and glucose monitoring for children, adolescents, and young people with diabetes. Pediatr Diabetes. 2022 Dec;23(8):1270-1276. doi: 10.1111/pedi.13455. PMID: 36537523; PMCID: PMC10107615.
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3. Nathan, D. M., Kuenen, J., Borg, R., Zheng, H., Schoenfeld, D., & Heine, R. J. (2008). Translating the A1C assay into estimated average glucose values. *Diabetes Care, 31*(8), 1473-1478. doi:10.2337/dc08-0545

Insulin Administration

The basics of insulin and types of insulin were discussed in Unit 2. In this chapter, we will focus on the routine administration of subcutaneous insulin by multiple daily injections (MDI therapy) in the inpatient setting.

A Note on Insulin Pumps:

Currently, **insulin pumps are not used for routine insulin administration in the inpatient setting**.

- Patients with known diabetes on CSII in the outpatient setting will likely need to be converted to a subcutaneous MDI regimen while admitted.
- In rare circumstances where patients are allowed to continue their insulin pumps, the patient/family will be in charge of their own insulin administration.
    - Hybrid-closed loop insulin pump systems may need to have automated insulin delivery discontinued temporarily (with backup basal rates updated as needed)

Basal Insulin Administration:

Basal insulin is usually administered once every 24 hours, most commonly around bedtime.

In children admitted with DKA, basal insulin is initiated and continued even while the patient is on an insulin drip.

For patients admitted with known diabetes, obtain the following information from the patient to ensure the correct type of long-acting insulin is given at the appropriate time:

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Rapid-Acting Insulin Administration:

Rapid-acting insulin in a basal/bolus regimen is used as **mealtime insulin** and **correction insulin**:

1. Carbohydrate coverage (**mealtime insulin**)
    - Mealtime insulin is given 15 minutes before breakfast, lunch, or dinner.

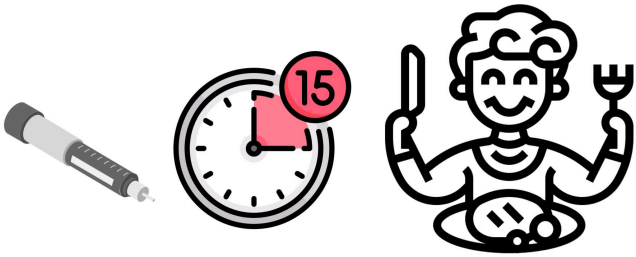

Figure 1 – Rapid-acting insulin is best dosed 15 minutes (or sometimes sooner) before a carbohydrate-containing meal.

- Additional mealtime insulin should be given for large snacks (>15g of carbs) or other meals that do not fall during routine mealtimes.
  - Children who are more insulin resistant may require carbohydrate coverage for snacks that are <15g of carbs (especially when their I:C ratios are less than 1:15)
- Mealtime insulin ≠ correction insulin, despite both being the same rapid-acting insulin. The principle of HOW rapid-acting insulin is being used makes the difference.
  - Terminology when discussing rapid-acting insulin administration is very important (as discussed in Unit 3: "Consistency of Terminology")
- **For unpredictable eaters:**
  - Discuss dosing mealtime insulin after eating with the on-call endocrine faculty or fellow.
  - In these cases, children should be:
    1. Encouraged to eat their carbohydrate-containing foods in the first 20-30 minutes

2. After 20-30 minutes, the rapid-acting insulin dose should be calculated/determined by the total amount of carbohydrates eaten from food during that 20-30 minutes time period.
3. After rapid-acting insulin administration, any remaining carb-containing food should be removed from the tray and the child can be allowed to eat the remaining "carb-free" foods on the tray.

2. Correction of hyperglycemia (**hyperglycemia correction**)

    - Blood glucose is always checked before mealtimes and will determine the need for additional rapid-acting insulin used for the "correction of" hyperglycemia or ketones (*if present*). This correction insulin is **<u>added to</u> the mealtime insulin dose**.

> *An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.uiowa.edu/pedsendocrinology/?p=317#h5p-22*

3. Correction of ketonuria/ketonemia (**ketone correction**)

Rules of Thumb for Correction Insulin:

Click on each of the following to read additional information!

