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ISPAD GUIDELINES

ISPAD Clinical Practice Consensus Guidelines 2022: Insulin treatment in children and adolescents with diabetes

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1 | WHAT IS NEW OR DIFFERENT

- Updated insulin treatment sections including new bolus and basal insulin formulations
- Refined recommendations on principles of intensive insulin treatment regimens
- Review of the role and rationale for new insulin analogs, biosimilars and diabetes technology devices for insulin therapy in pediatric diabetology
- Key considerations with regards to access to insulin and affordability

2 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

- Insulin treatment must be started as soon as possible after diagnosis (usually within 6 h if ketonuria is present) to prevent metabolic decompensation and diabetic ketoacidosis (DKA). **A**
- Intensive insulin regimens delivered by combinations of multiple daily injections or pump therapy with substitution of basal and prandial insulin aiming to have optimal glycemic level have become the gold standard for the treatment of diabetes in children across all age groups. **E**
- Insulin therapy must be individualized in order to achieve optimal glycemic targets to reduce complications of diabetes. **E**
- Achieving and improving glycemic targets by intensive insulin treatment have been conclusively shown to reduce diabetes complications, comorbidities, and mortality in adolescents and adults. **A** There is no reason to believe this is not the case also in younger children. **E**
- In all age groups, as close to physiological insulin replacement as possible and optimal glycemic control must be the aim using the locally available basal and prandial insulins. **A**
- Insulin treatment must be supported by comprehensive education appropriate for the age, maturity, and individual needs of the child and family regardless of the insulin regimen. **A**

- 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 if possible. **C**
- 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 blood glucose levels (BGLs). **B**
- All young people should have rapid-acting or regular insulin available for prevention and management of diabetes hyperglycemia and ketosis emergencies. **E**
- It is essential that a small supply of spare insulin should be readily available to all children and adolescents so that the supply is uninterrupted. **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. **B**
- Insulins need to be administered by insulin syringes or other injection devices calibrated to the type and concentration of insulin being used. **E**
- Regular checking of injection sites for site reactions, injection technique and skills to ensure proper insulin delivery remain a responsibility of parents, care providers and health professionals. **E**
- Health care professionals have the responsibility to advise parents, other care providers and young people on adjusting insulin therapy safely and effectively. This training requires regular review, pattern recognition, reassessment and reinforcement. **E**

3 | INTRODUCTION

Insulin has been the core life-saving treatment for diabetes since its discovery in 1921. Near normoglycemia has been well established as a goal of treatment of type 1 diabetes (T1D) 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* study (EDIC), confirmed that an improvement in long-term glucose control 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]

Despite significant advances in insulin treatment, clinical use of insulin is remarkably complex, and optimal glycemic control can be challenging to achieve and maintain. There is rarely a predictable treatment regimen that always applies to all persons, particularly for children and adolescents with T1D. The insulin requirement of children and adolescents with T1D is never static given the dynamic nature of growth, development, hormonal changes during childhood and adolescence, which necessitates frequent dose adjustments. Consequently, young people with T1D require a customized, highly dynamic, and engaging system to sustain optimal glycemic control and tackle multiple disruptors of daily life.

Exogenous insulin administration that recapitulates as closely as possible the physiologic pattern of insulin secretion by pancreatic β-cells has been considered the ideal insulin treatment to achieve optimal glycemic control. The physiology of insulin secretion includes a basal and a prandial pattern.[2] A healthy pancreatic β-cell secretes continuous basal (low level) insulin and an incremental postprandial (high level) insulin with meals to control BGLs in a tight range.[2] The fundamentals of pediatric insulin treatment attempt to replicate this pattern of basal insulin and prandial insulin secretion. This treatment approach has also been known as basal-bolus insulin or multiple daily insulin injection (MDI). This type of treatment allows more flexibility in the daily lives of persons living with diabetes by partially accommodating variable and sometimes unpredictable eating patterns. Furthermore, in randomized trials, better BG control has been achieved by using MDI regimens, either by insulin injections or pump treatment compared to a twice-daily insulin treatment.[1,3]

Young people with diabetes often require multiple daily injections of insulin, using combinations of rapid-, short-, intermediate-, or long-acting insulin before meals and at bedtime to maintain optimal BG control. Insulin pump treatment is another type of basal-bolus insulin treatment frequently used in children. There is some variation in insulin regimens, both within regions as well as among pediatric diabetologists in the same country, which may be explained by availability, cost or insurance coverage of newer insulin formulations or because of personal preference and experience of the individual with diabetes and their respective diabetes team.

The evolution of insulin formulations over the course of years has broadened the treatment options for the unique needs of young people with diabetes. New insulin analogs and diabetes technology tools have transformed insulin treatment during the past few decades. Regular and NPH/ultralente insulins that were used during the DCCT have been replaced by newer generation insulin formulations in many countries. The rapid-acting and long-acting insulin analogs were developed to provide a more physiologic insulin profile.

