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International Society for Pediatric and Adolescent Diabetes Clinical Practice Consensus Guidelines 2024: Insulin and Adjunctive Treatments in Children and Adolescents with Diabetes

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Summary of What Is New or Different

- Updated insulin treatment sections including new bolus and basal insulin formulations.
- Updated recommendations on the principles of intensive insulin treatment regimens, including a more intensive form of multiple daily injections (MDIs) with new-generation faster-acting insulins and ultra-long-acting insulins, automated insulin delivery to achieve a high level of treatment personalization, better glycemia, and empowerment for people with diabetes.
- Review of the roles and rationales for new insulin analogs, biosimilars, and diabetes technology devices for insulin therapy in pediatric diabetology.
- Summary of adjunctive medications used alongside insulin treatment that includes details on pramlintide, metformin, glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RA), and sodium-glucose cotransporter (SGLT) inhibitors.
- Key considerations with regard to access to insulin and affordability specifically innovative, multi-faceted approaches involving governments, healthcare providers, pharmaceutical companies, and advocacy groups to ensure that all persons with diabetes who need insulin can obtain it without financial hardship.

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Abstract
The International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines represent a rich repository that serves as the only comprehensive set of clinical recommendations for children, adolescents, and young adults living with diabetes worldwide. This chapter builds on the 2022 ISPAD guidelines, and updates recommendations on the principles of intensive insulin regimens, including more intensive forms of multiple daily injections with new-generation faster-acting and ultra-long-acting insulins; a summary of adjunctive medications used alongside insulin treatment that includes details on pramlintide, metformin, glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RA) and sodium-glucose cotransporter inhibitors; and key considerations with regard to access to insulin and affordability to ensure that all persons with diabetes who need insulin can obtain it without financial hardship.

List of Abbreviations

AID:	automated insulin delivery
BG:	blood glucose
BGL:	blood glucose levels
BMI:	body mass index
CGM:	continuous glucose monitor
COVID:	coronavirus disease
CSII:	continuous subcutaneous insulin infusion
DCCT:	diabetes control and complications trial
DKA:	diabetes ketoacidosis
DPP-4:	dipeptidyl peptidase-4
EDIC:	Epidemiology of Diabetes Interventions and Complications study
EMA:	European Medical Agency
FDA:	Food and Drug Administration
GLP-1:	glucagon-like peptide-1
GLP-1RA:	GLP-1 receptor agonists
ICR:	insulin:carbohydrate ratio
IDF:	International Diabetes Federation
IM:	intramuscular
ISF:	insulin sensitivity factor
ISPAD:	International Society for Pediatric and Adolescent Diabetes
IT:	injection technique
IV:	intravenous
LH:	lipohypertrophy
kg:	kilogram
MDI:	multiple daily injection
mm:	millimeters
ml:	milliliters
mmol:	millimol
NPH:	neutral protamine Hagedorn
RAI:	rapid-acting insulins
SGLT-1:	sodium-glucose cotransporter-1
SGLT-2:	sodium-glucose cotransporter-2
SMBG:	self-monitoring of blood glucose
TIR:	time in range
T1D:	type 1 diabetes
T2D:	type 2 diabetes
U:	unit
URI:	ultra-rapid-acting insulins
URLi:	ultra-rapid-acting lispro
WHO:	World Health Organization

Introduction

Insulin remains the mainstay of therapy for millions of individuals with type 1 diabetes (T1D) since its discovery in 1921. Near normoglycemia is a well-established goal of T1D treatment based on the results of the landmark Diabetes Control and Complications Trial (DCCT). The DCCT and its follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, confirmed that an improvement in long-term glycemia by intensified insulin therapy and extensive support and education, can reduce the incidence of complications and delay the progression of existing complications in T1D, in adolescents and adults [1, 2].

Despite significant advances in insulin formulations and modes of delivery, insulin treatment in practice is remarkably complex, and optimal glycemia is often challenging to achieve and maintain. Insulin requirements of children and adolescents with T1D are dynamic given changes in growth, development, and hormonal milieu during childhood and adolescence, which necessitate frequent dose adjustments. Consequently, young people with T1D require customized, flexible, and engaging approaches to sustain optimal glycemia and tackle the multiple rigors of daily life.

Currently, exogenous insulin administration is used as a pragmatic, but imperfect, approach to attempt to emulate physiologic patterns of pancreatic β-cell insulin secretion. A healthy pancreatic β-cell secretes continuous basal (continuous, low level) insulin and incremental postprandial (high level) insulin with meals to manage blood glucose levels (BGLs) in a tight physiologic range [3]. Pediatric insulin treatment, fundamentally, attempts to replicate these

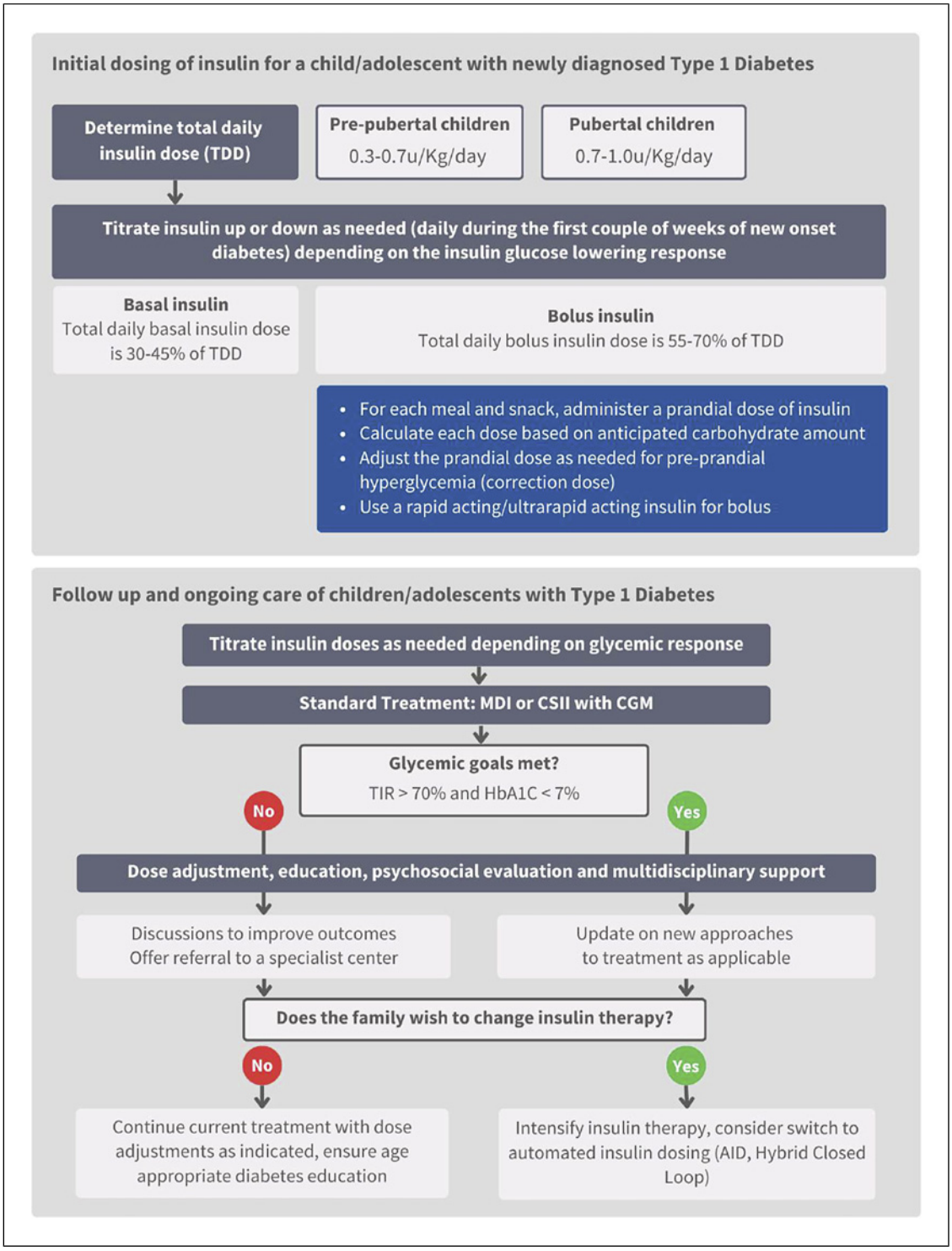

Fig. 1. Schematic representation of frequently used insulin therapy regimens in children with diabetes. RAI, rapid-acting insulin; CSII, continuous subcutaneous insulin infusion.

Table 1. Types of insulin preparations and action profiles (subcutaneous [SC] or inhaled administration)

Insulin (unit concentration)	Onset of action	Peak effect	Duration	Mechanism of acceleration/protraction
Mealtime insulin products				
Regular human insulin (U100)	30–60 min	2–4 h	5–8 h	Structurally identical to human insulin.
Insulin lispro* (U100)	15–30 min	1–2 h	≤5 h	The strength of self-association is decreased by the reversal of two amino acid residues in the B-chain terminus.
Insulin aspart* (U100)	15 min	1–3 h	3–5 h	The strength of self-association is decreased by substituting one amino acid in the B-chain terminus (aspart for proline at position B28).
Insulin glulisine (U100)	12–30 min	1.5 h	~5.3 h	The strength of self-association is decreased by substituting two amino acid residues in the B-chain.
Fastacting insulin aspart (U100)	5–20 min	~1.5–2.2 h	~5–7 h	Contains the excipients niacinamide and L-arginine to speed up the monomer formation and accelerate absorption of aspart insulin.
Fast-acting insulin lispro (U100)	~15–17 min	~2–3 h	~5–7 h	Contains citrate and treprostinil to accelerate SC absorption of lispro insulin.
Technosphere-inhaled insulin	–	53 min	2.5 h	Recombinant human insulin powder particles are adsorbed onto carrier Technosphere (FDKP) particles that carry the insulin into the alveoli where the particles dissolve and the insulin is quickly absorbed. The FDPK is not metabolized and is excreted in an inert form from the body.
Basal insulin products				
NPH insulin (U100)**	2–4 h	4–12 h	12–24 h	It is a crystalline suspension of insulin with protamine and zinc that play a role in the slow release of insulin from the precipitated NPH insulin crystals after SC injection.
Insulin glargine* (U100)	2–4 h	8–12 h No pronounced peak	~22–24 h	There is an amino acid substitution in the A-chain and two amino acid additions to the B-chain terminus causing an isoelectric precipitation after SC injection that slows insulin absorption.
Insulin detemir (U100)	1–2 h	4–7 h No pronounced peak	20–24 h	Removal of terminal B-chain amino acid and acylation with a 14-carbon fatty acid chain results in an insulin that reversibly binds albumin in the depot and circulation, retarding insulin absorption and action.
Insulin degludec (U100 and U200)	30–90 min	No pronounced peak	42 h	Removal of terminal B-chain amino acid and acylation with a 16-carbon fatty diacid results in an insulin that forms multihexamer chains in the depot and reversibly binds albumin in the circulation, retarding insulin absorption and action.
Insulin glargine (U300)	2–6 h	No pronounced peak	30–36 h	The absorption of the insulin glargine precipitate is further retarded given that it is formulated at a three-times-greater molar concentration than the original glargine (U100) formulation.