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Figure 2 is a Decision Tree that can be used when deciding what to do with a blood sugar reading.

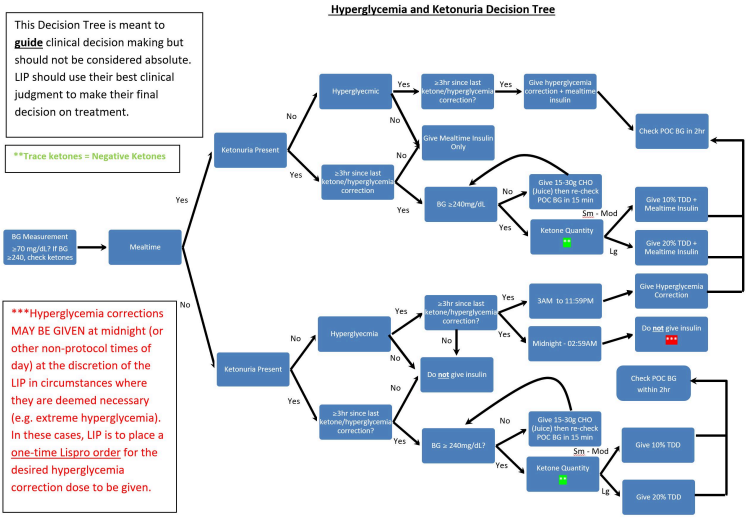

Figure 2 – Decision algorithm for managing hyperglycemia and ketones at the University of Iowa SFCH. Click the following link for a downloadable, larger version: Hyperglycemia and Ketone Management Decision Tree [Word Doc]

Remember, that 2-hour post-prandial blood sugars are for "information only" and are useful for guiding further insulin regimen adjustments.

Quiz Yourself:

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://pressbooks.uiowa.edu/pedsendocrinology/?p=317#h5p-42

Bibliography:

Figures:

1. Figure 1: Image Attribution: Created by Alex Tuttle by compilation of the following images from left to right: “Insulin icons” by vectorsmarket15, “15 minutes icon” by Freepik, and “Eat icons” by Eucalyp from Flaticon.com

Ketone Management

The presence of urine or blood ketones in a diabetic patient is an indication that there is significant insulin deficiency. Aggressive treatment of ketones with additional insulin is needed to prevent deterioration into diabetic ketoacidosis.

Ketones should be checked whenever blood glucose is >240mg/dL and whenever a patient is ill, <u>even if blood sugars are normal.</u>

How Are Ketones Checked?

Ketone monitoring in the inpatient setting is usually performed with:

1. Urine ketone dipstick (on Levels 9, 10, and 11 of SFCH)
2. Urinalysis (in ED or PICU)

Urine ketone dipsticks are used by patients at home (*Figure 1*).

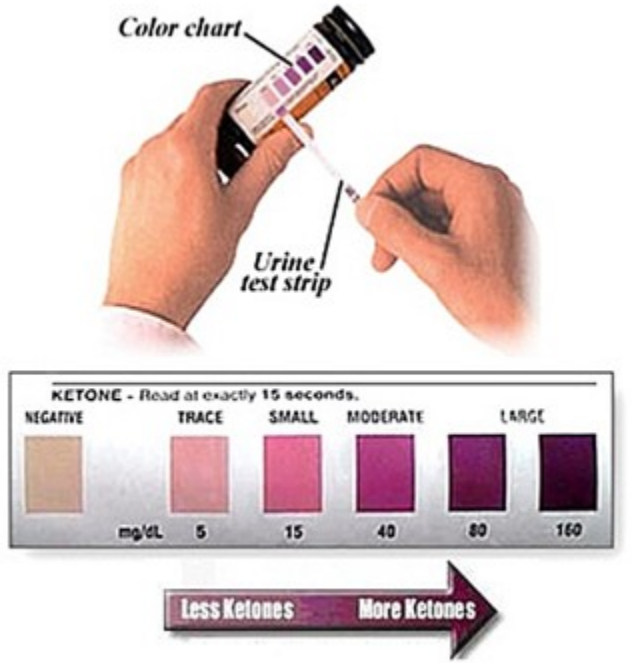

Figure 1 – After urine is applied to the ketone strip, it is compared against the color scale on the side of the bottle to determine the quantity of ketones (negative, trace, small, moderate, or large) present in the urine based on the colorimetric reaction. In the above example, the colorimetric reaction turns from a light shade of pink (trace) at the left, to progressively darker shades of purple when more ketones are present (large ketones being the darkest shades).