The availability of new insulins and the use of new technology have improved the management of diabetes. Increased risk of severe hypoglycemia was an adverse effect of intensive therapy during the DCCT.[1] In contrast to the DCCT experience, recent large diabetes registry studies have clearly shown a diminishing relationship of significant or severe hypoglycemia with lower glycemic targets in people with T1D.[4] On the other hand, the deleterious effect of hyperglycemia on the developing brain has been concerning and highlights the importance of controlling both hyperglycemia and hypoglycemia.[5]

4 | INSULIN FORMULATIONS

Insulin formulations (approved for pediatric use) are listed in Table 1 and are classified in three major groups as prandial, intermediate-acting and basal long-acting insulins. In general, prandial insulins consist of rapid-acting insulins that are intended for bolus injection before meals

TABLE 1 Types of insulin preparations (approved in pediatrics) and action profiles for subcutaneous (s.c.) administration

Insulin type	Onset of action (h)	Peak of action (h)	Duration of action (h)
Prandial insulins			
Ultra-rapid-acting analog (faster aspart)	0.1–0.2	1–3	3–5
Rapid-acting analogs (aspart, glulisine and lispro[a])	0.15–0.35	1-3	3–5
Regular/soluble (short acting)	0.5–1	2–4	5–8
Intermediate acting insulin			
NPH[b]	2–4	4–12	12–24[c]
Basal long-acting analog			
Glargine[a]	2–4	8–12	22–24[c]
Detemir	1–2	4–7	20–24[c]
Glargine U300	2–6	Minimal peak	30–36
Degludec	0.5–1.5	Minimal peak	>42

Note: 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 affected by the dose; that is, large doses tend to last longer than small doses.
[a]Biosimilar formulation approved in some countries.
[b]NPH: neutral protamine hagedorn insulin; isophane insulin.
[c]The duration of action may be shorter.

or use in insulin pumps. Basal insulins are long-acting insulins that are intended to be injected not more often than once or twice a day.

4.1 | Prandial insulins

Prandial insulin boluses attempt to mimic endogenous insulin secretion in response to a meal. In response to food intake, the β-cell normally releases insulin in a rapid first-phase followed by a second-phase with prolonged release of insulin into the portal circulation. Rapid-acting insulins (RAI) have been developed to more closely mimic the physiological response of endogenous human insulin to food intake, to improve control of postprandial BG excursions, and to reduce the risk of hypoglycemia.[6] A correction insulin bolus dose of RAI can be given premeal or in-between meals to normalize glycemia.

4.1.1 | Regular (short-acting) insulin

Regular soluble insulin (identical to human insulin) is still used as an essential component 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.

4.1.2 | Rapid-acting insulins

RAI is manufactured by modifying human insulin, namely, by changing the amino acid sequence or by the addition of free fatty acid chains to the original molecule that primarily leads to altered absorption from the subcutaneous tissue. These alterations serve one of two main purposes; (1) mimic physiologic prandial insulin secretion by accelerating insulin absorption into the bloodstream for a rapid onset of action relative to human regular insulin and (2) shorter duration of action that provides enough time to control postprandial BGLs while preventing late hypoglycemia.

RAIs have a more rapid onset of action and a shorter duration of activity compared to regular human insulin when administered subcutaneously. This glucose lowering action profile of RAI allows for insulin injection closer to meal onset, allowing postprandial glycemic control with greater flexibility in daily life. In brief, one unit of RAI has the same glucose-lowering effect as one unit of regular insulin, however, the timing profile differs between regular insulin and the RAI.

Three RAIs are approved for use in adult and pediatric persons: 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, but no significant clinical outcome differences in time of action and duration have been reported.[7–10] They all have a rapid onset and shorter duration of action than regular insulin (Table 1).

We recommend considering the following points when using RAI

- RAI should be given ideally 10–15 min before meals or immediately before meals given the strong evidence that the rapid action not only reduces postprandial hyperglycemia, but nocturnal hypoglycemia may also be reduced.[11–15]
- 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.[14] Nevertheless, premeal insulin dosing results in lower postprandial BG values for children with more predictable eating habits.[11]

- When hyperglycemia is present, RAI should be given in advance of eating.
- RAIs correct hyperglycemia, with or without ketosis, quicker than soluble insulin owing to their faster glucose-lowering action.
- Are used as prandial or snack boluses in combination with longer acting insulins (see basal bolus regimens).
- Are used in insulin pumps.

4.1.3 | Ultra-rapid-acting insulins

Faster onset and offset of insulin action, replicating physiologic insulin action, is highly desirable to provide greater glycemic control, minimize hypoglycemic episodes and reduce weight gain.

Ultra-rapid-acting insulins are intended to improve the time-action profile of prandial insulins to cover the rapid increase in BG after meals and may be particularly useful for pumps and automated insulin delivery (AID) systems. Because human insulin and RAI generally exist in solution as stable hexamers, the delay in absorption is largely accounted for by the time it takes for hexamers to dissociate into monomers and dimers before they enter the circulation. Faster-acting insulin aspart contains the excipients niacinamide and L-arginine to speed up the monomer formation. This new insulin has a faster onset and offset than aspart insulin and should better control initial post-meal spikes in BGLs and causes less hypoglycemia hours later.[16] The ultra-fast-acting insulin aspart has been approved by the European Medical Agency (EMA) for (children ≥1 year old) and the U.S. Food and Drug Administration (FDA) for (children ≥2 years old).[16]

In children and adolescents with T1D (1–18 years old), mealtime and postmeal faster-aspart combined with insulin degludec provided effective glycemic control compared to insulin aspart in a multicenter, randomized, double blind clinical trial of 26 weeks duration. There were no additional safety concerns for insulin faster-aspart versus insulin aspart throughout the study.

Ultra-rapid-acting lispro is approved for adults with diabetes. The pharmacodynamic and pharmacokinetic action of ultra-rapid-acting lispro has been investigated in a small-scale meal study in children (6–18 years old); however, it is not yet approved for young people with diabetes.

Other investigational ultra-rapid-acting insulin analogs (BioChaperone® Lispro, AT 247)[17] are being tested in adult subjects with diabetes.