Older generation insulins that are currently not in use are not included in the table. All insulins used must be produced under "Good Manufacturing Practice/Good Laboratory Practice" conditions. Peak and duration of action of a specific insulin formulation is affectesd by the dose, i.e., large doses tend to last longer than small doses. References for the table: mealtime insulin: [5, 9–13]; basal Insulin [14–17]. *Biosimilar formulation approved in some countries. **Neutral protamine Hagedorn (NPH) insulin; isophane insulin.

patterns using a treatment approach known as basal-bolus insulin treatment (Fig .1, 2). Two methods of intensive basal-bolus insulin treatment are multiple daily insulin injections (MDIs) and continuous subcutaneous insulin infusion (CSII) by insulin pumps. These methods permit flexibility in the daily lives of persons living with diabetes by partially accommodating variable eating patterns. Furthermore, in randomized trials, better glycemia has been achieved by using intensive insulin treatment regimens, either by insulin injections or pump treatment, compared to insulin administered twice daily [1, 4].

In the past few decades, new insulin analogs and diabetes technology tools have transformed insulin treatment. Regular and neutral protamine Hagedorn (NPH)/ultralente insulins used during the DCCT have been replaced by newer generation insulin formulations in many countries. These rapid-acting and long-acting insulin analogs were developed to provide a more physiologic insulin profile and studies have documented improved glycemic management with the insulin analogs over regular insulin [5].

Severe hypoglycemia was an adverse effect of intensive therapy during the DCCT [1]. In contrast, recent large diabetes registry studies have clearly shown a diminishing relationship of significant or severe hypoglycemia with lower glycemic targets in people with T1D [6, 7]. Additionally, the deleterious effect of hyperglycemia on the developing brain has been concerning and highlights the importance of managing both hyperglycemia and hypoglycemia [8].

Insulin Formulations

- Insulin treatment should commence as soon as possible after T1D diagnosis (within 6 h if ketonuria is present) to prevent metabolic decompensation and diabetic ketoacidosis (DKA) [**A**].
- Intensive insulin regimens delivered by combinations of MDIs or pump therapy with substitution of basal and prandial insulin aiming to have optimal glycemia are the gold standard for the treatment of T1D in children across all age groups [**A**].
- Premix insulin regimen using NPH and regular soluble insulin should not be considered a best practice treatment for T1D [**E**].
- All young people should have rapid-acting or regular insulin available and a means to inject this insulin for prevention and management of diabetes, hyperglycemia, and ketosis emergencies [**E**].

Insulin formulations can be classified into two major groups as mealtime (prandial) insulins and basal insulins (Table 1). In general, mealtime insulins consist of regular, rapid-acting, and ultra-rapid insulins intended for bolus administration and/or infusions in pumps. Basal insulins are long-acting and ultra-long-acting insulins that are intended to be injected not more often than once or twice a day. Newer generation, investigational basal insulins may allow once a week basal insulin injections in the near future.

Mealtime Insulins

Mealtime insulin boluses attempt to mimic endogenous insulin secretion in response to ingested carbohydrate. A healthy β-cell secretes insulin at a low basal rate while fasting. In response to food intake, insulin is released in rapid peaks by a rapid first-phase followed by a second-phase with prolonged release of insulin into the portal circulation. Rapid-acting insulins (RAIs) are designed to match the physiological response of endogenous human insulin to food intake more closely, to improve management of postprandial blood glucose (BG) excursions, and to reduce the risk of hypoglycemia [18]. "Correction" RAI insulin bolus doses can be given pre-meal or in-between meals to reduce high glucose concentrations.

Regular (Short-Acting) Insulin

Regular insulin (identical to human insulin), also known as soluble insulin, is still used in many parts of the world

- Either as pre-meal bolus injections in basal-bolus regimens (given 20–30 min before meals) together with intermediate-acting insulin 2–3 (or even 4) times daily or a basal long-acting analog given once or twice daily.
- Or combined with intermediate-acting insulin in a twice-daily regimen.

Rapid-Acting Insulin

- RAI should be given ideally 10–15 min before meals or, at least, immediately before meals, given the strong evidence that the rapid action not only reduces postprandial hyperglycemia but nocturnal hypoglycemia may also be reduced [**A**].
- When hyperglycemia is present, RAI should be given in advance of eating [**B**].
- In exceptional cases, with the goal of matching actual food intake and insulin more closely and minimizing the potential for hypoglycemia in erratic eaters, RAI can be given after the meal to more accurately titrate the insulin doses [**B**].
- RAIs correct hyperglycemia, with or without ketosis, quicker than regular insulin owing to their faster glucose-lowering action [**A**].
- RAIs are used as prandial or snack boluses in combination with longer-acting insulins (see basal-bolus regimens) [**A**].
- RAIs are used in insulin pumps for providing both basal and bolus coverage [**A**].

RAIs (see Table 1) are manufactured by modifying human insulin to alter subcutaneous (SC) tissue absorption. Insulin assembles into dimers and hexamers in a concentration-dependent manner. Insulin's glucodynamic action occurs when it is in a monomeric state, therefore impairing the ability of insulin to self-associate into dimers or hexamers accelerates its glucose-lowering action. RAIs are based on the principle of weakened self-association resulting from the inversion of the amino acid sequence of human insulin and/or replacing the native sequence by other amino acids. These alterations can serve two main purposes: (1) accelerate insulin absorption into the bloodstream for a more rapid onset of action relative to human regular insulin and (2) shorten duration of action to manage postprandial BGL while preventing late hypoglycemia.

This glucose-lowering action profile of RAI allows for insulin injection closer to meal onset, allowing postprandial glycemic management with greater flexibility in daily life. Three RAIs are approved: insulin lispro (indicated in all persons regardless of age), insulin aspart (≥1 year age), and insulin glulisine (≥6 years age). The three RAIs differ in their amino acid composition and chemical properties, without significant reported clinical outcome differences in time of action and duration [19–22].

Ultra-Rapid-Acting Insulins

Ultra-rapid-acting insulins (URI) are intended to improve the time-action profile of prandial insulins to cover rapid increases in BGL after meals and may be particularly useful for pumps and automated insulin delivery (AID) systems. URIs have been engineered with modified properties of regular insulin and RAI to achieve more desirable absorption and glucose-lowering action profiles as summarized in Table 1.

Faster-acting insulin aspart has a faster onset and offset than aspart insulin, and mitigates initial post-meal spikes in BGL and causes less hypoglycemia hours later [23]. Faster-acting insulin aspart (a.k.a Fast-acting insulin aspart) is approved by the European Medical Agency (EMA) for (children ≥1 year old) and the US Food and Drug Administration (FDA) for (children ≥2 years old) [23].

In a 26-week multicenter, randomized, double-masked clinical trial of children and adolescents with T1D (1–18 years), mealtime and post-meal fast-acting insulin aspart combined with the longer active insulin (insulin degludec) was safe and mealtime fast-acting insulin aspart provided superior HbA1c values compared with insulin aspart [24].

Ultra-rapid-acting lispro (URLi) is FDA-approved for children (≥1 year) with diabetes [25]. URLi use in children with T1D has been investigated in a Phase 3, randomized, treat-to-target study and found safe and non-inferior to insulin lispro concerning the change in HbA1c for mealtime and post-meal (up to 20 min after the start of a meal) URLi injection [26]. When dosed at the beginning of meals, URLi reduced 1-h post-meal BGL and post-meal BGL excursions versus lispro [26]. Additional URI analogs (Bio-Chaperone® Lispro, AT 247) are being investigated in adults [27].

Human insulin inhaled powder is the fastest-acting exogenously administered insulin since it is absorbed quickly from the lungs, eliminating the inherent delays of SC injection. It has been approved in adults with diabetes but not yet approved for children. The results of a previous phase 2 clinical trial assessing the drug's pharmacokinetics and safety found that inhaled insulin (Afrezza®) is safe in children with T1D, ages 8–17 years [28]. A larger phase 3 trial is also underway to compare inhaled insulin (Afrezza®) to injected insulins and assess its safety over a longer period of use [29].

Intermediate-Acting Insulin

- There is a risk of hypoglycemia, especially overnight, when NPH is used as the basal insulin [**A**]. A fixed schedule of meals and snacks may be required to prevent this hypoglycemia [**E**].
- NPH provides suboptimal glycemia when compared to the newer basal insulins. If available, affordable, and feasible, newer basal insulins may be preferred over NPH for day-to-day management of T1D [**A**].

For over half a century, isophane NPH was the primary basal insulin. Adding protamine to insulin delays insulin dissociation and slows insulin monomer absorption into the circulation. NPH's duration of action is longer than that of human regular insulin but not sufficient to regulate lipolysis and hepatic glucose production for people with severe insulin deficiency when administered once daily. Rather, it requires twice-daily administration [30]. NPH is, however, an imperfect basal insulin given that it has a small peak that occurs 4–7 h after administration [31, 32].

Insulin regimens based on intermediate-acting NPH and short-acting (regular) were used for

decades; however, they could not effectively optimize glycemia given their insulin action profiles. First, NPH use requires a fixed schedule of meals and snacks to mitigate hypoglycemia. Second, and even more problematic, is the small peak action that occurs with the evening NPH dose at the time of minimal insulin need between midnight and 4:00 a.m., increasing the risk of nighttime hypoglycemia [33]. In addition, the dose-effect dissipates in the early morning hours (i.e., 4:00 a.m. to 8:00 a.m.) during the time of greater insulin requirements, contributing to morning hyperglycemia and the so-called "dawn phenomenon" [34]. A third problem with NPH is the high day-to-day variability of its glucose-lowering action [31]. NPH insulin has to be resuspended by rolling it gently 12 to 15 times prior to injection. Insufficient resuspension of NPH adds to the day-to-day variability of the glucose-lowering effect and is reflected by greater glycemic variability and hypoglycemia [35]. This greater variability of the glucose-lowering action of NPH insulin compared to newer basal insulins is well-documented [31, 36, 37].

Nevertheless, NPH insulin use has some advantages. It costs less than many other basal insulins. The number of daily insulin injections can be reduced because NPH can be mixed with regular insulin and RAI. The peak of NPH action given in the morning may provide some insulin coverage for a morning snack or lunch for school-going children who have limited resources to inject insulin at school and have lunch at a consistent time with a consistent daily carbohydrate cotent [38, 39]. NPH has been used with regular insulin to prevent hyperglycemia due to intermittent enteral feeds for persons with T1D and type 2 diabetes (T2D) [40, 41]. In addition, it can be used as a bridge to the longer-acting basal insulins given in the evening when transitioning from IV insulin in the morning or during the honeymoon period [39, 42]. Despite these particular circumstances, it should be emphasized that NPH provides suboptimal glycemic management compared to current basal-bolus insulin therapies in the day-to-day management of T1D.

Basal Insulin Analogs

A basal insulin analog is intended to mimic the steady insulin secretion profile of a healthy pancreas during the fasting state to stop ketogenesis and hepatic glucose output. Basal insulin coverage may be achieved by SC injected basal insulin analogs (grouped as long-acting insulins) or by CSII (generally using rapid-acting analogs) through an insulin pump.

