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ISPAD CLINICAL PRACTICE CONSENSUS GUIDELINES

ISPAD Clinical Practice Consensus Guidelines 2018: Insulin treatment in children and adolescents with diabetes

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1 | SUMMARY OF WHAT IS NEW/DIFFERENT

Refined recommendations on intensive regimens for differential substitution of basal and prandial insulin.

Review of the role of new insulin analogs, biosimilars, and devices for insulin therapy in pediatric diabetology are included.

2 | RECOMMENDATIONS/EXECUTIVE SUMMARY

- Insulin treatment must be started as soon as possible after diagnosis (usually within 6 hours if ketonuria is present) to prevent metabolic decompensation and diabetic ketoacidosis [A].
- Intensive insulin regimens delivered by combinations of multiple daily injections or pump therapy with differential substitution of basal and prandial insulin aiming to have optimal metabolic control have become the gold standard for all age groups in pediatric diabetology [E].
- Insulin therapy must be individualized for each patient in order to achieve optimal metabolic control [D/E].

- Improvements in glycemic control by intensive insulin treatment reduce the risks of acute and long-term complications [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]. Although no insulin injection regimen satisfactorily mimics normal physiology, pre-mixed insulins are not recommended for pediatric use [C]. When insulin is provided through a help organization, the recommendation should be to provide regular and NPH as separate insulins, not premixed [E].
- Whatever insulin regimen is chosen, it must be supported by comprehensive education appropriate for the age, maturity and individual needs of the child and family [A].
- Aim for appropriate insulin dosage throughout 24 hours to cover basal requirements and higher dosage of insulin in an attempt to match the glycemic effect of meals [E].
- Delivering prandial insulin before each meal is superior to post-prandial injection and should be 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 [B].
- All children should have rapid-acting or regular insulin available for crisis management [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 [A].
- Children and adolescents should be encouraged to inject consistently within the same area (abdomen, thigh, buttocks, arm) at a particular time in 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 concentration of insulin being used [E].
- Regular checking of injection sites, injection technique and skills 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, reassessment and reinforcement [E].

3 | INTRODUCTION

Insulin treatment that mimics normal physiological patterns as closely as possible remains the cardinal principle of treatment for type 1 diabetes. Since the last guidelines were published in 2014[1] the changes have been modest with respect to insulin treatment, but the different modes have been refined especially when it pertains to insulin pump treatment (Continuous subcutaneous insulin infusion [CSII]). Overall there has been a paradigm shift toward multiple daily injection and CSII over the last decades. While previously therapies have focused on avoiding painful injections in children, leading to regimens with little flexibility and dietary restrictions, currently intensive regimens with differential substitution of basal and prandial insulin have become the gold standard in pediatric diabetology. However, there is wide variation in insulin regimens, both within regions as well as between pediatric diabetologists in the same country that are unrelated to inadequate funding of modern insulins or devices by national health care systems, or insurance companies. Much of the variation can be explained by personal preference and experience of the respective diabetes team. As outcome comparisons through benchmarking and registries are implemented more widely in pediatric diabetes—it is anticipated that more guidance of regimens associated with better long-term prognosis will become available[2,3].

Insulin therapy started in 1922 using regular insulin before each main meal and one injection in the night, usually at 1 AM. After 1935, with the development of intermediate- and long-acting insulin, most patients moved to one or two injections per day. Already in 1960, a study showed that patients who were diagnosed between 1935 and 1945 and using one or two injections/day had a much higher risk of retinopathy after 15 years of diabetes compared to those diagnosed before 1935 using multiple daily injections (61% vs 9%).[4]

Up to now, no randomized controlled studies have compared the long-term outcome of treatment modalities using older more traditional insulins with newer regimens when both groups receive equal educational input. But the fact that the traditional insulins have certain clinical limitations has led to the development of new analogs, rapid and long-acting. These insulins resulted in some improvement in the care of diabetes, but their beneficial extent in a long-term clinical setting is not fully established.

Adult data is not readily transferable to pediatric patients of different age groups.[5] Studies have shown different pharmacokinetic profile of insulin analogs in young children and adolescents compared to adults.[6–9] These data highlight the necessity to study the effects of new insulins in all age groups separately.

In randomized trials, better blood glucose control has been obtained using multiple daily injections (MDI) and pumps compared to a twice daily treatment.[10,11] The Diabetes Control and Complications Trial (DCCT) proved convincingly that intensive insulin therapy including a multidisciplinary approach concerning insulin dose adjustment and education in adolescents with multiple injections or pumps, resulted in a lower rate of long-term complications[11] Cognitive impairment 18 years after the conclusion of the DCCT study was shown to be unrelated to the rate of hypoglycemia during intensive therapy, removing one of the barriers of attempting stricter metabolic control.[12,13] Also, in a cross-sectional clinical setting HbA1c, hypoglycemia and diabetic ketoacidosis were not associated with the number of injections per day in pediatric populations.[14]

Unequivocal evidence for the benefit of different modalities of treatment in children are lacking. Carefully structured randomized studies are needed. The fact that these MDI, analogs and CSII are more expensive than conventional treatment has been an obstacle to the implementation of the use of them in many countries. The DCCT which was performed with regular and NPH/ultralente insulin had a higher incidence of hypoglycemia and weight gain in those of the intensive group compared with the standard treatment group. Although the importance of these new analog insulins for the reduction of hypoglycemia observed in registries[15] cannot be distinguished from advances in devices or education, efforts should be made to have all treatment options available to tailor the modality of therapy to the individual needs of patients with T1D.

The DCCT study and its follow-up EDIC (Epidemiology of Diabetes Interventions and Complications) study confirmed that an improvement in long-term glucose control, as obtained with intensified insulin therapy including extensive support and education, can reduce the incidence of complications and delay the progression of existing complications in type 1 diabetes, in adults as well as in pediatric patients.[11,16,17] These results have established intensive treatment aimed at glycemic levels as near to normal as possible as the gold standard from the very onset of diabetes.

Continuous glucose monitoring, both in patients using pump and MDI (age 6-70), has been shown to facilitate improved HbA1c without increasing the number of severe hypoglycemia reactions. In addition, the improvement in HbA1c was less in the group that used the sensor

<70% of the time compared with those who used the sensor more frequently.[18] Moreover, the emerging results from recent studies using sensor augmented pump therapy with automatic insulin suspension, hypbrid-and full "closed loop systems" are even more promising in achieving better glycemic control.[19–21]

4 | INSULIN AVAILABILITY

Children and adolescents with type 1 diabetes are dependent 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 Life for a Child organization, are working toward making insulin available for all children and adolescents with diabetes and promoting universal insulin labeling.

4.1 | Insulin formulation and species

Many formulations of insulin are available; most have some role in the management of type 1 diabetes (Table 1).

Human insulin is worldwide in distribution and use, but in many countries these are being superseded by analogs. Porcine or bovine insulins may be cheaper, but are virtually unavailable and subject to minimal use across the globe. The production of zinc-containing insulins (Lente, Ultralente) has been stopped.

The time action of most insulins is dose-dependent in that a smaller dose has a shorter duration of effect and earlier (22,23) peak, but there is some evidence that lispro[22] and aspart[23] have the same time action irrespective of dose. The results of these studies are obtained from a relatively small number of adult subjects, and the results in children may result in different profiles of action.