Human insulin inhaled powder is the fastest acting exogenous insulin given that the insulin is absorbed quickly from the lungs eliminating the delays after subcutaneous injection. It has been approved in adults with diabetes but is not yet approved for children. A clinical trial of this inhaled insulin for pediatric use is ongoing.

4.2 | Intermediate-acting insulin

For over half a century, isophane NPH (neutral protamine Hagedorn) was the primary form of basal insulin used. The addition of protamine to insulin delayed the dissociation of insulin and slowed the absorption of insulin monomers into the circulation. The duration of action of NPH is longer than that of human regular insulin, but is not sufficient to sustain daily physiological basal insulin needs for people with severe insulin deficiency when given once a day. Its action profile requires twice daily administration to provide the background insulin needed to regulate lipolysis and hepatic glucose production.[18] The strategy is hampered by a small peak that occurs 4–7 h after administration.[19,20]

Insulin regimens based on intermediate-acting NPH and short-acting (regular) insulins have been used for decades to regulate BGLs, however, are limited in their ability to achieve optimal glycemia given the limitations of their insulin action profiles. First, the use of NPH requires a fixed schedule of meals and snacks throughout the day to avoid hypoglycemic events. Second, even more problematic, is the small peak action that occurs with the evening NPH dose. This peak glucose lowering action occurs at the time of minimal insulin need between midnight and 4 am, increasing the risk of nighttime hypoglycemia.[21] In addition, the dose-effect dissipates in the early morning hours (i.e., 4 to 8 am) during the time of greater insulin requirements, contributing to morning hyperglycemia and the so-called "dawn phenomenon"[22] A third problem of NPH insulin is the high day-to-day variability of its glucose lowering action.[19] 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.[23] The greater variability of the glucose lowering action of NPH insulin compared with newer basal insulins has been verified by various studies.[19,24,25]

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 RAI. The peak of NPH action given in the morning may provide some insulin coverage for 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 amount of carbohydrate everyday[26,27] NPH has been used with regular insulin to prevent hyperglycemia due to intermittent enteral feeds for persons with T1D and T2D.[28,29] 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.[27,30]

4.3 | Basal insulin analogs

A basal insulin analog is intended to mimic the steady insulin secretion profile of a healthy pancreas during the fasting state. The action of basal insulin secretion is fundamental to stop ketogenesis and hepatic glucose output. Basal insulin coverage may be achieved by subcutaneously injected basal insulin analogs that are grouped as long-acting insulins or continuous subcutaneous infusion of rapid-acting insulin analogs by an insulin pump.

Glargine. Insulin glargine was the first of the newer generation of basal insulin analogs and largely eliminated the need for twice-daily

NPH. Glargine has two modifications made to the human insulin structure including a glycine substitution for asparagine on position A21, and two arginine residues attached to the carboxy-terminal of the beta chain. The resulting shift of the isoelectric point makes glargine soluble at a pH of 4, and precipitates in the neutral pH of subcutaneous fat. This allows for 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 from persons in regard to stinging and burning on injecting, yet overall studies appear to show greater quality of life and satisfaction compared to NPH.[31–33]

A multi-national randomized controlled trial (RCT) with 125 children aged 2–6 years using continuous glucose sensors showed once a day glargine was as efficacious as twice daily NPH.[34] While the ideal is to minimize injections and keep glargine to a once daily administration, there are situations that may warrant twice a day regimen.[35,36]

Detemir. Insulin detemir has the amino acid threonine at B30 omitted and a 14-carbon fatty acid covalently attached to the lysine at B29. The fatty acyl side chain stabilizes the hexamers and prolongs the persistence of insulin detemir at the injection site by slowing hexameric dissociation and subsequent monomeric absorption. In addition, the fatty acyl chain enables binding to serum albumin and reduces the amount of free insulin available for engagement with insulin receptors. Subsequently, the disposition of detemir to peripheral tissues and its clearance from the body are slower than regular insulin. Insulin detemir has a slow onset of action, with a peak at 4–7 h and a duration of action up to 20–24 h. The complex then dissociates with a time frame between 6 and 23 h. Anecdotally, detemir insulin causes less local pain compared with the injection of glargine, which is an acidic solution.

Detemir may be administered once or twice daily based on clinical needs and BGL monitoring, but frequently two daily doses are required given its shorter duration compared to glargine. In a pediatric study, 70% of the participants used detemir twice daily.[37] In another trial twice daily detemir showed no clinical advantage over once daily detemir, but those in active puberty often required twice-daily therapy.[38]

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 control.[39]

Detemir is characterized by a more reproducible pharmacokinetic profile than glargine in children and adolescents with T1D. In comparison to glargine, detemir was shown in a double-blind RCTin children 8 yo to 17 yo with T1D to have less within subject variability.[40] Detemir use has been shown to reduce risk for overall and nocturnal hypoglycemia versus NPH in a 52 week study[24] and a lower risk of nocturnal and severe hypoglycemia compared to glargine in a multicenter study.[41]

In adults, studies with detemir have shown less weight gain, which has been observed also in children and adolescents. Although the precise mechanism remains unclear, it is likely that the weight-sparing effect of insulin detemir can be explained by a combination of mechanisms.[42] Human studies have shown changes in cerebral mechanisms leading to decreased appetite with detemir infusion as well as preferential liver utilization over peripheral tissue resulting in less lipogenesis.[42–47]

Detemir is approved for children by EMA for children ≥1 year old and FDA for children ≥2 years old.