Glargine

Insulin glargine was the first newer generation of basal insulin analog. Glargine has two modifications to the human insulin structure: a glycine substitution for asparagine on position A21, and two arginine residues attached to the carboxy terminal of the beta chain. The resulting shift isoelectric point shift makes glargine soluble at a pH of 4, and so it precipitates in the neutral pH of SC fat. This permits the slow steady release of insulin glargine from its crystalline structure over an approximate 24-h period without a peak. The acidity while in solution has led to complaints of stinging and burning on injecting, yet overall studies appear to show greater quality of life and satisfaction with glargine compared to NPH [43–45].

Data from adults with T1D suggest that similar or improved glycemic control is achieved by administering glargine in the morning and evening, or using a split dose without any further increase in severe hypoglycemic episodes. Splitting the glargine dose does not offer any advantages in glycemic parameters in adults. While there is no FDA approval for twice-a-day dosing of glargine insulin, the choice between once-daily and twice-daily injections could be individualized based on the child's specific needs. Please see the "Notes on Distribution of Daily Insulin Dose" section below for more information.

Detemir

Insulin detemir omits the amino acid threonine at B30 and has a 14-carbon fatty acid covalently attached to the B29 lysine. The fatty acyl side chain stabilizes the hexamers and prolongs absorption by slowing hexameric dissociation and subsequent monomeric absorption. In addition, the fatty acyl chain enables serum albumin binding and reduces the amount of free insulin available for engagement with insulin receptors. The complex dissociates with a time frame between 6 and 23 h. Subsequently, the disposition of detemir to peripheral tissues and its clearance from the body are slower than regular insulin. Anecdotally, detemir insulin causes less local pain compared with the injection of acidic glargine.

Detemir may be administered once or twice daily based on clinical needs; most often, two daily doses are required to be given its shorter duration compared to glargine. In one study, 70% of children used detemir twice daily [46]. In another trial, twice-daily detemir showed no clinical advantage over once-daily detemir, although early-pubertal children often required twice-daily therapy [47].

When performing conversion between other basal insulins and detemir, prescribers should be aware that higher doses of detemir as compared with glargine may be necessary to achieve the same glycemic management [48]. Detemir is approved by EMA for children ≥1 year old and FDA for children ≥2 years old). Brand name detemir pens (LevemirFlexPens®) were discontinued in the USA on April 1, 2024, and vials will be unavailable after December 31, 2024 [49].

Glargine U300

Glargine U300® is a more concentrated formulation (300 units/mL) of the original insulin glargine U100 product (Lantus®), resulting in flatter pharmacokinetic and pharmacodynamic profiles and prolonged duration of action (>24 h) because of a more gradual and protracted release from the more compact SC depot. There is less diurnal variation in glucose-lowering activity with U300 compared to the same dose of U100 glargine [50]. The full glucose-lowering effect may not be apparent for at least 3–5 days of use. The EDITION 4 trial, a randomized study on adults with T1D, and the EDITION JUNIOR trial, focusing on persons 6–17 years old with T1D, both showed non-inferiority of glargine U300 to glargine U100, with similar rates of hypoglycemia, and similar glycemic management [51]. However, some studies have shown that glargine U300 has reduced nocturnal hypoglycemia and improved glycemic stability compared to glargine in adults with T1D [52, 53]. Glargine U300 is EMA and FDA approved for children ≥6 years [54].

Degludec

Degludec is a novel ultra-long-acting analog (glucose-lowering effect beyond 24 h after SC injection). The insulin degludec molecule is structured by omitting the B30 threonine and attaching a side chain to the B29 lysine consisting of glutamic acid and a 16-carbon fatty acid with a terminal carboxylic acid group. Degludec forms soluble multi-hexamers after SC administration, which then slowly dissociate and result in a slow and stable release of degludec monomers into the circulation. Moreover, the monomer binding to albumin in the circulation slows the disposition of degludec to peripheral tissues and clearance from the body, extending the action for up to 42 h or longer. Because the half-life of degludec is 25 h, dose adjustments are made every 3–4 days without insulin stacking [55]. Pharmacokinetics also allows flexibility with dose administration and, in adults, can be given once a day at any time of the day as long as 8 h has elapsed since the previous injection [56]. This allows for the same time of day dosing even when crossing time zones [57].

A large randomized open-label study in adults with T1D supported non-inferiority of degludec compared to glargine U300 for time in range (TIR) and continuous glucose monitor (CGM)-derived hypoglycemia [58]. When regular doses are used, however, glargine U300 can have significantly less hypoglycemia after exercise. This is negated when 75% of the basal dose is used prior to the exercise [59].

Results in young people with T1D indicate that the long-acting properties of degludec are also preserved in this age group [60]. More consistent glucose-lowering action with degludec is expected once steady state is reached. The long half-life of this basal long-acting analog translates into reduced peak-trough fluctuations and a more consistent glucose-lowering action (flatter time-action profile) over 24 h. Furthermore, the ultra-long action profile of degludec should allow children to have a less stringent timing of basal insulin administration from day to day, which may be beneficial in the erratic lifestyles encountered frequently in the adolescent population, particularly athletes.

In the pediatric regulatory trial, insulin degludec once daily was compared with insulin detemir once or twice daily, with prandial insulin aspart in a treat-to-target, randomized controlled trial in children 1–17 years with T1D, for 26 weeks (n = 350), followed by a 26-week extension (n = 280). Degludec achieved equivalent long-term glycemia, as measured by HbA1c with a significant reduction of fasting plasma glucose at a 30% lower basal insulin dose when compared with detemir. Rates of hypoglycemia did not differ significantly between the two treatment groups; however, hyperglycemia with ketosis was significantly reduced in those treated with degludec, potentially offering a particular benefit for persons prone to DKA [61]. Degludec is EMA and FDA approved for children ≥1 year [62].

Once-Weekly Basal Analogs

There is ongoing research to develop novel basal insulin analogs for once-weekly administration. The Icodec ultra-long-acting, weekly basal insulin analog includes three amino acid substitutions (A14Glu, B16His, B25His) that increase molecular stability, reduce enzymatic degradation and insulin receptor-mediated clearance. 20-carbo icosane fatty acid attached to the insulin amino acid chain via a hydrophilic

linker to insulin leads to durable binding to circulating albumin and very protracted release. These modifications extend Icodec insulin's half-life to about 8 days with a flat and stable pharmacokinetic profile, low peak-to-trough variations, and evenly distributed glucose-lowering efficacy with a weekly dosing interval. A randomized open-label study (Once-Weekly Insulin Icodec vs. Once-Daily Insulin Degludec Study [ONWARDS] 6 trial), involving 582 adults with T1D showed non-inferiority of Icodec compared to once daily degludec when treating to target at 26 weeks, and statistically better with Icodec at 52 weeks. However, there was also greater frequency of clinically significant hypoglycemic events with Icodec, and greater satisfaction with degludec. There may be a bias to the satisfaction metrics, given the baseline HbA1c for this cohort was 7.6% and their inability to titrate as frequently with a once-weekly insulin provided them with less locus of control [63]. Icodec is not EMA or FDA approved for children; however, it has EMA-approval for adults with all forms of diabetes [64].

A similar pharmacokinetic profile is seen with Basal Insulin Fc (insulin efsitora alfa), which is a protein combining a single-chain insulin variant with a human IgG2 Fc domain. While there are currently no pediatric data for once-weekly insulins, non-inferiority for glycemic management and hypoglycemia risk has been demonstrated with Basal Insulin Fc compared to degludec in a study with 266 adults with T1D [65–67].

Premixed Insulin

Premixed insulins contain a fixed ratio mixture of prandial and basal insulins and are not routinely used for diabetes care of children. Premixed insulins eliminate the flexibility offered by separate adjustment of the two types of insulin, which is especially useful for children with variable food intake.

Though not recommended, premixed insulins are infrequently used to reduce the number of injections when adherence to the regimen is a problem. There are limited data regarding the use of premixed insulins in young children. There is some evidence suggesting suboptimal metabolic management when premixed insulins are used in adolescents. Higher rates of DKA and severe hypoglycemic risk have been reported in children, adolescents, and young adults with T1D using premixed insulin as compared to a basal-bolus insulin regimen [68, 69].

Traditionally, premixed insulins were a mixture of NPH and regular insulin (or rapid-acting). The premixed insulins available in various countries have different ratios of NPH/regular (rapid) insulin: 10:90, 15:85, 20:80, 25:75, 30:70, 40:60, 50:50. Premixed insulins are suitable for use in pen injector devices but require resuspending the insulin before use by tipping or rolling it 20 times to ensure complete and uniform resuspension of NPH insulin [35]. Premix insulin regimen using NPH and regular soluble insulin is not recommended as a best practice treatment.

The most recent addition to the premixed insulin analog group is a mixture of RAI aspart (30%) with long-acting insulin degludec (70%). The insulin degludec and aspart premix showed similar pharmacodynamic properties to the two injections being given separately with the rapid absorption characteristics of aspart and flat and stable profile of degludec maintained separately so the dose can be easily titrated [70]. Degludec/aspart is approved for children with diabetes by the EMA (children ≥2 years old) and FDA (children ≥1 year old) [71].

Safety of Insulin Analogs

As insulin analogs are molecules with a modified structure compared to human insulin, safety concerns have been raised due to changes in mitogenicity in vitro [72]. In 2013, the EMA concluded that insulin glargine-containing medicines (Lantus®, Optisulin®, Sanofi) for diabetes do not increase the risk of cancer [73].

Biosimilar Insulins

Biosimilar insulins demonstrate similarity to existing insulins. In contrast to generic drugs, which are believed to be chemically identical to their reference product, biologics such as insulin demonstrate slight differences in their available counterparts given the use of different manufacturing techniques and materials (e.g., host cells, tissues). The FDA regulatory transition of insulins in March 2020 opened a regulatory pathway for biosimilar insulin products in the USA and led to the approval of three glargine biosimilars (Basaglar®: FDA approved for children ≥4 years old; Abasaglar®EMA approved for children ≥2 years old; Semglee® FDA approved for children ≥6 years old, EMA approved for children ≥2 years old; Rezvoglar® FDA approved for children) and a lispro biosimilar insulin for adults and children with diabetes (Admelog® FDA and EMA approved for children ≥4 years old 2017, Kixelle®insulin aspart approved by EMA 2021 for children ≥1 year old, Sar-Asp EMA approved in 2020 for children ≥1 year old) [74, 75].

Insulin Concentrations

- Dosing errors with diluted insulins can be serious. Special care must be taken while diluting the insulin either with its special diluent or normal saline and information conveyed to the care providers [**E**].

The most widely available insulin concentration is 100 IU/mL (U100). Regular and NPH insulins are available as 40 IU/mL vials in some countries. The syringe for administering the 40 IU/mL (red cap) insulin is different from 100 U/mL (orange cap). More concentrated formulations (U200, U300, U500) of some types of insulin are available to treat hyperglycemia in severely insulin-resistant persons (e.g., individuals requiring more than 200 total units of insulin daily).