A urinalysis (UA) will report ketones as negative, +1, +2 and +3, corresponding to the negative, small, moderate, or large ketones, respectively. Alternatively, some labs report the quantity of ketones in mg/dL for which: <5 = trace to negative, 15 = small, 40 = moderate, >80 = large.

Urine ketone tests detect acetoacetate (rather than beta-hydroxybutyrate) and represent average urine ketone

concentration since the last void. Thus, these are not the perfect method for accurately tracking ketones, as urine ketones may lag behind the development of mild ketonemia leading to delays in initiation ketone management. Conversely, the lag may also falsely represent ketonemia that has since resolved.

In severely dehydrated patients with low urine output, relying on UAs or ketone strips can delay initiating much-needed ketone corrections.

Despite these pitfalls, urine ketone monitoring is significantly cheaper, painless, and requires little in the way of supplies or technical skills training. Therefore, it is the preferred method for home ketone monitoring and is emulated during inpatient admission.

Serum beta-hydroxybutyrate levels can be sent to evaluate for ketones in the blood and is a much more accurate method for real-time ketone quantification. These can be useful in the inpatient setting when patients are not routinely voiding, are severely dehydrated, or if urine ketone results seem discrepant from the patient's clinical status. In the outpatient setting, some patients will have blood ketone meters that can be used to check blood ketones at home. However, we do not use these home ketone meters in the inpatient setting.

How Are Ketones Managed?

Ketone correction boluses of rapid-acting insulin injections are given every 3 hours to shut down ketone production.

These are relatively large insulin doses, representing 10% to 20% of an individual's total daily insulin dose requirement (TDD). Therefore, it is important to ensure blood sugar is >240mg/dL before treatment to avoid subsequent

hypoglycemia. Usually, this is not a problem, as patients are generally more insulin resistant when ketones are present.

Because we rely on urine ketones monitoring, **if a patient cannot void by the next three hours, it should be assumed that ketones are present at the level previously tested and treated as such.**

USE THE KETONE/HYPERGLYCEMIA DECISION TREE TO HELP GUIDE MANAGEMENT from the Insulin Administration Chapter.

Inpatient Ketone Management Example:

Insulin Regimen: TDD: 20 units, I:C of 1:10 (all meals), Hyperglycemia correction (HC) of 1:50 > 150

BG time	Pre-Breakfast (0800)	0820	1000	1030	1100	Pre-Lunch (1230)
BG:	132	252	180		270	200
Ketone Lvl:	Large			Moderate		
Carbs:	15g (Juice)	60 g		15g (Juice)		70g
Rapid-acting insulin dose:		10 units (6 u CC + 4u KC)			2 u KC	7 units CC **only**

BG time	1430	1445	Pre-Dinner (1745)	1945	2100	0000	0300
BG:	100	210	170	90	102	130	283
Ketone Lvl:	Small		?	Trace		Trace	Negative
Carbs:	30g (2 x Juice)	15g (1x juice)	15g (juice) + 65g		15g bedtime snack		
Rapid-acting insulin dose:		2 u KC	8.5 units (6.5u CC + 2u KC)		None		3u HC

The above chart represents a clinical scenario of a patient who has Large ketones at breakfast and is treated to clear ketones throughout the day.

Prior to breakfast, as the blood glucose is <240mg/dL, 15g of rapid-acting carbs (juice) are given and blood glucose is checked 15-20 minutes later. Now the blood glucose is >240mg/dL and the patient is going to eat breakfast, so mealtime insulin (CC) and the additional ketone correction are given (10 units total of rapid-acting insulin).

The next blood glucose is a scheduled 2-hr post-prandial blood glucose. Another ketone check and correction is not due until 1100 (3 hours after initial

ketone correction). The patient urinates at 1030 and has moderate ketones. 15g of juice is provided at this time, as the previous blood glucose was down-trending and <240mg/dL. The blood glucose at 1100 shows BG is 270mg/dL, so 2 units of ketone correction are given for the treatment of moderate ketones.