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 subcutaneous depot. There is less diurnal variation in glucose-lowering activity with U-300 compared with the same dose of U-100 glargine.[48] The full glucose lowering effect may not be apparent for at least 3 to 5 days of use. The EDITION 4 trial, which was a randomized study in adults with T1D, and the EDITION JUNIOR trial, focusing on persons 6–17 years old with T1D, showed non-inferiority of glargine U300 to glargine U100 with similar rates of hypoglycemia and similar glycemic control.[49] However, some studies have shown that glargine U300 has reduced nocturnal hypoglycemia and improved glycemic stability compared to glargine in adults with T1D.[50,51]

U300 is EMA and FDA approved for children ≥6 years.[52]

Degludec. Degludec is a novel ultra-long-acting analog (glucose lowering effect beyond 24 h after subcutaneous injection). The insulin degludec molecule is structured by omitting the B30 threonine from the human insulin molecule 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 multihexamers after subcutaneous administration, which then slowly dissociate and results in a slow and stable release of degludec monomers into the circulation. Moreover, the binding of monomers 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.[53] The pharmacokinetics also allow a lot of 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.[54]

Results in young people indicate that the long-acting properties of degludec are preserved also in this age group.[55] 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 a 24-h period. 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.

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 (RCT) in children 1–17 year with T1D, for 26 week ($n = 350$), followed by a 26-week extension ($n = 280$). Degludec achieved equivalent long-

term glycemic management, 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.[56] Degludec is EMA and FDA approved for children with diabetes ages 1 year and older.[57]

Once weekly basal analogs. There is ongoing research to develop novel basal insulin analogs intended 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. There are currently no pediatric data for once weekly insulins.[58,59]

4.4 | Premixed insulin

Premixed insulins contain a fixed ratio mixture of premeal 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 inferior metabolic control 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 TIDM using premixed insulin as compared to a basal-bolus insulin regimen.[60]

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.[23]

The most recent addition to the premixed insulin analog group is a mixture of rapid-acting insulin 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.[61]

Degludec/aspart is approved for children with diabetes by the EMA (children ≥2 year old) and FDA (children ≥1 year old).[62]

4.5 | Safety of insulin analogs

As insulin analogs are molecules with modified structure compared with human insulin, safety concerns have been raised due to changes in mitogenicity in vitro.[63] A potential link between glargine and cancer has been postulated, but in 2013 EMA concluded that insulin glargine–containing medicines (Lantus®, Optisulin®, Sanofi) for diabetes do not show an increased risk of cancer.[64]

4.6 | 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 United States 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).[65,66]

4.7 | Insulin concentrations

The most widely available insulin concentration is 100 IU/ml (U 100). 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 (U-200, U-300, U-500) 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), most commonly in adults.

Very young children, infants, and toddlers occasionally require small insulin doses, 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 manufacturer diluent is not available. Rapid-acting insulin can be diluted to 1/10 (U10) or U50 with sterile NPH diluent and stored for 1 month[67] for use in pumps

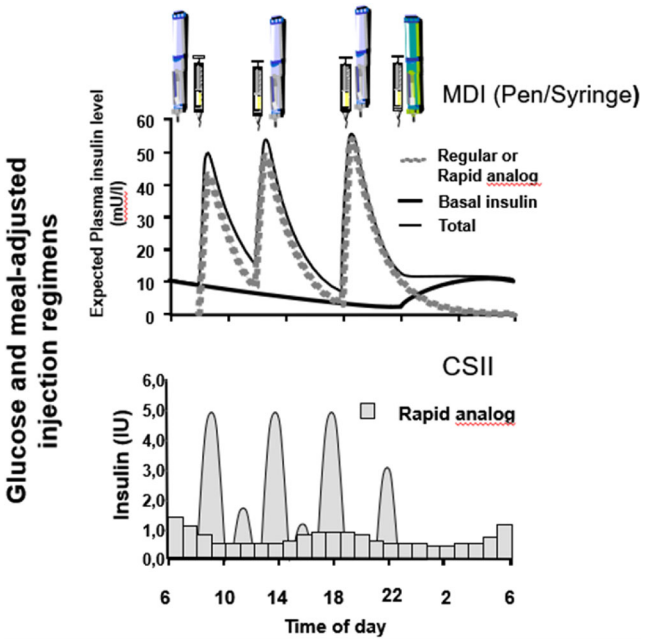

FIGURE 1 Schematic representation of frequently used regimens for insulin therapy in children with diabetes

for infants or very young children. Insulin diluted in a 1/5 ratio (U20 insulin; 20 units/ml) has been used successfully during automated insulin treatment in young children (3–6 years old) with T1D.[68–72] Dosing errors with unconventional insulin concentrations can be serious. Special care is needed in dilution and drawing up the insulin into the syringe. 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.

5 | PRINCIPLES OF INSULIN THERAPY

5.1 | 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 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[73] for insulin delivery and is depicted in Figure 1.

I. ***Glucose- and meal-adjusted injection regimens***

- Prandial insulin should be injected before each meal, and ideally giving a dose before snacks as well. Insulin doses are adjusted based on pre-meal glucose level, meal composition (particularly amount and type of carbohydrates) and expected physical activity in the coming hours. Prandial insulin daily requirements are approximately 55% to 70% of total daily dose.
- Basal/long-acting analog is administered once or twice daily; and is approximately 30%–45% of the total daily dose.
- Rapid-acting insulin immediately before[11,12] 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.[74,75] Ultra-fast-acting analogs may be given closer to the meal.[76–80] If regular insulin is used as prandial insulin, it should be administered 20–30 min before each main meal.[81]

II. ***Pump therapy***

- Insulin pump therapy is extensively reviewed in the chapter "*Technology: Insulin Delivery*" (see ISPAD 2022 consensus guidelines Chapter 17 Technology: Insulin Delivery for details)

III. ***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.
  - Three injections daily using a mixture of short-or rapid- and intermediate-acting insulins. Beyond the remission or honeymoon period, two injection regimens cannot control BG, and can cause frequent hypoglycemia (particularly in the context of food insecurity) and hyperglycemia
  - Different variations of the timing of administration have been used, but all these therapeutic schemes require a rigid schedule for meals and injections.
  - Prandial insulin is adjusted by glucose levels and 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 it 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.