Very young children, infants, and toddlers occasionally require small insulin doses and, therefore, may benefit from diluted insulin to allow for more precise dosing and measurement of insulin in <1 unit increments. Insulin is diluted with diluent obtained from the manufacturer. Aspart, Lispro and NPH insulins have special diluents produced by insulin manufacturers.

There have been some reports of using normal saline to dilute certain types of insulin when the manufacturer diluent is not available. The off-label use of normal saline to dilute insulin might be practical in certain scenarios; however, it comes with significant risks and challenges if not exercised with caution. These reports describe the use of RAI can be diluted to 1/10 (U10) or U50 with sterile NPH diluent and stored for 1 month or use in pumps for infants or very young children [76]. Insulin diluted in a 1/5 ratio (U20 insulin; 20 units/mL) has been described alongside automated insulin treatment in young children (3–6 years old) with T1D [77–81]. Please see International Society for Pediatric and Adolescent Diabetes (ISPAD) 2022 Consensus Guidelines Chapter 23: Managing Diabetes in Preschoolers for further details [82].

Dosing errors with unconventional insulin concentrations can be serious. Providers must ensure that persons are well educated about how to use concentrated and diluted insulins safely before it is initiated. Care must be taken to ensure that the same concentration is supplied each time new supplies are received. Parents with children using diluted insulin should inform clinicians regarding the type of insulin they have been using if they transfer their child's care to a new clinic or seek medical care by a clinician who is not familiar with the child's care such as an emergency room clinician to minimize insulin dosing errors.

Principles of Insulin Therapy

Insulin Regimens

The choice of the insulin regimen depends on the availability and affordability of supplies that each health system provides and the personal characteristics of each individual. Since lack of insulin is still considered a major factor influencing therapeutic choices particularly in children with T1D worldwide, one of the World Health Organization (WHO) five global coverage targets to be achieved by 2030 is that 100% of people with T1D have access to insulin and glucose monitoring. Despite clear recommendations for targets of insulin management in children and adolescents with T1D there is considerable variation in the therapeutic regimens and the nomenclature is confusing, but the following classification has been proposed [83] for insulin delivery and is depicted in Figure 2.

Glucose- and Meal-Adjusted Injection Regimens

- Prandial insulin should be injected before each meal/snack containing carbohydrates and between meals as needed to mitigate hyperglycemia. Insulin doses are calculated primarily based on pre-meal glucose level, meal composition (particularly amount and type of carbohydrates) and prior/expected physical activity. Prandial insulin daily requirements are approximately 55%–70% of total daily dose.
- Basal/long-acting analog is administered once or twice daily and is generally approximately 30–50% of the total daily dose.

RAI is injected immediately before meals [84, 85] and adjusted to glycemia, meal content and daily activity. Rapid-acting analogs may need to be given 15–20 min before the meal to have maximum effect, especially at breakfast [86, 87]. The build-up in insulin levels following repeated injections of prandial insulin at close intervals, referred to as insulin stacking, can occur if RAI injections are given at less than 2–3 h intervals and may increase the risk of hypoglycemia. Ultra-fast-acting analogs may be given closer to the meal [24, 88–91]. If regular insulin is used as prandial insulin, it should be administered 20–30 min before each main meal [22, 92].

Pump Therapy

Insulin pump therapy is extensively reviewed in the chapter "*Technology: Insulin Delivery*" (see ISPAD 2024 Consensus Guidelines Technology: Insulin Delivery for details [93]).

Less Intensive and Fixed-Dose regimens:

- Less intensive regimens include

  - Two or three injections daily using a mixture of short- or rapid- and intermediate-acting insulins. Beyond the remission or honeymoon period, two injection regimens cannot manage BGL and can cause frequent hypoglycemia (particularly in the context of food insecurity) and hyperglycemia
  - Different variations in the timing of administration have been used, but all these therapeutic schemes require a rigid schedule for meals and injections.
  - Prandial insulin is adjusted for glucose levels and food carbohydrate content.
- Fixed-dose insulin regimens
  - Fixed insulin dosage either without adjustment or minimally adjusted to daily varying meals. Insulin dosage defines the subsequent mealtimes and their amount of carbohydrates. Due to the limited flexibility, this poses significant challenges for matching insulin with the day-to-day variability of food intake and activity of children and adolescents.
  - Such regimens consisting of two injections daily of a mixture of short- or rapid- and intermediate-acting insulins (before breakfast and dinner/the main evening meal) may be chosen for a short period of time to reduce the number of injections when adherence to the regimen is a problem or during the honeymoon period.
  - Basal insulin only/premixed insulin only/free mixed insulin combinations are not recommended for the treatment of T1D unless there is no other option.

Guideline on Insulin Dosage

- Aim for appropriate insulin dosage throughout 24 h to cover basal requirements and bolus prandial insulin in an attempt to match the glycemic effect of meals [**E**].
- Delivering prandial insulin before each meal is superior to postprandial injection and is preferred [**A**].
- Administration of RAI analogs approximately 15 min before mealtime results in lower postprandial glucose excursions and more time spent in the target glycemic range [**A**].
- Daily insulin dosage varies greatly between individuals and changes over time. It therefore requires regular review and reassessment [**E**].
- The distribution of insulin dose across the day shows great individual variation. Regardless of mode of insulin therapy, doses should be adapted to the circadian variation based on the daily pattern of BGLs [**B**].

Regular reassessments of insulin dosage and behavior related to insulin administration are essential and should be evaluated at regular intervals (every 3 months). Adjustments to the insulin treatment plan should be made to account for specific factors influencing treatment choices, aiming to guarantee the attainment of personalized glycemic objectives. The optimal insulin dosage is the one that achieves the best glycemic management for an individual, balancing the prevention of hypoglycemia and hyperglycemia while minimizing the risk of long-term complications. See ISPAD 2022 Consensus Guidelines Chapter 7: The Delivery of Ambulatory Diabetes Care to Children and Adolescents with Diabetes for further details [94].

AID has been shown to be superior to MDI or non-automated insulin pumps in terms of achieving better TIR without increased hypoglycemia [95]. A randomized controlled trial of 96 participants aged 10–16.9 years showed a 14% difference in TIR after 2 years in favor of AID from diabetes onset group versus MDI management [96]. General principles of insulin treatment and outcomes are summarized in Figure 2 and Table 2. Insulin dosing is dependent on many factors including

- Age
- Weight
- Stage of puberty
- Duration and stage of diabetes
- State of injection sites
- Nutritional intake and distribution
- Exercise patterns
- Daily routines
- Intercurrent illness/ketosis
- Menstrual cycles

Within a few weeks after the initiation of insulin therapy, it is common for a young person with newly diagnosed T1D to enter a partial remission phase, also known as the honeymoon period, with an increase in endogenous insulin production. During the partial remission phase, the total daily insulin dose is usually <0.5 IU/kg/day.

Prepubertal children (outside the partial remission phase) usually require 0.7–1.0 IU/kg/day and, during puberty, insulin dose requirements may rise to 1–2 IU/kg/day or more [98]. The elevated insulin requirements during puberty are in part explained by the higher growth hormone secretion that characterizes this period [99] which induces insulin resistance; a phenomenon that is observed during adolescence in persons living with and without diabetes, but is exacerbated in those with diabetes [100–102].

Higher BG may be observed during the luteal phase of the menstrual cycle mediated by progesterone [103, 104]. RAI glucose-lowering action has been shown to be

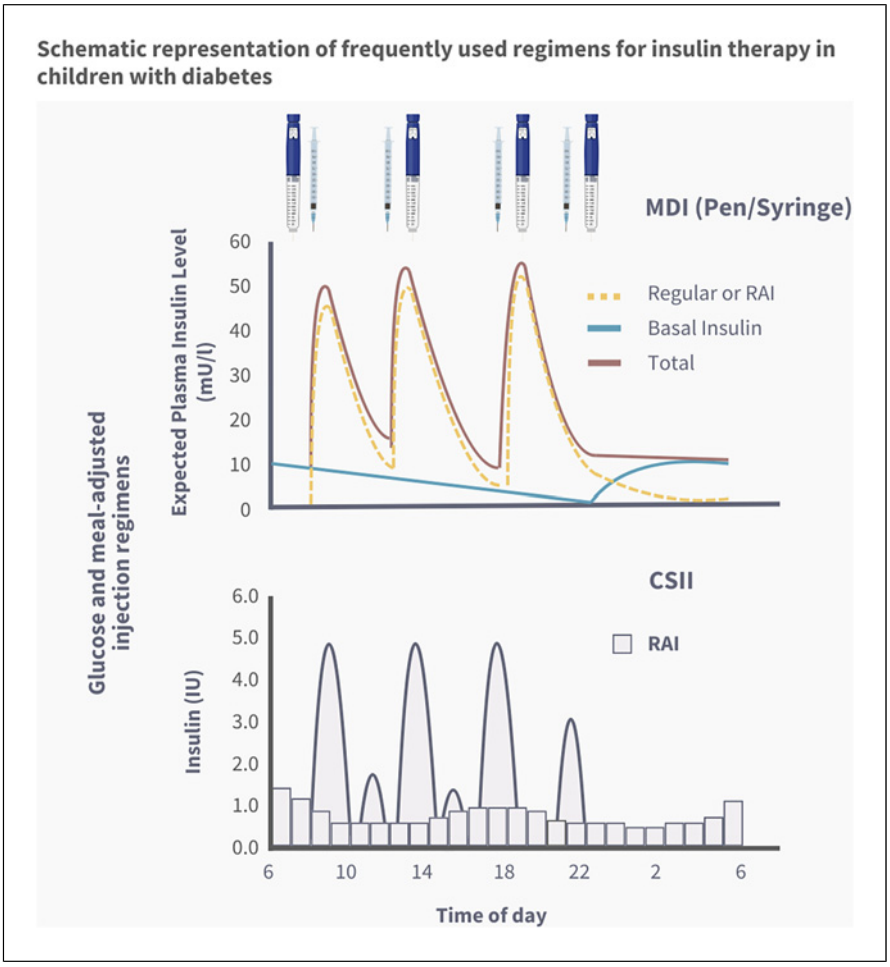

Fig. 2. General principles of insulin treatment in children and adolescents with T1D (injection treatment if initial treatment with AID is not feasible or affordable).

Table 2. Representative relative attributes of insulin delivery approaches in children and adolescents with T1D (modified from Holt et al. [97])

Injected insulin regimens	Flexibility	Lower risk of hypoglycemia	Higher costs
MDI with LAA + RAI or URI	+++	+++	+++
Less preferred, alternative injection regimens			
MDI with NPH + RAI or URI	++	++	++
MDI with NPH + short-acting (regular) insulin	++	+	+
Two daily injections with NPH + short-acting (regular) insulin or premixed	+	+	+
Continuous insulin infusion regimens			
Hybrid closed-loop technology	+++++	+++++	++++++
Insulin pump with threshold/predictive low-glucose suspend	++++	++++	+++++
Insulin pump therapy without automation	+++	+++	++++

Choices of insulin regimens in people with T1D. CGM improves outcomes with injected or infused insulin and is superior to glucose moniting by a meter. Inhaled insulin may be used in place of injectable prandial insulin in the USA. The number of plus signs (+) is an estimate of relative association of the regimen with increased flexibility, lower risk of hypoglycemia, and higher costs between the considered regimens. LAA, long-acting insulin analog; RAI, rapid-acting insulin analog; URI, ultra-rapid-acting insulin analog.

significantly reduced during the luteal phase of menstruation by an insulin clamp and simulation study [105, 106]. Hence, insulin doses may need to be modified during the different phases of the menstrual cycle.