5 | REGULAR INSULIN (SHORT ACTING)

Regular soluble insulin (usually identical to human insulin) is still used as an essential component of most daily replacement regimens in many parts of the world either combined with:

- Intermediate-acting insulin in twice daily regimen.
- As premeal bolus injections in basal-bolus regimens (given 20-30 minutes before meals) together with intermediate-acting insulin 2 to 3 (or even 4) times daily or a basal analog given once or twice daily.

An inhaled form of human insulin (Afrezza) has been approved as prandial insulin for adults in the United States.[24]

6 | RAPID ACTING INSULIN ANALOGS

Several novel insulin analogs have been developed. Three rapid acting types are currently available for children (aspart, glulisine, lispro). They have a rapid onset and shorter duration of action than regular insulin (see Table 1). No clinical significant differences have been found between the analogs[25] also in the pediatric population.[26]

TABLE 1 Types of insulin preparations and suggested action profiles for s.c. administration

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

Abbreviations: NPH, neutral protamine hagedorn insulin. All insulins used must be produced under "Good Manufacturing Practice/Good Laboratory Practice" conditions.
[a] The duration of action may be shorter.
[b] biosimilar glargine approved in some countries.
[c] Not yet approved worldwide or not for pediatric indication.

The different rapid acting analogs have different chemical properties, but no significant clinical difference in time of action and duration has been reported[27–29]; their advantages compared to regular (soluble) insulin are still under debate. The Cochrane review from 2016 stated that in patients with type 1 diabetes, the weighted mean difference of HbA1c was −0.1% in favor of insulin analog (−0.2% when using CSII).[5]

Despite the inconsistent benefit of insulin rapid acting analogs on blood glucose control in children and adolescents, they have contributed to broadening the treatment options for the unique needs of pediatric patients with type-1 diabetes across all age-groups, and allowed pediatric patients to safely reach equal or better glycemic control, with more flexibility in their daily lives.[30] A reduction in hypoglycemia has been reported, both for lispro[31–34] and aspart.[35,36] In the Cochrane review, the weighted mean deviation of the overall mean hypoglycemic episodes per patient per month was −0.2 (95% CI: −1.1 to 0.7) in favor of rapid acting insulin analogs.[5] In adolescents, a significantly reduced rate was found with analogs,[37] but in prepubertal children, no difference was found.[31,38] In the included pediatric studies, there was no difference found in prepubertal children[31,39] or adolescents.[37]

6.1 | The rapid acting analogs

- Should be given immediately before meals because there is evidence that the rapid action not only reduces postprandial hyperglycemia but nocturnal hypoglycemia may also be reduced.[31–34]
- In exceptional cases can be given after food when needed (eg, infants and toddlers who are reluctant to eat) or prandial doses can be split before and after the meal.[40]
- In the presence of hyperglycemia, the short acting analog should be given in advance of eating.

- Give a quicker effect than regular insulin when treating hyperglycemia, with or without ketosis, including sick days.
- Are most often used as prandial or snack boluses in combination with longer acting insulins (see basal bolus regimens).
- Are most often used in insulin pumps.

6.2 | Ultra-rapid-acting insulins

Ultra rapid acting insulins are intended to better match the time-action profile of prandial insulins to cover the rapid increase in blood glucose after meals and may be particular useful for pumps and "closed-loop" approaches. Because human insulin and rapid acting insulin analogs 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. Fiasp is the brand name for fast-acting insulin aspart containing the excipients niacinamide and L-arginine to speed up the monomer formation. The new insulin has a faster onset and offset than aspart insulin (IAsp) meaning it should better control initial postmeal spikes in blood sugar and cause less hypoglycemia hours later. The ultra-fast rapid-acting insulin aspart has been approved by the European Commission and FDA in 2017 for adults. The pharmacokinetic and pharmacodynamic results in adults have been preserved in children and adolescents[41] but the pediatric regulatory trials and the FDA approvals are still ongoing.

In adults with Faster aspart, insulin was detectable twice as fast in the blood compared to injection of IAsp, and also the insulin concentration in the first 30 minutes was doubled or, when administered via CSII, tripled when compared with IAsp.[42,43] The more pronounced pharmacological effects in CSII compared to the subcutaneous administration route may be due to the continuous influx of niacinamide by the insulin basal rate. Thus, when switching to FiAsp in CSII adaptations of the basalrate and bolus type (ie, split-wave bolus) may be necessary to achieve best results.

In the clinical phase IIIa study onset 1 in adults with type 1 diabetes, significantly better postprandial plasma glucose values 1 and 2 hours after a standardized meal were found with Faster aspart. In addition, after 26 weeks, the HbA1c value was improved by 0.15% points by faster aspart compared to insulin aspart.[44] Thus, an average HbA1c improvement was already achieved in the first major clinical study to the same extent that the Cochrane meta-analysis comparing short-acting insulin analogues in relation to human insulin[5] has reported. Fiasp taken 20 minutes after the start of a standardized meal was as effective as insulin aspart administered at meal for HbA1c reduction, and postprandial glucose lowering effect 2 hours after meal as insulin aspart taken just before mealtime.

Although trials with new ultra-rapid insulins LY900014 or Bio-Chaperone Lispro, have been presented on meetings no clinical studies in children have yet been published.

7 | IV INSULIN

Regular and rapid-acting and ultra-rapid insulins are equally suited for IV therapy in the following crisis situations[45]:

- Diabetic ketoacidosis.
- Control of diabetes during surgical procedures.

However, regular insulin is less expensive.

8 | INTERMEDIATE ACTING INSULINS

The action profiles of the isophane NPH (neutral protamine Hagedorn) insulins make them suitable for twice daily regimens, tailored basal substitution and for prebed dosage in basal-bolus regimens. As they are in suspension adequate preinjection mixing has to be ensured. In one study, the insulin concentration in used vials and cartridges of NPH insulin that had not been mixed thoroughly varied between 5 and 200 U/mL.[46,47] Nevertheless, they are associated with greater inter- and intraindividual variability compared to soluble basal insulins[48] and the peak effect makes them less functional when carbohydrate counting is practiced. However, it may be tailored as a part of a twice daily basal insulin regimen to allow coverage for snacks for children who are not prepared to inject at school recess.[49]

9 | BASAL INSULIN ANALOGS

The currently available basal insulin analogs are glargine, detemir and degludec, which have different modes of action. Insulin glargine is a clear insulin which precipitates in situ after injection whereas insulin detemir is acylated insulin bound to albumin. These analogs have reduced day-to-day variability in absorption compared to NPH-insulin, with detemir having the lowest within-subject variability.[50,51] So far, the reduction in hypoglycemia rather than in HbA1c is the most prominent feature,[52] both for glargine[49,53–58] and detemir.[59–62] Degludec, a new ultra-long basal analog which has a longer duration of action than detemir or glargine, has been approved for children and adolescents. A new preparation of glargine, Glargine 300, with longer duration of action than glargine has been approved for use in adults.

They show a more predictable insulin effect with less day-to-day variation, compared to NPH insulin.[48] Basal analogs have less of a peak than NPH and allow basal dosing independent of meal times. In most countries, the two basal analogs glargine and detemir are not formally approved for children below the age of 2 years, while degludec is approved as young as 1 year old. There is a report of successful use of glargine in children from <1 to 5 years of age.[63] Basal analogs are more expensive (approximately +50%-100%).