6 | GUIDELINE ON INSULIN DOSAGE

The appropriate insulin dosage is one that will achieve the best glycemic control for an individual without causing hypoglycemia, hyperglycemia and reducing the likelihood of development of long-term complications. Insulin dosing may be dependent on many factors such as:

- Age
- Weight
- Stage of puberty
- Duration and phase of diabetes
- State of injection sites
- Nutritional intake and distribution
- Exercise patterns
- Daily routine
- Results of BG monitoring and glycated hemoglobin
- Intercurrent illness
- Menstrual cycles

Within a few weeks after the initiation of insulin therapy, it is common for a young person with newly diagnosed diabetes 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 to 1.0 IU/kg/day and during puberty, insulin dose requirements may rise to between 1 and 2 IU/kg/day.[82] The elevated requirements of insulin during puberty are in part explained by the higher growth hormone secretion that characterizes this period[83] 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.[84–86]

Higher BGL may be observed during the luteal phase of the menstrual cycle mediated by progesterone.[87,88]

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 to be combined with NPH to provide full daytime basal insulin coverage.[36,89] Glargine can be given before breakfast, before dinner or at bedtime with equal effect, but nocturnal hypoglycemia occurs significantly less often with breakfast injection.[19] When switching to glargine as basal insulin, the total dose of basal insulin needs to be reduced by approximately 20% to avoid hypoglycemia.[89] Thereafter, the dose should be individually adjusted according to BG trends.
- Detemir is most commonly given twice daily in children.[37,90] 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.[39] A twice daily regimen consisting of NPH injection in the morning and detemir injection at night time with RAI for breakfast and dinner has been used to optimize glycemic control during the honeymoon phase of T1D as a bridge to insulin pump treatment.[27] A broad range of dose adjustments have been described in various small scale studies while switching from glargine insulin to degludec (100%–150% of the glargine dose).[91,92] Minor increase in basal insulin ratio with respect to total daily dose of insulin has been experienced in prepubertal subjects.[92]
- Degludec is administered once daily and can be given at any time. In pediatric persons, 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 need and glycemic excursions after lunch and snacks in children who are unable to receive insulin injections at school.[26]

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 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).[93] 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.[94] 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.

- The insulin: carbohydrate ratio (ICR) 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 BG before and after the meal differ more than 2 to 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 for deciding bolus doses. See ISPAD 2022 Consensus Guidelines Chapter 10 on Nutritional Management in Children and Adolescent with Diabetes for further details.
- 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 one unit of rapid-acting insulin will lower the BG; for groups that are more insulin resistant, the insulin sensitivity factor has also been calculated dividing 1500 by the total dose. For mmol/L, use the "100 rule," that is, divide 100 by total daily insulin dose.[95] The "1500 rule" maybe used when regular insulin is used for correction dosing.

6.1 | 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.

6.1.1 | Soon after diagnosis

Insulin adjustments should be made frequently to achieve the target BGLs soon after a new diagnosis of T1D. Many centers make daily insulin dose adjustments during the first few week of diagnosis.[96] The appearance of the honeymoon period requires drastic and prompt decreases in insulin daily dose to avoid hypoglycemia.[97,98]

6.1.2 | Insulin dose adjustments for well-established diabetes

Adjustments of insulin dosing are made before meals and adjusted based on glucose levels, obtained either by frequent SMBG or CGM.[89] The long-acting basal insulin dose is titrated to regulate overnight, fasting glucose level. Postprandial hyperglycemia is best controlled by a well-timed injection of prandial insulin and sufficient insulin coverage for the food intake. Correction dose should be added to the prandial insulin dose if premeal BGL is above target range. Post-prandial 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.

6.2 | Advice for persistent trend deviations from target BGL

- For elevated glucose level before breakfast—the advice is to increase pre-dinner or pre-bed intermediate- or long-acting insulin dose (glucose determination during the night are recommended to ensure that this change does not result in nocturnal hypoglycemia).
- For elevated BGLs after a meal—the advice is to increase pre-meal ultra-rapid/rapid/regular insulin dose.[99]
- For elevated BGLs before lunch/dinner meal—the advice is to increase pre-breakfast basal insulin or increase dose of pre-breakfast ultra-rapid/rapid/regular acting insulin if on a basal-bolus regimen. However, snacking before the meal without an insulin dose should be ruled out. When using rapid-acting insulin in a basal-bolus regimen, the dose or type of basal insulin may need to be adjusted if BGLs rise several hours after the meal (during the post-prandial fasting state) as the analog insulin has most of its effect within 2 to 3 h after injection.[95] 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%.[100,101] 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.[102]
- Administration of rapid-acting insulin analogs ~15 min before mealtime results in lower postprandial glucose excursions and more time spent in the 3.5–10.0 mmol/L range, without increased risk of hypoglycemia.[75]
- When using carbohydrate counting, persistent elevations of post-meal glucose levels may require adjustment to the insulin to carbohydrate ratio.[103] If post-prandial hyperglycemia persists after correction insulin dosing, the insulin sensitivity factor 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 advice may be helpful when there are changes of routines, travel, school outings, educational holidays/diabetes camps, or other activities which may require adjustment of insulin doses.