Notes on distribution of daily insulin dose: In children and young people on basal-bolus insulin regimens, the basal insulin may represent between 30% and 50% of total daily insulin and is administered as follows:

- Glargine is often given once a day at approximately the same time each day. However, many children may need to receive two daily doses of glargine or also receive NPH that is injected separately to provide full daytime basal insulin coverage [107, 108]. Glargine can be given before breakfast, before dinner or at bedtime with equal effect, but nocturnal hypoglycemia occurs significantly less often with breakfast injection [31]. Twice a day, glargine injection (morning and nighttime injection) in young children with diabetes is used in clinical practice, especially if there is a tendency for BG to rise or fall significantly at certain times of the day. Administering glargine at the same time each day helps ensure a consistent supply of basal insulin, more stable and predictable BG management. When switching from NPH to glargine as basal insulin, the total dose of basal insulin needs to be reduced by approximately 20% to avoid hypoglycemia [108]. The dose should be individually adjusted according to BG trends.
- Detemir is most commonly given twice daily in children [46, 109]. When transitioning to detemir from NPH, the same doses can be used to start with but may require an increase in detemir dose according to SMBG results [48]. A twice-daily regimen consisting of NPH injection in the morning and detemir injection at nighttime with RAI for breakfast and dinner has been used to optimize glycemic management during the honeymoon phase of T1D as a bridge to insulin pump treatment [39].
- Degludec is administered once daily and can be given at any time. In children with diabetes, degludec is generally given at the same time of the day, but in adults, it can be given at any time of the day as long as 8 h has elapsed since the previous injection. This benefits those with erratic schedules, like adolescents, those who have variable work hours, or individuals traveling across time zones. It is also convenient when transitioning back and forth from insulin infusion pump therapy to injections, as experienced by athletes or adolescents wishing to take a break from the insulin pump. However, given the >24-h duration of action of degludec, care should be taken to reduce the basal pump settings by ~20% for the first 1–2 days when making a switch to the pump to avoid hypoglycemia.
- Glargine U300 is administered once daily at approximately the same time of day. Given its concentrated form of glargine U100 and subsequent longer duration of action, it is particularly helpful for those with high basal insulin needs or those that desire morning basal insulin administration without the need for an additional evening basal insulin injection.
- NPH insulin has been used in the morning to help cover daytime basal insulin needs and glycemic excursions after lunch and snacks in children who are unable to receive insulin injections at school [38].

Calculation of Bolus Insulin Doses

For intensive insulin treatment, a fundamental aspect is calculating bolus insulin dose based on carbohydrate content and glucose levels.

- The "500-rule" is often used to obtain an initial insulin to carbohydrate ratio when starting with carbohydrate counting (divide 500 by the total daily dose – basal and bolus insulin – to find the amount of carbohydrates in grams that 1 unit of bolus insulin [short/rapid/faster-acting insulin] will cover) [110]. However, the 500 rule may need to be individually adjusted to allow more insulin for breakfast and less insulin for a meal preceding or immediately after exercise [111].

This "rule" may be different in toddlers and very young children and a 330 or 250 rule (gives 50%–100% more insulin) instead of 500 might be used in preschool-age children. To evaluate and further tailor the child's insulin dosing, it is necessary to repeatedly observe and calculate the correct proportion between insulin and CHO from real-life meals. See ISPAD 2022 Consensus Guidelines Chapter 23 on Management of Diabetes in Preschoolers for further details [112].

- The insulin:carbohydrate ratio for an individual meal, for example, breakfast, can be calculated by dividing the carbohydrate content in grams by the insulin dose in units. This method often gives the most accurate results for an individual meal and can preferably be used for breakfast when there usually is an increased insulin resistance. If the BGL before and after the meal differ by more than 2–3 mmol/L (36–54 mg/dL), the correction factor (see below) can be used to calculate out how much more (or less) insulin should be given for a certain meal.
- Fat and protein intake affects the insulin requirements and should be considered when deciding bolus doses. One protein and fat-protein unit (FPU) equals 100 kcal of fat or protein and requires the same amount of insulin (as an extended bolus) as 10 g of carbohydrates. This may result in post-meal hypoglycemia, and more

recent studies have found a lower need of insulin for protein, around 200 kcal equaling 10 g of carbs [113]. See ISPAD 2022 Consensus Guidelines Chapter 10 on Nutritional Management in Children and Adolescent with Diabetes for further details [82].
- Correction doses (also called insulin sensitivity factor [ISF], correction factor) can be used according to the "1800 rule," that is, divide 1800 by total daily insulin dose to get the mg/dL, that 1 unit of RAI will lower the BGL; for groups that are more insulin resistant, the ISF has also been calculated dividing 1,500 by the total dose. For mmol/L, use the "100 rule," that is, divide 100 by total daily insulin dose [114]. The "1500 rule" may be used when regular insulin is used for correction dosing.
- For BGL below the target BGL, the Bolus Calculator (feature on some pumps) uses a Correction Factor to reduce a portion of a meal bolus dose.

Insulin Dose Adjustments

Insulin adjustments are essential to reach glycemic goals. The daily or weekly BG patterns and trends measured by self-monitoring of blood glucose (SMBG) or CGM patterns should be taken into account when adjusting insulin doses. The family should be educated and empowered to perform these adjustments.

Immediately following the Diagnosis

Insulin adjustments should be made frequently to achieve the target BGL soon after a new diagnosis of T1D. Many centers provide daily insulin dose adjustments during the first few weeks after diagnosis [115]. The honeymoon period (when present) may require drastic and prompt decreases in insulin daily dose to ameliorate hypoglycemia [116, 117]. Most centers advocate for teaching carbohydrate counting right from the outset of diabetes diagnosis, emphasizing the importance of seeking frequent guidance and support from the diabetes team to adeptly adjust insulin doses post-diagnosis. AID treatment should be considered, when feasible and affordable, from the onset of T1D for better glycemic management. Please refer to ISPAD Clinical Practice Consensus Guidelines 2024: Screening, Staging, and Strategies to Preserve Beta Cell Function in Children and Adolescents with T1D Chapter for management of diabetes stages 1–3.

Insulin Dose Adjustments for Well-Established (Stage 4) Diabetes

The planned insulin regimen should be adjusted periodically based on overall glycemia, child's response to the initial regimen, growth, level of exercise, and changes in weight and insulin sensitivity over time. In the context of basal-bolus or MDI regimens, insulin dosing adjustments are executed pre-meals and in response to regular SMBG or CGM assessments [108]. Furthermore, daily or weekly BG patterns and CGM TIR trends should be considered when fine-tuning and adjusting insulin doses.

Advice for Persistent Trend Deviations from Target BGL

- For elevated glucose levels before breakfast – the advice is to increase pre-dinner or pre-bed intermediate- or long-acting insulin dose (glucose determination during the night is recommended to ensure that this change does not result in nocturnal hypoglycemia).
- For elevated BGL after a meal – the advice is to increase the pre-meal ultra-rapid/rapid/regular insulin dose [118].
- For elevated BGL before lunch/dinner meal – the advice is to increase pre-breakfast basal insulin or increase the dose of pre-breakfast ultra-rapid/rapid/regular-acting insulin (for elevated BGL before lunch) if on a basal-bolus regimen. However, snacking before the meal without an insulin dose should be ruled out. When using RAI in a basal-bolus regimen, the dose or type of basal insulin may need to be adjusted if BGL rise several hours after the meal (during the postprandial fasting state) as the analog insulin has most of its effect within 2–3 h after injection [114]. Missed mealtime insulin boluses are a major cause of suboptimal glycemia in children and adolescents with diabetes. Omitting >1 meal-related injection per week leads to an increase in HbA1c of 0.3%–0.8% [119, 120]. There are new and promising adherence metrics that may be easily interpreted and used for early intervention to improve following the treatment plan during clinic visits [121].
- Administration of RAI analogs approximately 15 min before mealtime results in lower postprandial glucose excursions and more time spent in the 3.5–10.0 mmol/L (~63–180 mg/dL) range, without increased risk of hypoglycemia [87].
- Correction dose should be added to the prandial insulin dose if pre-meal BGL is above target range. Postprandial glucose testing performed at the time of the prandial insulin peak (1.5–2 h after the injection) is essential to determine the glucose-lowering effect of prandial insulin dose.
- When using carbohydrate counting, persistent elevations of post-meal glucose levels may require adjustment to the insulin to carbohydrate ratio [122]. If postprandial hyperglycemia persists after correction insulin dosing, the ISF should be reviewed.

- Unexplained hypoglycemia requires re-evaluation of insulin therapy and dose. Unexplained hyperglycemia may be caused by a "rebound phenomenon," which is described as hypoglycemia followed by hyperglycemia that is potentiated by excessive eating to treat the hypoglycemia along with the effects of hormonal counter-regulation.
- Day-to-day insulin adjustments may be necessary for variations in lifestyle routines, especially exercise or dietary changes.
- Special education may be helpful when there are changes in routines, travel, school outings, educational holidays/diabetes camps, or other activities which may require adjustment of insulin doses.

Administration and Storage of Insulin

- All young people should have rapid-acting or regular insulin available and a means to inject this insulin for prevention and management of diabetes, hyperglycemia, and ketosis emergencies [**E**].
- A small supply of spare insulin should be readily available to all children and adolescents to ensure no interruption in their care [**E**].
- Children and adolescents should be encouraged to inject consistently within the same area (abdomen, thigh, buttocks, arm) at a particular time of the day but must avoid injecting repeatedly into the same spot to prevent lipohypertrophy (LH) [**B**].
- Insulins need to be administered by insulin syringes or other injection devices calibrated to the type and concentration of insulin being used [**E**].
- Parents and care providers should all regularly check children's injection sites for site reactions [E].
- Care providers and healthcare professionals should regularly assess parent/child injection technique (IT) and skills to ensure proper insulin delivery [**E**].
- Healthcare professionals have the responsibility to advise parents, other care providers and young people on adjusting to insulin therapy safely and effectively. This training requires regular review, pattern recognition, reassessment and reinforcement [**E**].

Insulin Injection and Absorption

Injection Technique

- HCPs need to make individuals with diabetes and/or their care providers demonstrate their IT, either by performing an actual injection or by injecting into a pad or foam pillow. This can be used as a teaching occasion, praising what they do correctly and correcting any improper practices [**E**].
- Injections should only be given to clean, healthy sites using clean hands. Disinfecting the skin is generally not required [**E**].
- Injections must be given SC, not IM. The 4 mm pen needle has the lowest risk of IM injection and allows wider zones for rotation [**E**].
- A 4-mm needle is preferred for all injectors regardless of age, sex, ethnicity, or body mass index (BMI). It should be inserted perpendicular to the skin (90° to skin surface) – not at an angle – regardless of whether a skinfold is raised [**E**].
- Very young children (≤6 years of age) and very thin adults (BMI <19 kg/m^2) should always inject into a lifted skinfold. Other children, adolescents, and adults may inject without a skinfold [**E**].
- Inspect injection sites during each visit, at a minimum annually, both visually and by palpation to aid in detection of LH. If LH is present, show child/caregiver the lesion and instruct not to inject into it. Clinicians should teach children/caregivers what to feel and look for and engage them/caregivers in surveying injection sites [**E**].
- If LH is present, switch injections to healthy tissue, decrease the dose of insulin, and closely monitor glucose excursions. Reductions often exceed 20% of the original dose [**E**].
- Rotate injections systematically to avoid LH, injecting at least 1 cm (approximate width of an adult finger) from previous injections [**E**].
- Needles are designed as sterile, single-use devices. It is best to avoid reusing them whenever possible. Note that excessive reuse (more than five times) has been associated with LH [**C**].