10 | GLARGINE

Insulin glargine was the first basal analog that was approved for clinical use. The changes of the molecular structure shift the isoelectric point from a pH of 5.4 to 6.7, making the molecule more soluble at an acidic pH and less soluble at physiological pH. In the neutral subcutaneous space, higher-order microcrystals form that slowly release insulin, giving a long duration of action. Review of pediatric studies in the past 6 years of once daily insulin glargine found a reduced rate of

hypoglycemia, and a greater treatment satisfaction in adolescents compared to conventional basal insulins despite a comparable or small improvement in HbA1c.[64] However, in a Finnish retrospective study, no difference concerning hypoglycemia and HbA1c was found when glargine was compared to NPH as basal insulin.[65] A randomized controlled trial in 125 preschool children aged 2 to 6 years using continuous glucose monitoring confirmed that a single injection of glargine appears at least equally effective to NPH usually injected twice daily also in the very young age. Thus, glargine received regulatory approval for this age group.[66]

The effect of glargine lasted for up to 24 hours in adults, however, a waning effect can be seen approximately 20 hours after injection.[67] Lack of an accumulation effect of glargine given on consecutive days has been shown in one study.[68] Some children report a burning sensation when injecting glargine due to the acid pH.[69]

11 | GLARGINE U300

The new ultra-long-acting basal insulin analog, glargine U300 (Toujeo), is a higher-strength formulation (300 units/mL) of the original insulin glargine U100 product (Lantus), resulting in flatter pharmacokinetic and pharmacodynamics profiles and prolonged duration of action (>24 hours) because of a more gradual and protracted release from the more compact subcutaneous depot. The full glucose lowering effect may not be apparent for at least 3 to 5 days of use. The metabolism of glargine U300 is the same as that of glargine U100, with the M1 metabolite (21^A-Gly-human insulin) being the main active, circulating moiety.[70,71] This is important as it implies that the neutral safety profile with regard to cardiovascular outcomes and cancer incidence that was demonstrated for glargine U100 in the ORIGIN trial[72] should also be applicable for the new glargine U300 formulation. In adults, similar rates of overall and nocturnal hypoglycemic events were registered in the first phase 3 randomized controlled EDITION 4 trial in type 1 diabetes.[73,74] By contrast, another trial in Japanese adults with type 1 diabetes showed significant reductions in confirmed hypoglycemic events at any time of the day and in particular during nighttime.[75] A study using masked CGM recordings[76] observed less daily fluctuations in glucose control together with reduced nocturnal confirmed hypoglycemia. Pediatric studies for regulatory approval are still ongoing and more data are required to fully elucidate the effectiveness of Toujeo on reducing the risk of hypoglycemia in type 1 diabetes, preferably with the use of CGM to reveal clinically important improvements in daily glucose control and variability.

12 | DETEMIR

Detemir is an insulin analogue in which a fatty acid (myristic acid) is bound to the lysine amino acid at position B29. It is quickly absorbed after which it binds to albumin in the blood through its fatty acid at position B29. It then slowly dissociates from this complex. A study with detemir in adults found the time of action to be between 6 and 23 hours when doses between 0.1 and 0.8 U/kg were given.[77] Dosing

can be done once or twice daily based on metabolic needs and glucose monitoring. In a pediatric study, 70% of the patients used detemir twice daily.[60] In another trial twice-daily detemir showed no clinical advantage over once-daily detemir, but those in active puberty often required twice-daily therapy.[78] 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.[79] In adults, studies with detemir have shown less weight gain,[62] which has been observed also in children and adolescents.[60] 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.[80]

Detemir is characterized by a more reproducible pharmacokinetic profile than glargine in children and adolescents with type 1 diabetes.[51] Detemir showed a reduced risk for overall and nocturnal hypoglycemia vs NPH in 52 week study[81] and a reduced risk of nocturnal, severe hypoglycemia compared to glargine in a multicenter study.[82]

13 | DEGLUDEC

Degludec is a novel ultra-long acting analog which forms soluble multi-hexamers after subcutaneous administration, which then slowly dissociate and results in a slow and stable release of degludec monomers into the circulation extending the action for up to 40 hours.[83] Results in pediatric patients indicate that the long-acting properties of degludec are preserved also in this age group.[84] The ultra-long action profile of degludec should allow less stringent timing of basal insulin administration from day to day[83] which may be of use in the erratic lifestyles encountered frequently in the adolescent population. Another feature of degludec is that it can be mixed with short-acting insulins without the risk of forming hybrid hexamers and erratic pharmacokinetics/dynamics. 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 to 17 years with type 1 diabetes, for 26 weeks (n = 350), followed by a 26-week extension (n = 280). Degludec achieved equivalent long-term glycemic control, as measured by HbA1c with a significant reduction of fasting plasma glucose at a 30% lower basal insulin dose when compared with to 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 patients prone to DKA.[85]

14 | SAFETY OF INSULIN ANALOGS

As insulin analogs are molecules with modified structure compared to human insulin, safety concerns have been raised due to changes in mitogenicity in vitro.[86] In previous guidelines we have commented on the issue of a potential link between insulin analogs and cancer. A series of four highly controversial epidemiological papers in *Diabetologia*[87–90] had indicated such possibility for glargine. These studies evaluated mostly subjects with T2D. In a new statement

published online in May 2013 the European Medicines Agency (EMA) has concluded that insulin-glargine-containing medicines (Lantus, Optisulin, Sanofi) for diabetes do not show an increased risk of cancer. The EMA also notes that there is no known mechanism by which insulin glargine would cause cancer and that a cancer risk has not been seen in laboratory studies[91] or the long-term ORIGIN trial.[72] Treatment with insulin analogs is associated with development of specific and cross-reacting antibodies, but no correlation between insulin antibodies and basal insulin dose or HbA1c in children was found.[92] Presently, there are no safety concerns that would preclude the use of insulin analogs in the pediatric age group.

15 | PREMIXED INSULIN PREPARATIONS

Premixed insulins (fixed ratio mixtures of premeal and basal insulins) are used in some countries particularly for prepubertal children on twice daily regimens. Although they reduce potential errors in drawing up insulin, they remove the flexibility offered by separate adjustment of the two types. Such flexibility is especially useful for children with variable food intake. Premixed insulins may be useful to reduce the number of injections when adherence to the regimen is a problem.

Recently, premixed insulins have also become available with rapid-acting analogs. Biphasic insulin aspart 30 (30% aspart and 70% aspart bound to NPH) given for three main meals combined with NPH at bedtime was equally efficient as premixed human insulin (70% NPH) given for morning and bedtime with regular insulin for lunch and dinner in adolescents.[93] There is no clear evidence that premixed insulins in young children are less effective, but some evidence of poorer metabolic control when used in adolescents.[14] Premixed insulins with regular (or rapid acting): NPH in different ratios, for example, 10:90, 15:85, 20:80, 25:75, 30:70, 40:60, 50:50 are available in various countries from different manufacturers. Premixed insulins are suitable for use in pen injector devices.