The patient then prepares to eat lunch at 1230. As a ketone correction was given in the preceding 3 hours, additional correction insulin cannot be given, so only mealtime insulin for carbohydrate coverage is provided at this time.

You ask the nurse to encourage the patient to urinate at the 2-hour post-prandial glucose check which shows small ketones. Although he is due for another ketone correction, the juice must be given to boost blood glucose to >240mg/dL, so you give 30g of juice and find blood glucose improved 15 minutes later to 210mg/dL. As the blood glucose is not >240mg/dL, you ask the patient to drink another 15g of juice. At this point, you can assume the blood glucose will rise to >240mg/dL with this additional treatment and give the 2 units of ketone correction for treatment of small ketones to avoid further delays in treatment.

3 hours later the patient is ready for dinner, however, our patient won't urinate. At this point, you should assume the patient still has small urine ketones (unless you send a STAT serum Beta-hydroxybutyrate). Because you don't want to keep the patient from eating, you presumptively treat for small ketones with his meal. 15g of juice was given before eating the meal to provide "uncovered carbs" since blood glucose is not >240mg/dL.

The 2-hr post-prandial dinner glucose is 90mg/dL and your patient's ketones are now trace! You encourage your patient to drink water to promote continued clearance of ketones and ask for the patient to void around midnight to ensure ketones are remaining trace or negative.

Once ketones are trace or negative x 2 consecutive checks, additional ketone checks are only needed if blood glucose is >240mg/dL. In this case, the patient's BG check at 0300 is 283mg/dL, so you have him recheck ketones which are still negative, so instead, you give a hyperglycemia correction and ask the nurse to check a blood glucose 2 hours later at 0500 before his next routine blood glucose before breakfast.

Manage A Simulated Patient!

Click the following link (https://slimgec.github.io/ds1/) to access a diabetes ketosis simulator produced by Dr. Catherina Pinnaro.

This simulator will first give you a patient scenario and ask you to calculate an initial insulin regimen. It will then ask you to manage this patient's ketones and hyperglycemia until they have cleared. The simulator will provide feedback on your performance; the same scenario can be repeated as often as desired.

Preventing Ketosis In the Fasting or

NPO Patient:

Dr. Norris's article, "The Most Common Cognitive Error that Physicians Make When Treatment Patients with Type 1 Diabetes", (2020), expertly explains a common cognitive error in managing a patient with diabetes who is NPO. This error is withholding dextrose-containing fluids.

In this article, Dr. Norris uses an analogy to compare the metabolic processes that occur during the omission of the IV dextrose to cutting the fuel to the engine of the plane and the pilot letting go of the stick.

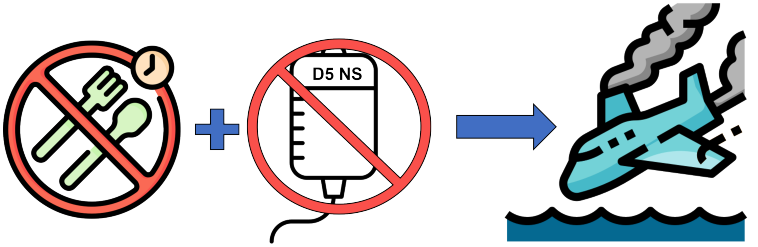

Figure 2 – Diabetic patients who are NPO without dextrose fluids may"crash and burn" into DKA due to insulin deficiency.

....it is poor practice to allow patients with diabetes to develop diabetic ketoacidosis while admitted! So take a moment to read the short article and discover why the provision of dextrose is necessary for our diabetes patients who are NPO!