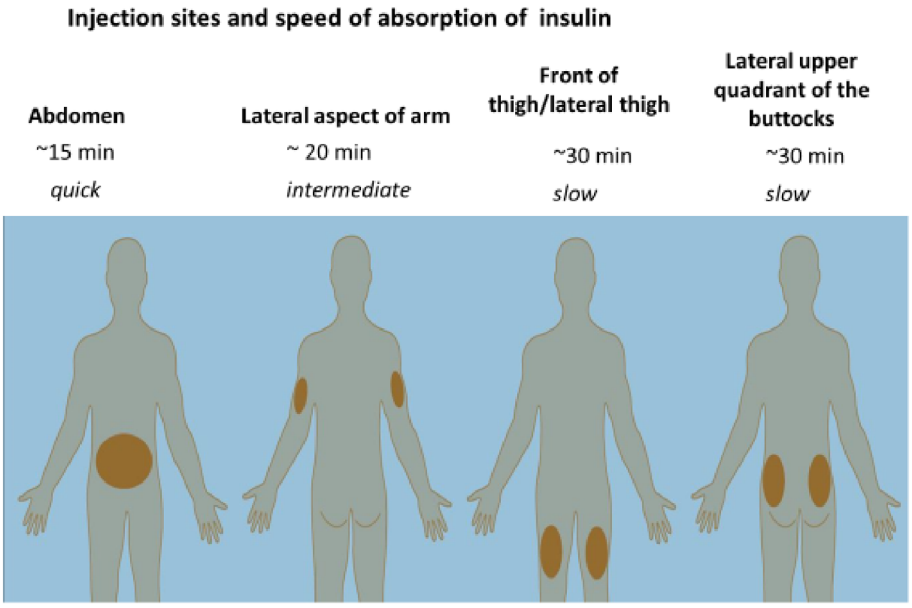

FIGURE 2 Schematic representation of injection sites and relative timing of insulin absorption (Insulin [regular insulin, rapid acting insulin analogs and NPH] is more readily absorbed from the abdomen and deltoid region compared to thigh and buttocks. The long acting insulin preparations has been reported to be less susceptible to changes in absorption rate associated with the site of injection)

7 | ADMINISTRATION AND STORAGE OF INSULIN

7.1 | Insulin injection and absorption

7.1.1 | Injection technique (IT)

Proper insulin injection technique is essential to use insulin safely and optimize glucose control. Insulin should be injected into subcutaneous tissue, not intramuscularly given that intramuscular injection can lead to more rapid and unpredictable insulin absorption and variable effects on glucose. The insulin injection sites are shown in Figure 2, and most important aspects of IT are described in Table 2.

Several other aspects are important when considering the injection technique;

- Needle length. The traditional needle length of 8–13 mm (27 G) were replaced by 4–6 mm needles given that longer needles might increase the risk of intramuscular (IM) injections. The probability of IM injection with the 6 versus 4 mm needle was reported to be dramatically higher in children and adolescents.[104]
- Insulin injections with 4 mm needles has been shown to be the safest strategy for preventing IM injections in children and adolescents.[105]
- 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 subcutaneous injection, avoiding intramuscular injection.[106] 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.[107]
- With 4–6 mm needles, the injections can be given perpendicularly without lifting a skin fold but only if there is enough subcutaneous fat, which often is the case in pubertal girls (at least 8 mm as the skin layers often are compressed when injecting perpendicularly).[108] Lean boys, however, have a thinner subcutaneous fat layer, especially on the thigh.[108,109] When injecting into the buttocks, the subcutaneous fat layer is usually thick enough to inject without lifting a skin fold. There is a risk of intradermal injections if 4–6 mm needles are not fully inserted into the skin.
- Rotation of insulin injection sites, within the same injection region, should be taught from diagnosis.
- Pen injection technique 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,[18] 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.[18]
- Injecting cold insulin can sometimes make the injection more painful, therefore, it is recommended that insulin is injected when it is at room temperature.
- A delay of 5–15 s after pushing in the plunger helps to ensure complete expulsion of insulin through the needle.[110]
- Leakage of insulin is common and cannot be totally avoided. Encouraging slower withdrawal of needle from 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 whenever 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

TABLE 2 Most important aspects of the injection technique

1. Have individuals demonstrate their injection technique, either by performing an actual injection or by injecting into a pad or foam pillow. Use this as a teaching occasion, praising what they do correctly and correcting any improper practices.
2. Injections should only be given into clean, healthy sites using clean hands. Disinfecting the skin is generally not required.
3. Injections must be given subcutaneously, not intramuscularly. The 4 mm pen needle has the lowest risk of IM injection and allows wider zones for rotation.
4. Needles that are 12.7 mm in length are not recommended for anyone and persons using 8 mm needles should be switched to shorter ones.
5. The 4 mm needle is preferred for all injectors regardless of age, sex, ethnicity, or BMI. It should be inserted perpendicular to the skin (90° to skin surface)—not at an angle—regardless of whether a skinfold is raised.
6. Very young children (≤6 years of age) and very thin adults (BMI <19 kg/m^2) should always inject with a 4 mm needle into a lifted skinfold. Other children, adolescents, and adults may inject without a skinfold.
7. Inspect injection sites during each visit, at a minimum annually, both visually and by palpation to aid in detection of lipohypertrophy. Make persons aware of the presence of any lipohypertrophy (LH), and instruct them not to inject into it. Use the LH lesion to teach them what to feel and look for and engage them in surveying their injection sites.
8. If lipohypertrophy is found, switch injections to healthy tissue and decrease the dose of insulin. Reductions often exceed 20% of the original dose. Closely monitor SMBG results.
9. Rotate injections systematically to avoid lipohypertrophy, injecting at least 1 cm (approximate width of an adult finger) from previous injections.
10. If possible, avoid reusing needles, which are sterile, one-use devices. Excessive reuse (more than five times) has been associated with lipohypertrophy.

cause drops of insulin appearing on the tip of the pen needle, if withdrawn too quickly.