16 | BIOSIMILAR INSULIN

With the biosimilar Glargin Insulin LY2963016 from Lilly and Boehringer, a first biosimilar insulin has been approved in several countries also for pediatric use[94] and others may be coming soon (ie, biosimilar insulin lispro). In contrast to common generic drugs, insulin molecules are much larger molecules. Basically, one has to distinguish between generics and biosimilars. In contrast to the small molecule drugs the comparative assessment of large protein molecules (biosimilars) is more complex. In addition to a consistency in the primary structure (amino acid sequence), the secondary and tertiary structure (three-dimensional convolution configuration) and comparable quaternary structure (stable association of two or more identical or different molecule units) has to be considered in order to allow comparable formation of hexamers after insulin injection. In this respect, the consistency and quality of the entire manufacturing process must be ensured. Smallest changes in the production process can easily have significant clinical consequences. The original product and biosimilar will therefore never be absolutely identical molecules. However, if

bioequivalence is established through proper clinical trials and pharmacovigilance on reporting of any side effects observed, the availability of different biosimilars might lower the price for insulin, make it more accessible and affordable for many pediatric patients with diabetes.

17 | INSULIN CONCENTRATIONS

The most widely available insulin concentration is 100 IU/mL (U 100). Treatment with U 40 (40 IU/mL), U50 or other concentrations such as U500 is also acceptable, subject to availability and special needs. Care must be taken to ensure that the same concentration is supplied each time new supplies are received. Very young children occasionally require insulin diluted with diluent obtained from the manufacturer, but special care is needed in dilution and drawing up the insulin into the syringe. Rapid-acting insulin can be diluted to U10 or U50 with sterile NPH diluent and stored for 1 month[95,96] for use in pumps for infants or very young children. Switching children from U40 to U100 insulin may increase practical problems in drawing up insulin, but has not shown a decline in glycemic control in a large pediatric cohort.[97] Newer formualtions of lispro 200 IU/mL (U 200) and regular insulin 500 UI/mL have been marketed for adult patients requiring high doses.

18 | STORAGE OF INSULIN

Regulatory requirements state that the labeled insulin product must retain at least 95% of its potency at expiry date.[98] At room temperature (25°C, 77 °F), insulin will lose <1.0% of its potency over 30 days. In contrast, insulin stored in a refrigerator will lose <0.1% of its potency over 30 days.[98] Storage recommendations are more often based on regulatory requirements regarding sterility than loss of potency.[98] The individual manufacturer's storage recommendations and expiry dates must be adhered to. These usually recommend that:

- Insulin must never be frozen.
- Direct sunlight or warming (in hot climates or inside a car on a sunny day) damages insulin.
- Patients should not use insulin that has changed in appearance (clumping, frosting, precipitation, or discoloration).
- Unused insulin should be stored in a refrigerator (4°C-8°C).
- After first usage, an insulin vial should be discarded after 3 months if kept at 2°C to 8°C or 4 weeks if kept at room temperature. However, for some insulin preparations, manufacturers recommend only 10 to 14 days of use in room temperature.
- In hot climates where refrigeration is not available, cooling jars, earthenware pitcher[99] or a cool wet cloth around the insulin will help to preserve insulin activity.

Equally, manufacturers´ guidelines for storage of unused pens or cartridges in use should be adhered to, which can differ from storage of vials. In children on small doses of insulin, 3 mL cartridges or vials, instead of 10 mL vials should be chosen to avoid wasting of insulin.

19 | INJECTION SITES

The usual injection sites are (Figure 1):

- Abdomen (the preferred site when faster absorption is required and it may be less affected by muscle activity or exercise).
- Front of thigh/lateral thigh (the preferred site for slower absorption of longer acting insulins).
- The lateral upper quadrant of the buttocks (the whole upper quadrant is useful).
- Lateral aspect of arm (in small children with little subcutaneous fat, intramuscular injection is more likely and it may cause unsightly bruising).
- Rotation of injection sites are important also within the same area of injection
- Cleaning or disinfection of skin is not necessary unless hygiene is a real problem. Infection at injection sites is rare.[101]

20 | PROBLEMS WITH INJECTIONS

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. Adding a small amount of corticosteroids to the insulin may help.[102] Lipohypertrophy with the accumulation of fat in lumps underneath the skin are common in children.[103] Lipoatrophy was said to be uncommon since the introduction of highly purified insulins and analogues.[104] But recent reports indicate that lipoatrophy is a problem increasing in patients using insulin analogues and possible mostly in patients on pumps.[105,106]
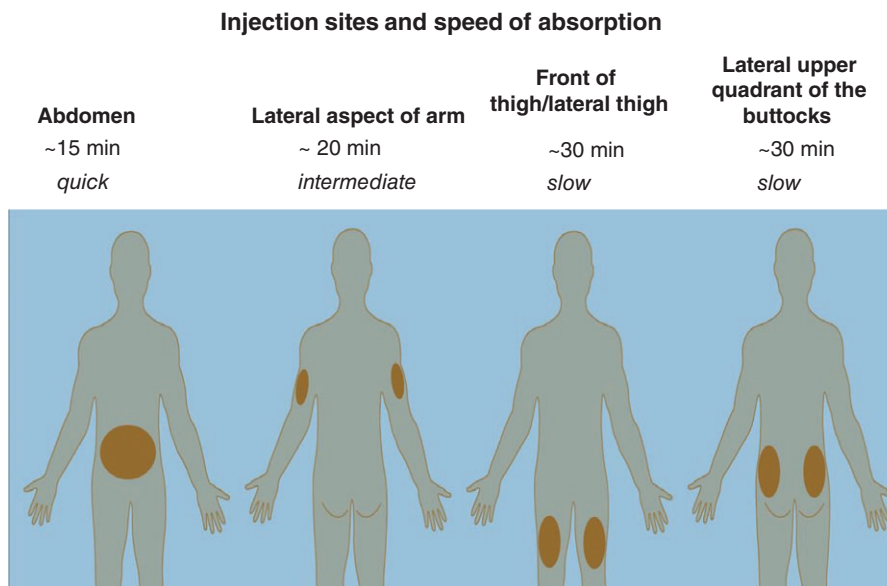
Painful injections are a common problem in children. Check angle, length of the needle, and depth of injection to ensure injections are not being given intramuscularly and that the needle is sharp. Reused needles can cause more pain.[107] Indwelling catheters (Insuflon, i-port) can decrease injection pain.[108] Leakage of insulin is common and cannot be totally avoided. Encourage slower withdrawal of needle from skin, stretching of the skin after the needle is withdrawn, or pressure with clean finger over the injection site. Bruising and bleeding are more common after intramuscular injection or tight squeezing of the skin. Use of thinner needles has shown significantly less bleeding at the injection site.[109]

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 cause drops of insulin appearing on the tip of the pen needle, if withdrawn too quickly.[110]

21 | INSULIN ABSORPTION

Insulin activity profiles show substantial variability both day to day in the same individual and between individuals, particularly in children.[7,111] The onset, peak effect and duration of action depend upon many factors which significantly affect the speed and consistency of absorption. Young people and care providers should know the factors which influence insulin absorption such as:

- Age (young children, less subcutaneous fat → faster absorption).
- Fat mass (large subcutaneous fat thickness,[112] lipohypertrophy,[113] also with rapid-acting analogs[114] → slower absorption).