Bibliography:

1. Pinnaro, C., Christensen, G. E., & Curtis, V. (2021). Modeling Ketogenesis for Use in Pediatric Diabetes Simulation. *Journal of Diabetes Science and Technology, 15*(2), 303-308. doi:10.1177/1932296819882058
2. Norris, A. (2022, February 3). *The most common cognitive error that physicians make when treating patients with type 1 diabetes*. News & Views From the Division Director: University of Iowa Stead Family Children's Hospital. https://pendia.peds.uiowa.edu/2020/06/type-1-diabetes-inpatient-management/

Figures:

3. Figure 2: Figure 2 was created by Dr. Alex Tuttle using a compilation of the following icons: "Crash icon" by pongsakornRed and "Fasting icons" by Freepik, both found at Flaticon.com

Hyperglycemia Management

Hyperglycemia is usually defined as any blood glucose >150mg/dL. However, the threshold at which hyperglycemia is treated varies based on the individual patient and their individualized glycemic targets.

For critically ill diabetic patients in the PICU, studies have found that tight glycemic control (80-110mg/dL) did not improve clinical outcomes but led to a greater incidence of hypoglycemia than more relaxed glycemic targets of 80 to 150-180mg/dL. (Zhao et al., 2018)(Agus et al., 2017)

Example: Individualized Treatment of Hyperglycemia

Julius, a 4-year-old with T1DM, has a correction factor of 0.5 units for every 50 > 200mg/dL.

Tara, a 16 year-old with T1DM, has a correction factor of 1 unit for every 25 > 150mg/dL.

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Symptoms of hyperglycemia were discussed in Unit 1.

Causes of Hyperglycemia:

- Eating carbohydrates AND excessive protein-rich "carb-free" foods
- Over-treatment of a low blood sugar
- Not taking enough insulin for carbohydrate coverage or hyperglycemia correction
- Not taking insulin 15-20 minutes before eating
- Forgetting to take insulin
- Sedentary activity
- Stress
- Illness or infections
- Injury or surgery
- Medications (such as steroids)

It is normal in diabetes to have post-prandial spikes of hyperglycemia. However, blood sugar should return to a

normal range within 2-3 hours after rapid-acting insulin administration if the patient gets the appropriate amount of carbohydrate coverage (and hyperglycemia correction if needed). A mismatch in the timing of insulin delivery can also lead to higher post-prandial meal spikes.

Consequences of Hyperglycemia:

Long-standing hyperglycemia leads to endothelial damage and destruction of the microvasculature and microvasculature of the cardiovascular system. Explore the following figure to learn more about the long-term consequences of diabetes and how we screen for these.

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https://pressbooks.uiowa.edu/pedsendocrinology/?p=321#h5p-24

Treatment of Hyperglycemia:

See the Rules of Thumb for Correction Insulin and the Management Algorithm for details regarding when to administer hyperglycemia correction vs. when to administer ketone correction.
In brief:

1. The correction factor is used to determine if insulin is needed for correction of hyperglycemia before protocolized times (mealtimes and 0300)
2. Hyperglycemia correction can be considered at non-protocolized times for severe hyperglycemia but should be discussed with the on-call pediatric endocrinology provider first.

    - If non-protocolized hyperglycemia correction is to be given, a one-time EPIC order needs to be placed.

3. Never give hyperglycemia correction within three (3) hours of another hyperglycemia correction **OR** ketone correction.
4. Always check for ketones when BG is >240mg/dL and, if present, correct ketones **BEFORE** considering correction of hyperglycemia.

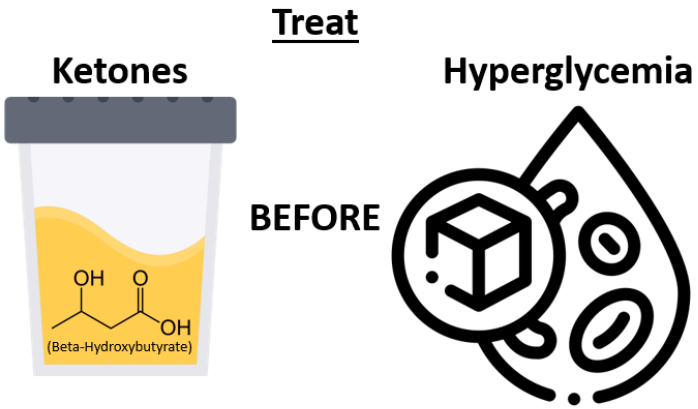

Figure 1 – Correction with rapid-acting insulin should be used to treat ketones if they are present until they are trace or negative. Once ketones are cleared, the focus can be turned back to the use of rapid-acting insulin to treat hyperglycemia.