- Inspection of injection sites and screening for lipohypertrophy regularly is essential to detect insulin injection site scar tissue. Injection sites should be inspected and palpated by diabetes care professionals at every clinic visit and more frequently if lipohypertrophy is detected. Self-inspection of insulin injection sites is recommended in between clinic visits.

Self-injection

There is great individual variation in the appropriate age for children being able to self-inject, depending on developmental maturity rather than chronological age. Most children over the age of 10 years either give their own injections or help with them.[111] Younger children sharing injection responsibility with a parent or other care provider may help to 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 overnight stay with a friend, school excursion or diabetes camp. Parents or care providers should not expect that self-injection will automatically continue and be prepared to resume responsibility for the child's insulin injections. Younger children on multiple injection regimens may need help to inject in sites difficult to reach (e.g., buttocks) to avoid lipohypertrophy.

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. Rapid-acting insulin analogs may be mixed in the same syringe with NPH immediately before injecting.[112] It is recommended that neither glargine insulin nor detemir insulin be mixed with any other insulin before injection,[113] because this mixture blunts the early glucose lowering action and prolongs the time-action profile of the rapid-acting insulin as compared with separate injection of the analogs.[113,114]

7.1.2 | Injection site adverse events

Lipohypertrophy is a common complication of insulin therapy. Injection site rotation is necessary to avoid lipohypertrophy, an accumulation of subcutaneous fat in response to the adipogenic actions of insulin at a site of multiple injections.

- Lipoatrophy is rare since the introduction of highly purified insulins; however, recent reports suggest that the frequency of lipohypertrophy continues to be high.[115] Reduction of lipohypertrphy is proven to improve glycemic control. Examination and palpation of insulin injection sites for the presence of lipohypertrophy and other site reactions should be performed during each clinic visit.[116]
- Painful injections are a common concern in children. We recommend checking angle, length of the needle, and depth of injection to ensure injections are not being given intramuscularly and that the needle is sharp if there are concerns regarding painful injections. Reused needles can cause more pain.[117,118] A proportion of people with diabetes have a severe long-lasting dislike of injections which may influence their glycemia. For these persons, an indwelling catheters (Insuflon®, i-port®) or insulin pump therapy can decrease injection pain[118–120] and may improve treatment compliance.[120] These devices may help with frequent injections in the very young child.[118]
- 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 the 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 intramuscular injection or tight squeezing of the skin. Use of thinner needles have been shown to result in significantly less bleeding at the injection site.

7.1.3 | Insulin absorption

Insulin activity profiles show substantial variability both day to day in the same individual and between individuals. Many factors affect 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[121–123]:

- **Insulin concentration, volume and dose (the subcutaneous depot.)**. Smaller subcutaneous depot,[123] lower insulin concentration[124] 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.[113,114]
- **Injection site**. Regular insulin is absorbed fastest from the abdomen, slower from the arm, followed by the thighs and buttocks (Figure 1).[125] These regional differences are less apparent with rapid- and long-acting insulin analogs.[121,122,126,127] The absorption of glargine[128] and degludec are not significantly influenced by the injection site.[129]
- **Intramuscular (IM) injection.** IM administration route is associated more rapid insulin absorption, which is more evident during exercise.[130,131] 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.[132,133]
- **Exercise**. Insulin absorption can be increased with exercise, with the location and depth of the injection being contributing factors.[134] Leg injection with leg exercise leading to faster absorption.[135] Glargine is not affected by exercise.[136,137]
- **Lipohypertrophy**. Lipohypertrophy significantly delays insulin absorption.[138]
- **Obesity**. Increased subcutaneous fat delays insulin absorption due to a reduction in subcutaneous blood flow.[139]

Two devices which apply heat to the injection site have been developed which have been shown to decrease insulin requirements and enhance insulin absorption leading to an earlier peak of insulin action together with less hypoglycaemia. *Insupad* is a device that warms an area 2 cm x 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.[132]

7.2 | Devices for insulin delivery

7.2.1 | Insulin syringes

Syringes are available in a variety of sizes in different countries, ensuring accurate dose delivery, but 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.[140]
- Small syringes with half- or one 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.
- Insulin syringes must have a measuring scale consistent with the insulin concentration (e.g., U 100 syringes).
- 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).
- It is advisable that 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.

7.2.2 | Pen injector devices

Pen injector devices containing insulin in prefilled cartridges have been designed to 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 subcutaneous tissue, in order to give time for any air bubble in the cartridge to expand.[110,140] Pens need to be primed before use, so that a drop of insulin shows at the tip of the needle.

Special pen injection needles of small size (4–6 mm) and diameter are available and may cause less discomfort on injection.[141] Pen injectors of various sizes and types are available from the pharmaceutical companies. Some pens can be set to half 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 are 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 should not be shared.