Injection sites and speed of absorption

Abdomen	Lateral aspect of arm	Front of thigh/lateral thigh	Lateral upper quadrant of the buttocks
~15 min	~ 20 min	~30 min	~30 min
quick	*intermediate*	*slow*	*slow*

FIGURE 1 Schematic representation of injection sites and relative timing of insulin absorption. For details see Reference [100]

- Dose of injection (larger dose → slower absorption[111])
- Site and depth of s.c. injection (abdomen faster than thigh[115]; no good data exist on absorption from thigh vs buttock).
- S.c. vs i.m. injection (i.m. injection → faster absorption in thigh.[116] Accidental i.m. injections can cause variable glucose control.
- Exercise (leg injection, leg exercise → faster absorption).[117]
- Insulin concentration, type and formulation (lower concentration → faster absorption).[118]
- Ambient and body temperature (higher temperatures→ faster absorption).[112]
- In general, the absorption speed of rapid-acting analogs is less affected by the above mentioned factors .[119–121]
- There is no significant difference in the absorption of glargine from abdomen or thigh.[122] Exercise does not influence glargine absorption.[123] There is a risk of hypoglycemia if injecting glargine intramuscularly, particularly in young and lean individuals.[124]

Note: Faster absorption usually results in shorter duration of action.

Hyaluronidase may increase absorption speed, either added to insulin, or injected prior to inserting an insulin pump infusion set ("pre-administration").[125] Long-term effectivity and safety need to be established before this can be recommended for a pediatric population.

Insupad is a device that warms an area 2 × 4 cm just prior to injection of bolus insulin. The device should be re-sited daily; it has been shown to reduce the total daily insulin dose by 20%, and achieve a 75% reduction in hypoglycemic episodes. The Insupatch has been developed for insulin pump therapy and has an integral heating element that is activated when a bolus is delivered. The action of insulin aspart peaks at 73 minutes without heat and at 43 minutes with heat.[126] With these new devices the insulin requirements are lower and can achieve an earlier peak reducing the areas under the curve (AUC) for glucose and also to reduce the risk of hypoglycemia.

22 | ADMINISTRATION OF INSULIN

Current injection recommendations for patients with diabetes have been summarized.[127]

22.1 | Devices for insulin delivery

22.1.1 | Insulin syringes

Syringes are available in a variety of sizes in different countries, ensuring accurate dose delivery, but it is desirable to have small syringes with half or 1 unit per mark (eg, 0.3 mL, 100 U/mL) available for small children, making it possible to dose in half units.

Plastic fixed-needle syringes with small dead space are preferable to glass syringes.

Plastic fixed-needle syringes are designed for single use. However, many individuals with diabetes successfully re-use them without significant increase in risk of infection.[100] Reuse should be

discouraged if there is concern about hygiene or injection pain as they become blunted when reused.[107]

Insulin syringes must have a measuring scale consistent with the insulin concentration (eg, U 100 syringes).

Syringes must never be shared with another person because of the risk of acquiring blood-borne infection (eg, 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 (eg, 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.

22.1.2 | Pen injector devices

Pen injector devices containing insulin in prefilled cartridges have been designed to make injections easier and more 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 seconds) before withdrawing the needle, in order to give time for any air bubble in the cartridge to expand.[110,127] Pen needles 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.[109] Pen injectors of various sizes and types are available from the pharmaceutical companies. Some pens can be set to 1/2 unit increments. Half-unit pens are particularly useful for dosing in young children and during the remission phase when small dosing increments may help to avoid hypoglycemia. A few pens have a memory for taken doses, which can be practical especially for teenagers. Availability is a problem in some countries and although pen injectors may improve convenience and flexibility, they are a more expensive method of administering insulin. Pen injector devices are useful in children on multiple injection regimens or fixed mixtures of insulin but are less acceptable when free mixing of insulins is used in a 2- or 3-dose regimen.

22.1.3 | Needle length

The traditional needle length of 8 to 13 mm (27 G) were replaced by thinner needles that are 4 to 8 mm long (30-32 G). Today there is no longer any reason for using needles longer than 6 mm.[127] A two-finger pinch technique is recommended for all types of injections to ensure a strict subcutaneous injection, avoiding intramuscular injection.[128]

With 4 to 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).[129] Lean boys, however, have a thinner subcutaneous fat layer, especially on the thigh.[129,130] 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 to 6 mm needles are not fully inserted into the skin.

22.1.4 | Subcutaneous indwelling catheters

Such catheters (eg, Insuflon, i-port) inserted using topical local anesthetic cream, may be useful to overcome problems with injection pain at the onset of diabetes.[108] The use of indwelling catheters does not affect metabolic control negatively.[131] In children with injection problems, HbA1c has been lowered by using Insuflon.[132] 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.[133,134] Indwelling catheters should be replaced every 2-4 days to prevent scarring and a negative effect on insulin absorption.[135,136]

22.1.5 | 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 inserted through the skin rapidly. Automatic injection devices for specific insulin injectors are available.[137]

22.1.6 | 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 CSII,[138] but problems with jet injectors have included a variable depth of penetration, delayed pain and bruising.[139] 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.[140]

22.1.7 | Continuous subcutaneous insulin infusion

The use of external pumps is increasing and is proving to be acceptable and successful,[138–147] even in young infants.[141,142] For extensive review of CSII read Chapter 22 "*Diabetes Technology*" [to be published later as part of the ISPAD Clinical Practice Consensus Guidelines 2018 Compendium].

Insulin pump therapy is at present the best way to imitate the physiological insulin profile. Insulin is infused subcutaneously at a pre-programmed basal rate and boluses are added to counterbalance the intake of carbohydrates. CSII has mostly been compared to MDI with NPH as the long-acting insulin. A reduction in hypoglycemia and improved blood glucose control has been reported. One randomized study has recently confirmed these findings when glargine was the basal insulin in use,[143] although in a study with people naive to CSII or insulin glargine, glycemic control was no better with CSII therapy compared with glargine-based MDI therapy.[144] Several studies have compared the use of analogs and regular insulin in pumps.[32,145] Insulin pumps from the onset have been found to result in superior metabolic control when compared to 1 to 2 injections/day[10] but not to MDI.[143]

In this study, diabetes treatment satisfaction was higher with CSII. In children <6 years of age, pumps enabled better long-term metabolic control and lowered the risk of severe hypoglycemia better than MDI, especially when initiated at diagnosis.[146] Data from a large pediatric survey showed a low incidence of acute complications at a mean HbA1c-level of 8.0%.[147] An international consensus on pediatric indications and instructions for use has been published.[148] The most recent meta-analysis of six pediatric randomized controlled trials with 165 patients showed a reduction of HbA1c by 0.24% with CSII compared to MDI (mostly using NPH as basal insulin).[149]

Randomized studies in the preschool group have failed to show better glycemic control.[150,151] However, parents of preschool children who switch from multiple daily injections to insulin pumps report more flexibility and freedom, as well as less stress and anxiety related to their child's care.[152] Registry data suggest a decrease in HbA1c and reductions in rates of severe hypoglycemia after implementation of insulin pumps in preschool children.[153,154] Insulin pumps are recommended from the onset of diabetes in preschool children, if available.[155]