Bibliography:

1. Zhao, Y., Wu, Y. & Xiang, B. Tight glycemic control in critically ill pediatric patients: a meta-analysis and systematic review of randomized controlled trials. *Pediatr Res* **83**, 930–935 (2018). https://doi.org/10.1038/pr.2017.310
2. Agus, M. S. D., Wypij, D., Hirshberg, E. L., Srinivasan, V., Faustino, E. V., Luckett, P. M., . . . Nadkarni, V. M. (2017). Tight Glycemic Control in Critically Ill Children. *New England Journal of Medicine, 376*(8), 729-741. doi:10.1056/NEJMoa1612348

Figures:

1. Figure 1: This figure was created by Dr. Tuttle using the following icons: “jar icons” by Nikita Golubev at Flaticon.com and “sugar blood diabetes” by Pike Picture from Noun Project (CC BY 3.0).

Hypoglycemia Management

Hypoglycemia is a fall in blood sugar level that exposes a patient to potential harm and there can be no single numerical definition of hypoglycemia for all patients and situations. In clinical practice, a glucose of 70-80mg/dL is used as the clinical alert or threshold value for initiating treatment for hypoglycemia (Abraham et al., 2018). This hypoglycemia treatment threshold is defined by age:

1. Children 1-5 years of age: <80 mg/dL
2. Children >6 years of age: <70 mg/dL

Causes of Hypoglycemia:

- Taking too much insulin (intentional or unintentional)
- Eating fewer carbohydrates than what was dosed for
- Heavy/intense or prolonged physical activity
- Drinking alcohol
- Gastrointestinal illness leading to vomiting and poor carbohydrate absorption
- Celiac disease and other malabsorptive gastrointestinal conditions
- Addison's disease or Hyperthyroidism/Grave's disease

Symptoms of Hypoglycemia:

Figure 1 – Common symptoms of hypoglycemia. Not all symptoms may be present at once. Image attribution: "Low Diabetes Cliparts #2653044" at clipart-library.com

The inability of a patient to recognize these symptoms is **hypoglycemia unawareness.** When this is persistent, it can significantly increase the risk of severe hypoglycemia. Impaired awareness may be corrected by avoidance of hypoglycemia.
When the brain demands more glucose than what is available from the blood (**neuroglycopenia**) neurological symptoms can occur and include:

- Syncope
- Seizures
- Coma
- Death

This may occur when serum blood glucose is <35mg/dL.

Treatment of Hypoglycemia:

If a patient exhibits symptoms of mild hypoglycemia, a blood sugar should be checked immediately to determine if treatment is necessary.
Treatment entails administering rapid-acting glucose to normalize blood sugar, ideally **without over-correction of blood sugar.** The goal is to increase blood glucose by only 55-70mg/dL.
To avoid over-correction:

1. Check a blood sugar 15-20 minutes after giving glucose
    - 15 minutes is about the time it takes ingested carbohydrates to affect systemic blood sugars.
        - Checking a blood sugar before 15 minutes is too soon as there has not been enough time for the ingested carbohydrates to take effect. This can lead to the erroneous administration of more carbohydrates and subsequent hyperglycemia.
2. If BG is still <90mg/dL after 15-20 minutes, then repeat treatment with the appropriate amount of carbohydrates (*Figure 2*).

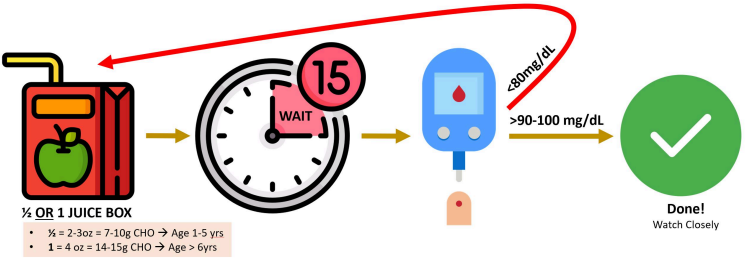

Figure 2 – Management of hypoglycemia involves rapidly normalizing blood sugar without over-correcting. A systematic approach for the treatment, waiting (15-20 minutes), and rechecking blood sugar is needed to avoid over-treatment of hypoglycemia.