7.2.3 | 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,[118] especially in the very young child. The use of indwelling catheters does not negatively affect metabolic control.[120] In children with injection problems, HbA1c has been lowered by using Insuflon.[119] However, the use of a basal analog and a short- or rapid-acting insulin at the same injection time in an indwelling catheter is not advisable in case of possible interaction of the two insulins.[113,114,119] Indwelling catheters should be replaced every 2–4 days to prevent scarring and a negative effect on insulin absorption.[142,143]

7.2.4 | 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.[144]

7.2.5 | Jet injectors

High-pressure jet injection of insulin into the s.c. 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 control comparable both to conventional injections and continuous subcutaneous insulin infusion (CSII),[145] but problems with jet injectors have included a variable depth of penetration, delayed pain and bruising.[146] 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.[147]

7.2.6 | Continuous subcutaneous insulin infusion

The use of external pumps is increasing and is proving to be acceptable and successful,[145–154] even in young infants.[148,149] For extensive review of CSII please see ISPAD 2022 consensus guidelines Chapter 22 on "Diabetes Technology: insulin delivery."

7.3 | Storage of insulin

7.3.1 | 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.[155]

Refrigeration problems may be more frequent than apparently thought, household refrigerators often do not meet manufacturers' recommendations, with temperatures often dropping below freezing point.[156] 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.[157]

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 considered as 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.

- When not in use, insulin can be stored in a refrigerator at 2–8°C, until the expiration date (not in or too near the freezer section or cooling element).
- Insulin should be discarded if it has been frozen, as freezing can compromise the integrity of both the formulation and the vial itself.

7.3.2 | 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.[158]

- When in use, insulin can be stored at room temperature (below 25 or 30°C) for up to 4 weeks.[145,155,159]
- The time period recommended for use after opening a vial varies between 10 days and 8 weeks for different insulin formulations. We recommend following manufacturer's guidelines and drug inserts. Utilizing smaller volume penfills rather than vials will avoid wastage in children on smaller doses of insulin.
- 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 6 and 7 days, respectively. Ideally, the insulin in the reservoir should be changed with infusion set/ line changes every 48–72 h. 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 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 provides a warning when temperature limits are exceeded.

7.3.3 | 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).
- Insulin should not be in the checked baggage but should always be in the hand luggage carried in the cabin.
- Traveling with extra, back-up insulin is recommended.

8 | INPATIENT INSULIN TREATMENT

Insulin use during inpatient treatment of young people with T1D is required during DKA, peri-operative management and severe infections. Intravenous insulin infusion is preferred in critically ill children. Regular and rapid-acting and ultra-rapid insulins are equally suited for IV therapy.[160] Regular insulin has traditionally been used for IV infusion for inpatient management of diabetes. Non-critically ill children admitted for hospital care could be treated with the currently used subcutaneous insulin regimen with some alterations to the dose.[161]

Therapy with insulin in an inpatient setting might be necessary in certain other scenarios such as hyperglycemia induced by stress perioperatively, 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.[162,163]

8.1 | Intravenous insulin treatment

Treatment with intravenous insulin is the e standard of care in treatment of pediatric DKA[164] and is extensively reviewed in the ISPAD 2022 Consensus Guideline Chapter 13 on Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State.

8.2 | Subcutaneous insulin

While low-dose insulin infusion is the standard of care for DKA, subcutaneous insulin therapy with aspart or lispro or regular insulin have been used in the management of DKA in adults and children in certain hospitals around the globe.[165–169] The treatment with subcutaneous insulin was important for the treatment during COVID-19 pandemics and was recently reviewed as an ISPAD Guideline Consensus. This suggests use of subcutaneous administration of short-acting (regular) insulin every 4 h as an another alternative treatment method in mild DKA when IV infusion or rapid-acting insulin analogs are not available.[165] 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.[165] Dosing frequency may be increased to every 2 or 3 h if acidosis is not improving.

9 | INSULIN AVAILABILITY AND AFFORDABILITY

Children and adolescents with T1D depend on insulin for survival and should have access to adequate amounts of at least regular and NPH insulin. ISPAD and the international diabetes federation (IDF), through the Life for a Child program, are working toward making insulin available for all children and adolescents with diabetes and promoting universal insulin labeling.

Although 2021 marked the Centenary of the discovery of insulin, access to this life-saving medicine remains problematic in many settings.[170] The concept of access to insulin needs to be considered with two factors in mind. First, availability: is insulin at the facility or pharmacy when the individual goes to get it.[171] Second, affordability: can the individual pay for their 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 public and private sectors. This knowledge should help guide persons with diabetes to find the most affordable option to ensure that people with diabetes engage with their insulin regimen as desired.

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 Health Care packages in their countries.

10 | RESEARCH AND NEW DEVELOPMENTS

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

not yet tested in children. Another exciting development is *smart insulins*. 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.

Combination of insulin with adjunctive medications is another novel intervention to enhance insulin treatment. Long-acting insulin (insulin glargine or degludec) and glucagon-like peptide-1 (GLP-1) receptor agonist premixed injectable products are approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin. Adjunct treatment with premixed insulin has a potential utility to address additional treatment challenges during T1D treatment such as the increasing rates of overweight and obesity in persons with T1D.

Insulins of today continue to save lives of children with diabetes, and insulins of tomorrow will be key to improve the way we treat diabetes and ease the burden of diabetes for people with diabetes.

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CONFLICT OF INTEREST

E. Cengiz is a scientific advisor for Eli Lilly, Novo Nordisk, Adocia and Arecor. TD has received speaker's honoraria and research support from or has consulted for Astra Zeneca, Bayer, Boehringer, Dexcom, Eli Lilly, Lifescan, Medtronic, Novo Nordisk, Provention Bio, Roche, Sanofi, Ypsomed and is a shareholder of Drea Med Ltd. TA, JF, DB, SH, MP, E. Codner have no disclosures.

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