The positive effects on glycemic control and hypoglycemia in non-randomized observational studies have probably been influenced by the patient selection in these studies, such as good compliance and/or poor metabolic control. Pump therapy has also been found effective in recurrent ketoacidosis.[156,157] This highlights the importance of individualizing the decision of the modality of therapy for every situation. An insulin pump is an alternative to treatment with MDI (including basal analogs) if HbA1c is persistently above the individual goal, hypoglycemia is a major problem or quality of life needs be improved.[154,158] Pump therapy is an option for many patients to improve treatment satisfaction. In a review of five pediatric studies comparing CSII vs MDI, a majority of the patients and families chose to continue with CSII after the completion of the studies, even in studies where insulin pumps showed no objective benefit.[159] A randomized study of CSII vs MDI from the onset of diabetes in 7- to 17-year old children also found a significant improvement in treatment satisfaction in spite of no difference in HbA1c.[143] Insulin pump use is reportedly increasing particularly in the younger age group during recent years, as clinicians become more comfortable with this form of treatment. In countries with a high pump penetration, centers are starting, particularly their preschool children, from diabetes onset with CSII. There is circumstantial evidence that this is associated with a more rapid recovery of mothers from depressive symptoms associated with the diagnosis of a chronic disease in their child.[160]

CSII gives a more physiological insulin replacement therapy.[142,161] The newer generation of "smart" pumps that automatically calculate meal or correction boluses based on insulin-to-carbohydrate ratios and insulin sensitivity factors[162] have shown some benefits, that is, reduced glucose variability[163] and a higher percentage of postmeal glucose readings within target level.[164]

Insulin pump treatment may be hazardous when education and adherence to therapy is inadequate, because of the smaller depot of subcutaneous insulin and the sudden rise in ketones when insulin supply is interrupted. Pump stops for 5 hours in adult patients resulted in beta-hydroxybutyrate levels of ~1 to 1.5 mol/L but not DKA. Short disconnection of the pump gives a blood glucose increment of

$\approx$1 mg/dL/min, that is, 1.5 mol/L per 30 minutes.[165] The risk of DKA when using pumps comparing with MDI is unchanged in several studies,[166,167] and even lower in a long-term cohort study.[168] The recent population-based cohort study in the Diabetes Prospective Follow-up Initiative in Germany, Austria, and Luxembourg of 30 579 patients with type 1 diabetes younger than 20 years using propensity score matching, compared insulin pump therapy with multiple ($\geq$4) daily insulin injections and provided evidence for improved clinical outcomes associated with insulin pump therapy in children, adolescents, and young adults with type 1 diabetes. Pump therapy was associated with lower rates of severe hypoglycemia (9.55 vs 13.97 per 100 patient-years; difference, −4.42 [95% CI, −6.15 to −2.69]; $P < 0.001$) and diabetic ketoacidosis (3.64 vs 4.26 per 100 patient-years; difference, −0.63 [95% CI, −1.24 to −0.02]; $P = 0.04$). Glycated hemoglobin levels were lower with pump therapy than with injection therapy (8.04% vs 8.22%; difference, −0.18 [95% CI, −0.22 to −0.13], $P < 0.001$). Total daily insulin doses were lower for pump therapy compared with injection therapy (0.84 vs 0.98 U/kg; difference, −0.14 [−0.15 to −0.13], $P < 0.001$). There was no significant difference in body mass index between both treatment regimens.[169] A literature review found an increased risk of DKA in pediatric pump patients in some studies.[170] Data on national levels have shown both an unchanged[171] and an increased risk of DKA.[166,172] A Japanese study showed that tube- and catheter-related problems, such as occlusion, kinking or accidental pull-out of catheters in CSII frequently can cause DKA especially in young children.[173] Thus, recommended practical tools and standardized guidelines for empowering patients to prevent, diagnose, and troubleshoot insulin infusion set failure and other problems that contribute to unexplained hyperglycemia need to employed to realize the full benefit of insulin pump therapy along the continuum of diabetes education.[174,175]

Patients using insulin pumps, especially younger children, will benefit from being able to measure B-ketones via portable meters used in the home. The short interruption of insulin supply when changing infusion sets did not affect short-term glucose control. However, a 30-minute interruption of basal insulin infusion resulted in significant glucose elevation; approximately 1 mg/dL for each minute basal insulin infusion was interrupted (ie, 1.5 mol/L per 30 minutes).[176,177] Patients must be instructed on treatment of hyperglycemia, giving insulin with a pen or syringe in case of suspected pump failure (hyperglycemia and elevated ketone levels). Combining CSII with algorithms for automated fault detection by CGM may allow to reduce this problem further in the future.[178]

Rapid acting insulin analogs are used in most pumps, and a meta-analysis has shown a 0.26% lower HbA1c when comparing with human regular insulin.[5] Regular insulin is less often used in pumps but works well if rapid acting insulin is not available. Longer use of the infusion site may yield a faster peak of insulin and a shorter duration of insulin effect.[179,180] Of the three rapid acting insulins in current use, there are considerably more trial data relating to the use of insulin aspart and insulin lispro than to the use of insulin glulisine. The more widespread use of insulins aspart and lispro is supported by CSII studies that have demonstrated higher rates of occlusion and symptomatic hypoglycaemia with insulin glulisine than with either of the other rapid acting analogs.[181] Lower percentage of basal insulin and more than seven daily boluses are an option for better metabolic control when using pumps.[147] Motivation appears to be a crucial factor for the long-term success of this form of therapy.[182]

22.1.8 | Sensor-augmented pump therapy and "closed loop"

For extensive review of SAP and closed-loop system refer to Chapter 22 [to be published later as part of the ISPAD Clinical Practice Consensus Guidelines 2018 Compendium]. The positive effects of SAP are closely related to sensor wear and children and adolescents may find it difficult to wear the sensor continuously.[183] Nevertheless, in the STAR 3 1-year study, which included both children and adolescents, they were reported to achieve treatment satisfaction,[184] reduced HbA1c,[185] and glycemic variability.[186] Also, an automatic shut-off of the pump to prevent hypoglycemia when the sensor records a value below a preset threshold and the patient does not respond to alarms has been used successfully in children and adolescents,[187] as has been an insulin pump system that can suspend insulin delivery when glucose levels, as measured by CGM, are predicted to become low, and thus reduce the risk and duration of hypoglycemia.[188,189]

In September 2016, the FDA approved the first hybrid artificial pancreas system in the US: the Medtronic 670G System (Hybrid Closed-Loop-HCL) for patients from age 14 years and older while studies in younger children are ongoing.[190–193] Importantly, more than 85% of patients enrolled in the studies continue to use the system (Continued Access Program); one plus year data from home use of HCL in real-life shows similar outcomes. However, it is important to keep in mind that significant resources are needed for education in implementing newer technologies.

22.2 | Injection technique

Injections by syringe are usually given into the deep subcutaneous tissue through a two-finger pinch of skin at a 45° angle. A 90° angle can be used if the s.c. fat is thick enough. Pen injector technique requires careful education including the need to ensure that no airlock or blockage forms in the needle. A delay of 15 seconds after pushing in the plunger helps to ensure complete expulsion of insulin through the needle.[110]

22.2.1 | Self injection

It should be emphasized that a proportion of people with diabetes have a severe long-lasting dislike of injections which may influence their glycemic control. For these persons, an injection aid, i-port, Insuflon[108,132] or insulin pump[132] therapy may improve compliance.