Proper insulin IT is essential to use insulin safely and optimize glucose management. Insulin should be injected into SC tissue as IM injection can lead to more rapid and unpredictable insulin absorption and variable glucoses. The insulin injection sites are shown in Figure 3.

Several other aspects are important when considering the IT:

- Children <6 years old or very thin adults might inject perpendicularly into raised skin. A two-finger pinch technique is recommended for all types of injections to ensure a strict SC injection, avoiding IM injection [123]. The pinch-up technique with 4 mm needle is recommended for children ≤6 years old. It should be noted that a "pinch-up" method with 5 mm needles may paradoxically facilitate IM injections when children use this technique in the thigh [124].
- With 4 mm–6 mm needles, the injections can be given perpendicularly without lifting a skinfold but only if there is enough SC fat, which often is the case in pubertal girls (at least 8 mm as the skin layers often are compressed when injecting perpendicularly) [125]. Lean boys, however, have a thinner SC fat layer, especially on the thigh [125, 126]. When injecting into the buttocks, the SC fat layer is usually thick enough to inject without lifting a skinfold. There is a risk of intradermal injections if 4 mm–6 mm needles are not fully inserted into the skin.
- Rotation of insulin injection sites, within the same injection region, should be taught from diagnosis.

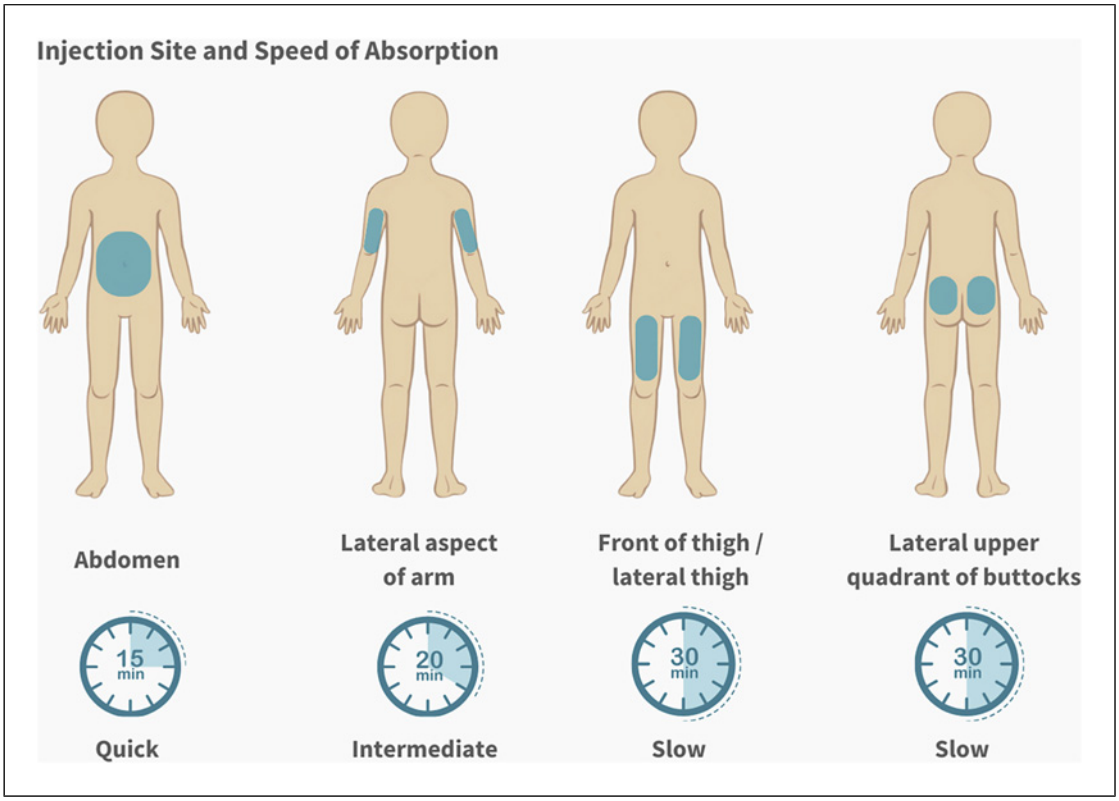

Fig. 3. Schematic representation of injection sites and relative insulin absorption. Certain insulins (regular insulin, rapid-acting insulin, analogs, and NPH) are more readily absorbed from the abdomen and deltoid region compared to thigh and buttocks. The long-acting insulin preparations, including glargine and degludec, are not significantly influenced by the site of injection.

- Pen IT requires careful education, reinforcing the importance of a 2-unit "air shot" before every injection to ensure the pen is working correctly.
- The NPH vial should be gently rolled (not shaken) at least 10 and preferably 20 times [30], to mix the insulin suspension before carefully drawing it up into the clear insulin. The position in which NPH is stored may also affect its activity [30].
- Insulin should be injected when it is at room temperature as injecting cold insulin can sometimes make the injection more painful.
- There should be a delay of 15 s after pushing in the plunger to help ensure complete expulsion of insulin through the needle [127].
- Leakage of insulin is common and cannot be totally avoided. Encouraging slower withdrawal of the needle from the skin, stretching of the skin after the needle is withdrawn, or pressure with clean finger over the injection site could minimize leakage of insulin.
- Bubbles in insulin should be removed when possible. If the bubble is not big enough to alter the dose of insulin, it should not cause problems. When using insulin pens, air in the cartridge can cause drops of insulin appearing on the tip of the pen needle, if withdrawn too quickly.

Self-Injection. The appropriate age for children to self-inject is variable and depends on developmental maturity rather than chronological age. Most children over the age of 10 years either give their own injections or help with them [128]. Younger children sharing injection responsibility with a parent or other care provider may help prepare the device or help push the plunger and subsequently, under supervision, be able to perform the whole task successfully. Self-injection is sometimes triggered by an external event such as an overnight stay with a friend, school excursion or diabetes camp. Parents or care providers should not expect that self-injection will automatically continue and should continue to monitor and be prepared to resume responsibility for the child's insulin injections. Younger children on multiple injection regimens may need help inject in sites difficult to reach (e.g., buttocks) to avoid LH.

Self-Mixing of Insulin. When NPH is mixed with short- or fast-acting insulin, it is most important that there is no

contamination of one insulin with the other in the vials. To prevent this, the regular (clear insulin) is drawn up into the syringe before NPH (cloudy). Insulins from different manufacturers should be used together with caution as there may be interaction between the buffering agents. RAI analogs may be mixed in the same syringe with NPH immediately before injecting [129]. It is recommended that neither glargine insulin nor detemir insulin be mixed with any other insulin before injection [130] because this mixture blunts the early glucose-lowering action and prolongs the time-action profile of the RAI as compared with separate injection of the analogs [130, 131].

Injection Site Adverse Events

LH, an accumulation of SC fat in response to the adipogenic actions of insulin at a site of multiple injections, is a common complication of insulin therapy [132]. LH reduction is proven to improve glycemia. Lipoatrophy has been rare since the introduction of highly purified insulins. Rotating injection sites, switching from a different RAI, using zinc-free RAI may prevent and address lipoatrophy [133]. Please refer to ISPAD 2022 Consensus Guidelines Chapter 18 on Other Complications and Associated Conditions in Children and Adolescents with Type 1 Diabetes for more information [134].

- Painful injections are a common concern. When this is an issue, we recommend checking angle, length of the needle, and depth of injection to ensure injections are not being given IM and that the needle is sharp. Reused needles can cause more pain [135, 136]. Some people with diabetes have a severe long-lasting dislike of injections which may influence their glycemia. For these persons, indwelling catheters (Insuflon®, i-port®) or insulin pump therapy can decrease injection pain [136–138]. These devices may help with frequent injections in very young children [136].
- Local hypersensitivity reactions to insulin injections are uncommon but when they do occur, formal identification of the insulin (or more rarely preservative) responsible may be possible with help from manufacturers. A trial of an alternative insulin preparation may solve the problem. If true allergy is suspected, desensitization can be performed using protocols available from the manufacturers.
- Bruising and bleeding are more common after IM injection or tight squeezing of the skin. Uses of thinner needles have been shown to result in significantly less bleeding at the injection site.

Insulin Absorption

Insulin activity profiles show substantial variability both day to day in the same individual and between individuals. Many factors affect the speed and consistency of insulin absorption, and it is important to be aware of these and to minimize those factors which are modifiable. Young people and their caregivers should be aware of the modifiable factors that can affect insulin absorption.

Factors affecting absorption of insulin [139–141] are as follows:

- Insulin concentration, volume, and dose (the SC depot): Smaller SC depot [141], lower insulin concentration [142], and lower insulin doses are associated with faster absorption.
- Mixture of insulins in the same syringe: Mixture of certain insulins in the same syringe affects absorption [130, 131].
- Injection site: Regular insulin is absorbed fastest from the abdomen (Fig. 3) [143]. These regional differences are less apparent with rapid- and long-acting insulin analogs [139, 140, 144, 145]. The absorption of glargine [146] and degludec are not significantly influenced by the injection site [147].
- Intramuscular (IM) injection: IM administration route is associated with more rapid insulin absorption, which is more evident during exercise [148, 149]. Accidental IM injection may explain variability in pharmacokinetics between injections in lean individuals and site selection and technique can avoid this.
- Temperature: Insulin absorption is increased by local or ambient heating, in both pump and MDI therapy [150, 151].
- Exercise: Insulin absorption can be increased with exercise, with the location and depth of the injection being contributing factors [152]. Leg injection with leg exercise leads to faster absorption [153]. Glargine absorption is not affected by exercise [154, 155].
- Lipohypertrophy: LH significantly delays insulin absorption [156].
- Obesity: Increased SC fat delays insulin absorption due to a reduction in SC blood flow [157].

Two devices which apply heat to the injection site have been developed which decrease insulin requirements and enhance insulin absorption, leading to an earlier peak of insulin action together with less hypoglycemia. *Insupad*® is a device that warms an area 2 cm × 4 cm just prior to injection of bolus insulin and *Insupatch* was developed for insulin pump therapy with an integrated heating element that is activated when a bolus is delivered [150]. Insulin injection site cooling and warming affected glargine insulin pharmacokinetics and pharmacodynamics in a small-scale study [158].