Enteral Replacement for Mild Hypoglycemia:

- Accomplished by using a source of rapid-acting carbohydrates (e.g. juice, non-diet soda, glucose tabs, etc.).
- Only used for patients who are alert and **able to eat or drink by mouth safely**
- Approximately 0.3g/kg of carbohydrates is needed for treatment which is equivalent to:
    - 5-10g of rapid-acting carbohydrate for a child <30kg (Aged 1-5 years old)
        - 2-3 oz of juice or non-diet soda
        - 2-3 oz of applesauce
    - 10-15g of rapid-acting carbohydrate for a child >30kg (Age > 6 years old)
        - 3-4 oz juice or non-diet soda
        - 3-4 glucose tabs

IV Replacement or Glucagon for Moderate to Severe Hypoglycemia (Emergency Treatment):

- For children with severe hypoglycemia or those who are unable to take rapid-acting carbohydrates by mouth (e.g., extremely irritable, refuse, lethargic, unconscious, seizing, etc.), treatment of hypoglycemia requires either:

1. **IV Dextrose Bolus** (D10 via peripheral IV or D12.5-D50 via central access line)
    - D10 boluses:
        - 0.5g/kg (=2cc/kg) > 8 years old
        - 0.25g/kg (=1cc/kg) < 8 years old
    - D50 bolus:
        - 0.5g/kg (=1cc/kg) –> higher risk for rebound hyperglycemia
2. **Glucagon** – given IV or by IM injection (ideal if no IV

access)

- 1mg for patients >25 kg
- 0.5mg for patients <25 kg

Maintain IV access on all diabetes patients in the inpatient setting so that severe hypoglycemia, if it occurs, can be quickly addressed with an IV D10 bolus.

Glucagon is usually effective in treating severe hypoglycemia by releasing endogenous glucose from glycogen stores *(Figure* 3). However, it is reserved as a "last resort rescue medication" in the hospital setting when patients do not have IV access as it causes significant nausea and possible vomiting as a side effect.

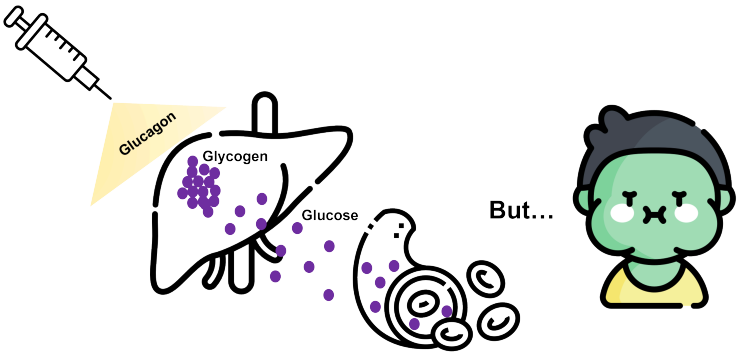

Figure 3 – Glucagon injected IV or Subcutaneously leads to the release of glycogen from the liver and an increase in blood glucose, but at standard rescue doses leads to nausea and potential vomiting

Bibliography:

1. Abraham MB, Jones TW, Naranjo D, Karges B, Oduwole A, Tauschmann M, Maahs DM. ISPAD Clinical Practice Consensus Guidelines 2018: Assessment and management of hypoglycemia in children and adolescents with diabetes. Pediatr Diabetes. 2018 Oct;19 Suppl 27:178-192. doi: 10.1111/pedi.12698. PMID: 29869358.

Figures:

1. Figure 2: This figure was created by Dr. Tuttle using the following icons: “Juice icons” by Smashicons, “15 minutes icon” by Freepik, “diabetes icons” by Freepik, and “Righ icons” by kliwir all found at Flaticon.com
2. Figure 3: This figure was created by Dr. Tuttle using the following icons: “Liver icons” by Freepik, “Blood vessel icons” by Freepik, “Injection icons” by Good Ware, and “Nausea icons” by Freepik all found at Flaticon.com