There is great individual variation in the appropriate age for children being able to self-inject.[194] The appropriate age relates to developmental maturity rather than chronological age. Most children over the age of 10 years either give their own injections or help with them.[192] 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 should accept phases of non-injection with the need for help from another person. Younger children on multiple injection regimens may need help to inject in sites difficult to reach (eg, buttocks) to avoid lipohypertrophy.

22.2.2 | Self-mixing of insulin

When a mixture of two insulins is drawn up (eg, regular mixed with NPH), it is most important that there is no contamination of one insulin with the other in the vials. To prevent this, the following principles apply: There is no uniformity of advice but most often it is taught that regular (clear insulin) is drawn up into the syringe before cloudy insulin (intermediate or long-acting). Vials of cloudy insulin must always be gently rolled (not shaken) at least 10, preferably 20 times,[46] to mix the insulin suspension before carefully drawing it up into the clear insulin. 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 injections.[195] A clinical study in healthy male volunteers (n = 24) demonstrated that mixing IAsp with NPH human insulin immediately before injection produced some attenuation in the peak concentration of NovoLog, but that the time to peak and the total bioavailability of IAsp were not significantly affected. If IAsp is mixed with NPH human insulin, IAsp should be drawn into the syringe first. The injection should be made immediately after mixing.[196] It is recommended that glargine should not be mixed with any other insulin before injection,[133] but there is some evidence that it can be mixed with insulin lispro and aspart without affecting the blood glucose lowering effect[197] or HbA1c.[198] The manufacturer recommends that detemir should not be mixed with any other insulin before injection. Although a small pediatric study could not find clinical differences between separate injections and self-mixing,[199] mixing aspart with detemir insulin markedly lowers the early PD action of aspart and prolongs its time-action profile as compared with the separate injection of these analogs.[134]

22.3 | Insulin regimens

The choice of insulin regimen will depend on many factors including: age, duration of diabetes, lifestyle (dietary patterns, exercise schedules, school, work commitments etc.), targets of metabolic control, and particularly individual patient/family preferences.

- The basal-bolus concept (ie, a pump or intermediate-acting/long acting insulin/basal analog once or twice daily and rapid-acting or regular boluses with meals and snacks[200]) has the best possibility of imitating the physiological insulin profile with dose adjustments.
- Most regimens include a proportion of short- or rapid-acting insulin and intermediate-acting insulin or long-acting basal analog, but some children may during the partial remission phase maintain satisfactory metabolic control (ie, an HbA1c close to the normal range) on intermediate or long-acting insulins only or alternatively prandial insulin without basal alone.

- A different insulin regimen may be recommended during weekdays and weekends as the eating and activity pattern during school days and weekends may be completely different.

23 | PRINCIPLES OF INSULIN THERAPY

23.1 | Frequently used regimens

Despite clear recommendations for insulin management in children and adolescents with type 1 diabetes there is little distinctiveness about concepts and the nomenclature is confusing. A classification was suggested to compare therapeutic strategies without the currently existing confusion on the insulin regimen.[201]

23.1.1 | Glucose and meal-adjusted injection regimens

- Of the total daily insulin requirements, approximately 30% to 45% (sometimes ~50% when insulin analogs are used) should be basal insulin, the rest with adjusted doses for preprandial rapid-acting or regular insulin.
- Injection of prandial insulin before each meal (breakfast, lunch, and main evening meal), should be given as rapid acting insulin immediately before (or in exceptional cases after)[31,40] and adjusted to glycemia, meal content and daily activity. Rapid-acting analogs may need to be given 15 to 20 minutes before the meal to have full effect, especially at breakfast.[202,203] If regular insulin is used for prandial insulin, it should be administered 20 to 30 minutes before each main meal (breakfast, lunch, and the main evening meal)[204]
- Intermediate-acting insulin twice daily (mornings, evenings).
- Basal/long-acting analog once or twice daily

23.1.2 | Less-intensive regimens

- Three injections daily using a mixture of short-or rapid- and intermediate-acting insulins before breakfast; rapid or regular insulin alone before afternoon snack or dinner/the main evening meal; intermediate acting insulin before bed or variations of this.
- Two injections daily of a mixture of short or rapid and intermediate acting insulins (before breakfast and dinner/the main evening meal).
- Prandial insulin is adjusted by glucose and carbohydrate content.
- Extra injections are given when needed.

23.1.3 | Fixed insulin dose regimens

- Set insulin dosage not 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.
- Insulin administration: 1 to 3 injections per day.
- Three injections daily using a mixture of short-or rapid- and NPH before breakfast; rapid or regular insulin alone before afternoon snack or dinner/the main evening meal; intermediate acting insulin before bed or variations of this. Variations of this regimen have been described.

- Such regimes 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 to reduce the number of injections when compliance (or adherence) to the regimen is a problem, during the honey-moon period, or if there is very limited access to diabetes care.
- Included: Basal insulin only/premixed insulin only/free-mixed insulin combinations (Figure 2).

23.1.4 | Pump therapy (CSII)

- Insulin pump regimes are gaining popularity with a fixed or variable basal rate and adjusted bolus doses with meals.

- Downloading pump data to a computer program allows for monitoring of patterns of bolus dosing.