Devices for Insulin Delivery

Insulin Syringes

Syringes are available in a variety of sizes. The following recommendations are desirable:

- Plastic fixed-needle syringes with small dead space are preferable to glass syringes.
- Plastic fixed-needle syringes are designed for single use. Reuse should be discouraged if there is concern about hygiene or injection pain as the needle becomes blunt when reused [159].
- Small syringes with half- or 1 unit per mark (e.g., 0.3 mL, 100 U/mL) are preferable for use in small children, making it possible to dose in half units.
- The insulin syringe must match the insulin concentration being used. 40 U/mL syringes (red cap) and 100 U/mL syringes (orange cap) have different markings and cannot be interchanged.
- Syringes must never be shared with another person because of the risk of acquiring blood-borne infection (e.g., hepatitis, HIV).
- All children and adolescents with diabetes should know how to administer insulin by syringe because other injection devices may malfunction.
- Appropriate disposal procedures are mandatory. Specifically designed and labeled "sharps containers" may be available from pharmacies and diabetes centers. Special needle clippers (e.g., Safeclip®) may be available to remove the needle and make it unusable. Without a "sharps container," syringes with needles removed may be stored and disposed of in opaque plastic containers or tins for garbage collection.

Pen injector Devices (Insulin Pens)

Pen injector devices containing insulin in prefilled cartridges make injections easier, more accurate, and flexible. They eliminate the need for drawing up from an insulin vial; the dose is dialed up on a scale, and they may be particularly useful for insulin administration away from home, at school or on holidays. When using a pen, it is advisable to count to 10 slowly or 20 quickly (wait about 15 s) before withdrawing the needle from the SC tissue, in order to give time for any air bubble in the cartridge to expand [127, 159]. Pens need to be primed before use, so that a drop of insulin shows at the tip of the needle.

Special pen needles of small size (4 mm) and diameter are available and may cause less discomfort on injection [160]. Some pens can be set to ½ unit increments that are useful for dosing in young children when small dosing increments are needed. A few pens have a memory for taken doses, which can be practical, especially for teenagers. Pen injector devices are useful in children on multiple injection regimens but less acceptable when insulin mixtures are used. Availability is a problem in some countries since they are a more expensive method of administering insulin. Insulin pens, vials, cartridges, pen needles, syringes should not be shared.

Subcutaneous Indwelling Catheters

Such catheters (e.g., Insuflon®, i-port®) inserted using topical local anesthetic cream, may be useful to overcome problems with injection pain at the onset of diabetes [136], especially in very young children. The use of indwelling catheters does not negatively affect metabolic management [138]. In children with injection problems, HbA1c has been lowered by using Insuflon® [137]. However, the use of a basal analog and a short- or RAI at the same injection time in an indwelling catheter is not advisable in the case of possible interaction of the two insulins [130, 131, 137]. Indwelling catheters should be replaced every 2–4 days to prevent scarring and a negative effect on insulin absorption [161, 162].

Automatic Injection Devices

Automatic injection devices are useful for children who have a fear of needles. Usually, a loaded syringe is placed within the device, locked into place and inserted automatically into the skin by a spring-loaded system. The benefits of these devices are that the needle is hidden from view and the needle is rapidly inserted through the skin. Automatic injection devices for specific insulin injectors are available [163].

Jet Injectors

High-pressure jet injection of insulin into the SC tissue has been designed to avoid the use of needle injection. Jet injectors may have a role in cases of needle phobia. The use of jet injectors has resulted in metabolic management comparable both to conventional injections and CSII [164], but problems with jet injectors have included a variable depth of penetration, delayed pain and bruising [165]. In a recent study, using a jet injector for insulin administration was associated with slightly altered variability in pharmacokinetic endpoints, but with about similar variability in pharmacodynamic endpoints compared to conventional administration [166].

Continuous Subcutaneous Insulin Infusion

The use of external pumps is increasing and is proving to be acceptable and successful [164–173], even in young infants [167, 168]. For an extensive review of CSII please see ISPAD 2024 consensus guidelines chapter "Diabetes Technology: Insulin Delivery" [93].

Storage of Insulin

- When in use, insulin can be stored at room temperature (below 25° or 30°C) for up to 4 weeks [**E**].
- When not in use, insulin can be stored in a refrigerator, until the expiration date (not in or too near the freezer section or cooling element) [**E**].
- Insulin should be discarded if it has been frozen as freezing can compromise the integrity of both the formulation and the vial itself [**B**].
- The time period recommended for use after opening a vial varies between 10 days to 8 weeks for different insulin formulations. It is suggested that manufacturer's guidelines and drug inserts be followed regarding the time period recommended for use after opening a vial [**E**].
- It is suggested that the insulin in the reservoir be changed with infusion set/line changes every 48–72 hours with the exception of seven day extended insulin pump infusion set [**E**].
- Insulin should not be in the checked baggage but should always be in the hand luggage carried in the cabin [**E**].
- Traveling with extra, back-up insulin is recommended [**E**].

Insulin Storage Recommendations for Insulin Not in Use

Insulin undergoes chemical and physical degradation over time, leading to reduced potency. This degradation is accelerated by exposure to high temperatures, direct sunlight, shear stress through agitation and increased air-liquid surface, which occurs as the volume of a vial decreases [174].

Refrigeration problems may be more frequent than apparently thought; some household refrigerators often do not meet manufacturers' recommendations, with temperatures often dropping below freezing point [175]. Mail order insulin, increasingly popular in some countries, might also increase exposure to extended temperature variations. A thermochromic vial monitor technology has been studied to detect if insulin has undergone excessive heat exposure [176].

Insulin should therefore always be inspected before use and discarded if it has been frozen or if there is any evidence of clumping, frosting, discoloration or precipitation. Individual manufacturer's recommendations for storage and expiration date should be adhered to where possible, and reduced insulin potency is considered a possible cause when insulin requirements increase unexpectedly. For more information on how insulin is stored in the absence of electricity, see ISPAD 2022 Consensus Guidelines Chapter 25 on Managing Diabetes in Limited Resource Settings [177].

Insulin Storage Recommendations for Insulin in Use

When in use, insulin is regularly exposed to the previously mentioned environmental risk factors and in the case of insulin pumps, which is worn close to the body, not only is the temperature in the reservoir increased, but constant movement can accelerate fibril formation [178]. When in use, insulin can be stored at room temperature (below 25° or 30°C) for up to 4 weeks [164, 174, 179]. Insulin used in insulin pumps should be changed more often. Manufacturers recommend insulin aspart and insulin lispro be kept in the pump reservoir at room temperature for no longer than 7 days. Ideally, the insulin in the reservoir should be changed with infusion set/line changes every 48–72 h with the exception of 7-day extended insulin pump infusion set. Product information on insulin glulisine states that it can be kept in the pump reservoir for 2 days at 37°C.

Young people and their caregivers should be aware of the importance of optimal storage to maintain the potency of their insulin, in particular the avoidance of exposure to high temperatures (e.g., *pumps left in the sun when disconnected, insulin stored in a car glove compartment*). A number of new insulin delivery devices (pumps, smart pens or pen caps) have an integrated temperature sensor and there are several products available to protect vials and pens from heat. Products dedicated to monitoring insulin temperature using a sensor and mobile app can be kept with any type of insulin and provide a warning when temperature limits are exceeded.

Storage of Insulin when Traveling

The following recommendations for transporting insulin during traveling are advised. There are several products (bags or cases) on the market for protecting insulin pens and vials from heat, although their performance has not been studied. When using ice packs, insulin pens or vials should never be kept directly on ice to avoid freezing (Hotel refrigerators could be less reliable).

Recent publications with regard to the heat stability of insulin, building on previous data, ascertained more information on the heat stability of insulin, including a Cochrane Review [179–181]. This is positive in that this might change how insulin is prescribed and dispensed and also give value to traditional methods of insulin storage, such as clay pots or animal skins [182].

Table 3. Adjunct therapy in T1D in youth

Adjunct medication	Mechanism of action	Advantages	Disadvantages	Approval/usage
Pramlintide (amylin analog)	Decreases glucagon secretion, reduces gastric emptying, induces satiety, and decreases hepatic glucose production	Modest reduction in HbA1c and weight loss	• Administered as a pre-meal SC injection • Increases injections burden • Risk of hypoglycemia Very expensive	Licensed in USA only since 2005, but not widely used till now fixed-dose combination with insulin under research
Metformin	Decreases hepatic glucose output; increases peripheral glucose uptake	• Weight loss Insulin dose reduction • Beneficial cardiovascular effect • Addition of metformin to insulin treatment improved glycemic management in adolescents with suboptimal HbA1c • No significant improvement in glycemic management at 6 months for adolescents who are overweight or obese	• Gastrointestinal adverse effects • Risk of hypoglycemia adolescents • Avoid in DKA, if eGFR <30 mL/min, cardiac or respiratory insufficiency, or receiving radiographic contrast materials	Further studies are required for optimal dose, duration, and indications for young people with T1D
GLP-1 receptor agonists (GLP-1RA)	Inhibits glucagon secretion, delays gastric emptying rate, and induces satiety resulting in weight loss	• Reduce body weight and BMI • Reduction in insulin dose • Improvements in glycemic management	Gastrointestinal side effects	Promising option but needs larger trials
SGLT-2 inhibitors	Inhibits glucose reabsorption in renal proximal convoluted tubules leading to glycosuria	Improves glycemic outcomes in adults with T1D	Increased risk for ketosis, euglycemic DKA, and genitourinary infections in adults	Phase 3 studies in pediatric population limited

Adjunctive Medications alongside Insulin

- There is limited evidence for the use of adjunctive medication in children and adolescents with T1D. Larger trials are needed to assess the impact on glycemic measures, weight, insulin resistance, and potential long-term benefits, including preventing or delaying microvascular and macrovascular complications, and the safety profile of these adjunctive therapies in the management of pediatric T1D [**E**].

Adjunctive glucose-lowering agents (Table 3) have been introduced to address unmet needs in diabetes treatment, help achieve glycemic targets, and prevent complications [183]. It is critical to note that none of these medicines replace insulin.

The only approved non-insulin anti-hyperglycemic pharmacological therapy in T1D is pramlintide, an amylin analog (approved in the USA for adults with T1D in 2005, not approved in Europe). Pramlintide is an injectable adjunct to insulin treatment in T1D and T2D. It decreases glucagon secretion, reduces gastric emptying, and induces satiety. The efficacy of pramlintide adjunct treatment for T1D is modest, with an average HbA1c reduction of 0.2–0.4% and a weight loss of about 0.5–1 kg [183]. Pramlintide use is limited by the risk of severe hypoglycemia and burden of injections. There are ongoing studies evaluating the efficacy of a combined amylin and insulin as a fixed dose [184, 185].

Cagrilintide is an investigational long-acting amylin analog being tested in persons with T2D. It has agonistic effects on both native amylin and calcitonin receptors [186].

Metformin is another anti-hyperglycemic medication that has been found to have a beneficial cardiovascular

effect by reducing cholesterol for people with T1D when used as an adjunct treatment. It has been shown to lead to weight loss of about 1.2 kg and a reduction of insulin dose by 2 units per day, and improve insulin sensitivity [187]. However, it does not have consistent effect on HbA1c [181]. Metformin is FDA approved for treatment of T2D and polycystic ovary disease for ages 10 and older.

Endogenous glucagon-like peptide-1 (GLP-1) is secreted from the gut postprandially. GLP-1 enhances glucose-induced insulin secretion, inhibits glucagon secretion, delays gastric emptying, and induces satiety, resulting in weight loss. People with T1D are unable to suppress glucagon during meals, which contributes to postprandial hyperglycemia, and this defect may be improved with GLP-1 receptor agonist (GLP-1RA) therapy when used as an adjunct to insulin treatment. In adults with T1D, GLP-1RAs reduce body weight and insulin dose and modestly improve glycemic management. GLP-1-based therapies could be considered adjunctive therapy in specific populations of children and adolescents with T1D and obesity. Gastrointestinal side effects of GLP-1RA (principally nausea) are related to gastric emptying delay, slowing carbohydrate absorption, and are observed in up to 30% of treated individuals. Hypoglycemia is also another potential side effect [188, 189]. GLP-1RAs are not ideal for persons living with gastroparesis. The GLP-1RA liraglutide is FDA approved for youth aged 10 years and older for obesity and T2D. Higher dose liraglutide, Saxenda® 3 mg is approved for weight loss in youth aged >12 years with obesity. Exenatide and Dulaglutide are FDA approved in youth aged 10 years and older.

GLP-1 and GIP are enzymatically inactivated by dipeptidyl peptidase-4 (DPP-4). DPP-4 inhibitor has not shown any benefit for HbA1c improvement when used adjunctively for adults with T1D [190].

The kidneys contribute to the pathophysiology of chronic hyperglycemia in people with T1D. Renal glucose reabsorption is increased in T1D by a maladaptive mechanism minimizing glycosuria and aggravating hyperglycemia. The SGLT-1 transporter is important for intestinal absorption of glucose, while the SGLT-2 transporter is primarily responsible for renal glucose reabsorption. SGLT-1 inhibition may promote glucose and appetite management by increasing the postprandial secretion of GLP-1 and polypeptide YY.

There is mounting evidence for the use of SGLT-2 and dual SGLT-1 and SGLT-2 inhibitors as add-on therapy in adults living with T1D. Canagliflozin, dapagliflozin, and sotagliflozin have shown efficacy in T1D with clinically and statistically significant reductions in HbA1c of about 0.4–0.5% (6–7 mmol/mol), insulin dose and body weight, without increasing the risk of hypoglycemia compared with placebo. In 2019, dapagliflozin was approved for use in Europe for adults with T1D who were overweight with persistent suboptimal glycemic management despite optimal insulin therapy. Dapagliflozin and ipragliflozin are both licensed in Japan.

SGLT-2 inhibitors, empagliflozin and dapaglifozin, are FDA approved for youth 10 years and older for treatment of T2D. Dapaglifozin is approved by the EMA for ages 10 years and older for the same indication.

Sotagliflozin is a dual SGLT 1 or SGLT-2 inhibitor that, when added to insulin in young adults with T1D and HbA1c above target for 12 weeks, numerically improved HbA1c and significantly improved HbA1c goal attainment, postprandial blood sugar, and body weight. Sotagliflozin as an adjunct to optimized insulin therapy in persons with T1D and unhealthy weight may help optimize glycemia and mitigate weight gain without increasing hypoglycemia risk in this high-risk population. In adults with T1D, adding sotagliflozin to insulin significantly reduced blood pressure and other markers of arterial stiffness and vascular resistance [191, 192]. Sotagliflozin was approved in Europe as an adjunct to optimal insulin therapy in adults with T1D and a BMI ≥27 kg/m^2. However, this indication in the UK and Europe has been withdrawn voluntarily by the manufacturing company due to concerns about increased ketosis and euglycemic DKA [193, 194].

Over the past decade, the therapeutic possibilities for the management of diabetes with adjunct medications have grown exponentially (see ISPAD 2024 Consensus Guidelines: Type 2 diabetes in Children and Adolescents for detailed information). The development of adjunct medications has offered new tools for improving not only glycemic management but also cardiovascular and kidney outcomes. There is minimal evidence for the use of adjunct medication in children and adolescents with T1D. Larger trials are needed to assess the impact on glycemic management, obesity, insulin resistance, long-term benefits with respect to microvascular and macrovascular complications, and the safety profile of these adjunctive therapies in the management of pediatric persons with T1D.

Inpatient Insulin Treatment

Insulin use during inpatient treatment of young people with T1D is required, particularly during DKA, perioperative management and severe infections. Intravenous

(IV) insulin infusion is preferred in critically ill children. Although regular insulin has traditionally been used for IV infusion for inpatient management of diabetes due to cost and availability, regular, rapid-acting, and ultra-rapid insulins are all equally suited for IV therapy [195]. Non-critically ill children admitted for hospital care could be treated with the currently used SC insulin regimen with some alterations to the dose [196].

Therapy with insulin in an inpatient setting might be necessary in certain other scenarios other than diabetes, such as hyperglycemia induced by stress peri-operatively, parenteral steroids, use of immunosuppressants during chemotherapy (L-asparaginase, tacrolimus, cyclosporine, sirolimus), neurologic drugs used during status epilepticus (valproate, phenytoin), and children with severe burns [197, 198].

IV Insulin Treatment

Treatment with IV insulin is the standard of care in the treatment of pediatric DKA [199] and is extensively reviewed in the ISPAD 2022 Consensus Guideline Chapter 13 on Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State [200].

Subcutaneous Insulin

While low-dose insulin infusion is the standard of care for DKA, SC insulin therapy with aspart or lispro or regular insulin have been used in the management of DKA in adults and children in some settings [201–205]. The treatment with SC insulin was important for the treatment during COVID-19 pandemic and was recently reviewed as an ISPAD Guideline Consensus [200]. This suggests use of SC administration of short-acting (regular) insulin every 4 h as another alternative treatment method in mild DKA when IV infusion or RAI analogs are not available [206]. A suggested starting dose is 0.13–0.17 units/kg/dose of regular insulin every 4 h (0.8–1 unit/kg/day in divided doses). Doses are increased or decreased by 10–20% based on the BGL before the next insulin injection [206]. Dosing frequency may be increased to every 2 or 3 h if acidosis is not improving [207, 208].

Insulin Availability and Affordability

Children and adolescents with T1D depend on insulin for survival and should have access to adequate amounts of appropriate types of insulin. Multiple global, national and health system factors impact the prescription of insulin and need to be considered to ensure that barriers do not impact the care provided to individuals by health professionals. Thus, an understanding and discussion of barriers to insulin access should be part of the interaction between healthcare providers and the people they treat. Health professionals should have intimate knowledge of the price of insulin; if insulin is available or not; and what insulin formulations are available in their country in both the public and private sectors. This knowledge should help guide persons with diabetes to find the most affordable option.

In parallel, health professionals can also play an active role in ensuring access to insulin by advocating for insulin to be included in the universal healthcare packages in their countries. The launch of the first global coverage targets for diabetes, including: "100% of people with T1D have access to affordable insulin and SMBG" presents the end goal that the diabetes community needs to meet. Affordability is essential for both health systems and individuals in order to ensure that the financial burden of insulin does not impact access to other fundamental elements of diabetes management, such as self-monitoring, healthcare workers, social support, etc. These considerations need to be included in how insulin, diabetes supplies and care are paid for with ideally these included in universal healthcare packages at the lowest cost or ideally free to the individual. Free insulin and care for individuals, however, requires that these costs be borne by the health system and society as a whole [209].

Perspectives and Conclusions

In recent years, the landscape of T1D management has witnessed a transformative shift, marked by groundbreaking research and novel developments in insulin therapies and closed-loop technologies [95]. In addition, the launch of the Global Diabetes Compact and first global coverage targets for diabetes, including specific targets for T1D, by the WHO, lay the foundations for policy and health system responses for T1D [209]. These advancements not only target enhanced glycemic management but also strive to improve the overall quality of life for individuals grappling with this chronic condition.

A century after its discovery, insulin treatment continues to evolve. While insulins with faster onset and shorter duration of action continue to be a hot topic, there has been significant progress in developing ultra-long-acting insulins. Clinical trials investigating the use of weekly insulin formulations have been promising in adult subjects but have not yet been tested in children.

Personalized medicine is gaining prominence in diabetes research, recognizing that each individual's response to insulin therapy can vary significantly. A new

generation of insulins, the smart insulins, will be very instrumental for precision diabetes management. Smart insulins are glucose-responsive insulin formulations that are chemically activated only if the glucose is above the target range; the insulin action ceases once BG is normalized. There are different investigational methods that are used to deliver smart insulins, and smart insulin formulations might be a game changer in diabetes treatment in the future if proven to be safe and efficient.

Beyond conventional insulin formulations, the development of synthetic insulins is at the forefront of innovation [210]. Researchers are engineering insulins with improved stability, longer duration of action, and reduced absorption variability. These advancements seek to address the challenges associated with current insulin therapies, such as the need for multiple injections and the risk of hypoglycemia. By refining insulin formulations, scientists aim to enhance treatment adherence and mitigate the burden on individuals managing T1D.

Combination of insulin with adjunctive medications is another novel intervention to enhance insulin treatment. Adjunct treatments have potential to address additional treatment challenges during T1D treatment such as the increasing rates of overweight and obesity in persons with T1D. However, as insulin is not a treatment for the underlying autoimmune condition in T1D, and even the most advanced diabetes technologies may add burden and are the risk of failure, disease modifying therapies and cellular solutions are prioritized in research [211]. Please see ISPAD Clinical Practice Consensus Guidelines 2024: Screening, Staging, and Strategies to Preserve Beta Cell Function in Children and Adolescents with T1D for detailed information [212].

In conclusion, the landscape of diabetes management is undergoing a profound transformation through innovative research into more physiological insulins, new methods to deliver insulin, pioneering diabetes technology and new adjuvant drugs as treatment modalities. As these diverse approaches converge, the prospect of a comprehensive and personalized treatment paradigm for youth with diabetes becomes increasingly promising.

Methodology

A literature search was conducted to gather updated evidence, using a combination of relevant medical subject headings (MeSH, Emtree) and free text terms specific to each chapter's focus. Studies published from 2021 to 2022 onward, related to children and young adults, were retrieved from MEDLINE. The Project Officer, in collaboration with chapter leads and co-authors, performed the literature searches. The resulting articles (with search terms summarized in the online suppl. material; for all online suppl. material, see https://doi.org/10.1159/000543169) were then uploaded to COVIDENCE for screening and review. Two authors/experts involved in drafting this guideline version independently screened the articles. Any disagreements were resolved by a third reviewer. Where relevant, further literature was included.

The draft chapter was posted on the ISPAD forum to allow feedback from the greater ISPAD membership. Modifications were made with authorship consensus, with the chapter receiving endorsement from the ISPAD editorial team. Literature search terms are summarized in online supplementary material 1.

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E.C. and L.P. co-directed the guideline development process. E.C., T.D., T.A., A.A., D.B., E.C., S.E., P.Z., L.N.W.M., S.M.N., M.P., and L.P. contributed equally to the content of individual chapters and participated in revising both the original manuscript and subsequent versions. E.C. synthesized these contributions to develop the original full draft of the guideline. L.P., as the editor of the guideline, supervised the overall development and revision process.

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