23.1.5 | Sensor-augmented therapies

- Continuous glucose monitoring systems (CGM) used together with CSII or MDI is well tolerated in children with diabetes, but the usage over time declined in studies.[205]
- Intermittently viewed continuous glucose monitoring (iCGM, Flash Libre) uses similar methodology to show continuous glucose measurements retrospectively at the time of checking. With iCGM, these trends can only be viewed after physically scanning
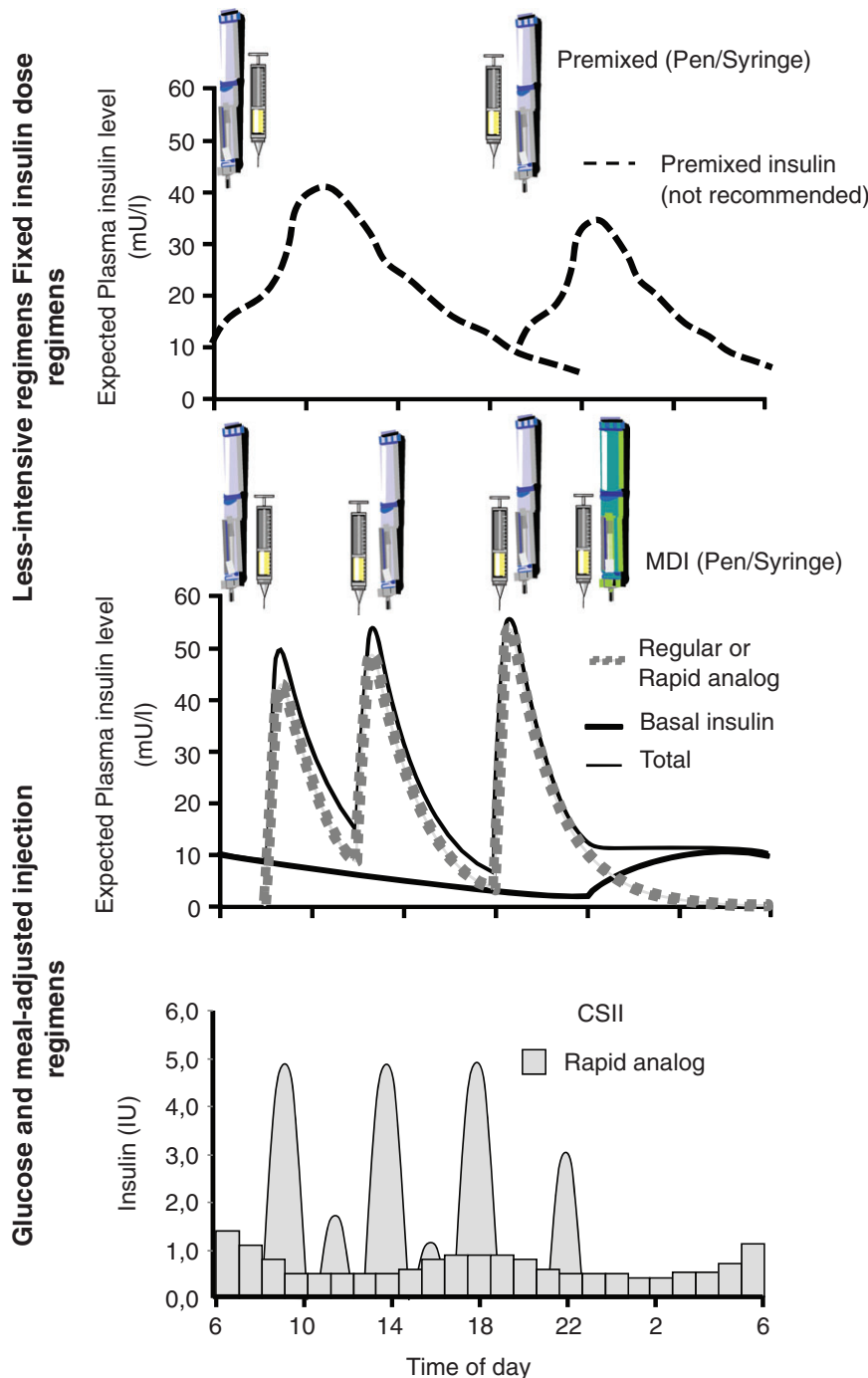
FIGURE 2 Schematic representation of frequently used regimens for insulin therapy in the pediatric and adolescent age group

the sensor. iCGM is quickly increasing in use in children above age four in countries where it is available.[206]

- Both real-time CGM and iCGM facilitate monitoring of time spent in the target glucose range ("time in range"). However, only real-time CGM can warn users if glucose is trending toward hypoglycemia or hyperglycemia.

NOTE: None of these regimens can be optimized without frequent assessment by self-monitored blood glucose (SMBG) or use of CGM.

24 | DAILY INSULIN DOSAGE

Dosage depends 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 blood glucose monitoring and glycated hemoglobin.
- Intercurrent illness.

25 | GUIDELINE ON DOSAGE

The "correct" dose of insulin is that which achieves the best attainable glycemic control for an individual child or adolescent without causing obvious hypoglycemia problems, and the harmonious growth according to weight and height children's charts.

- During the partial remission phase, the total daily insulin dose is often <0.5 IU/kg/day.
- Prepubertal children (outside the partial remission phase) usually require 0.7 to 1.0 IU/kg/day.
- During puberty, requirements may rise substantially above 1 and even up to 2 U/kg/day. Higher blood glucose levels are observed during luteal phase of menstrual cycle mediated by the endogenous progesterone level. Some individuals appear more responsive to menstrual cycle effects on insulin sensitivity. Women should be encouraged to use available self-monitoring technology to identify possible cyclical variation in blood glucose that might require clinician review and insulin dosage adjustment.[207,208]
- It has been observed that an excessive GH secretion in type 1 diabetes during puberty has significant effects on ketogenesis. Rise in beta-hydroxybutyrate and acetoacetate levels, between 2 AM and 3 AM, observed in puberty can be obliterated with suppression of GH. Hence, adolescent type 1 diabetic tends to decompensate very rapidly and develop DKA when the prebedtime insulin dose is omitted.[209]

26 | DISTRIBUTION OF INSULIN DOSE

In children on basal-bolus regimens, the basal insulin may represent between 30% (typical for regular insulin) and 50% (typical for rapid-acting insulin) of total daily insulin. Approximately 50% as rapid-acting or ~70% as regular insulin is divided up between 3 and 4 premeal boluses. When using rapid-acting insulin for premeal boluses, the proportion of basal insulin is usually higher, as short-acting regular insulin also provides some basal effect.

Glargine is often given once a day, but many children may need to be injected twice a day or combined with NPH to provide full daytime basal insulin coverage.[49,210] Glargine can be given before breakfast, before dinner or at bedtime with equal effect, but nocturnal hypoglycemia occurs significantly less often after breakfast injection.[80] When transferring to glargine as basal insulin, the total dose of basal insulin needs to be reduced by approximately 20% to avoid hypoglycemia.[208] After that, the dose should be individually adjusted. Detemir is most commonly given twice daily in children.[60] When transferring to detemir from NPH, the same doses can be used to start with, but be prepared to increase the detemir dose according to SMBG results.

27 | INSULIN DOSE ADJUSTMENTS

27.1 | Soon after diagnosis

- Frequent advice by members of the diabetes team on how to make graduated alterations of insulin doses at this stage is of high educational value.
- Insulin adjustments should be made until target BG levels and target HbA1c are achieved.
- Many centers teach carbohydrate counting already from the onset of diabetes

27.2 | Later insulin adjustments

- On twice daily insulin regimens, insulin dosage adjustments are usually based on recognition of daily patterns of blood glucose levels over the whole day, or a number of days or in recognition of glycemic responses to food intake or energy expenditure.
- On basal-bolus regimens, flexible or dynamic adjustments of insulin are made before meals and in response to frequent SMBG. In addition, the daily blood glucose pattern should be taken into account. The rapid-acting analogs require postprandial BG tests approximately 1 to 2 hours after meals to assess their efficacy. Insulin is preferably dosed based on food consumption (carbohydrates) and the current SMBG reading. Pumps have the possibility of delivering the bolus dose in different modalities (normal, dual, square) in order to reduce the postprandial blood glucose excursions.[211] Many newer insulin pumps allow programming algorithms (bolus guide) for these adjustments for current blood glucose and amount of carbohydrate intake.
- Downloading the blood glucose meter to a computer can help in discovering daily patterns in glucose levels.

28 | ADVICE FOR PERSISTENT DEVIATIONS OF BG FROM TARGET

- Elevated BG level before breakfast → increase pre- dinner or prebed intermediate or long-acting insulin (BG tests during the night are needed to ensure that this change does not result in nocturnal hypoglycemia).
- Rise in BG level after a meal → increase premeal rapid/regular insulin.
- Elevated BG level before lunch/dinner meal → increase prebreakfast basal insulin or increase dose of prebreakfast regular/rapid acting insulin if on basal-bolus regimen. When using rapid acting insulin for basal-bolus regimen, the dose or type of basal insulin may need to be adjusted in this situation as the analog has most of its effect within 2 to 3 hours after injection.
- When using carbohydrate counting, persistent elevations of post-meal BG may require adjustment in the insulin to carbohydrate ratio. 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 insulin will cover).
- 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 glucose before and after the meal differ more than 2 to 3 mol/L (20-30 mg/dL), the correction factor (see below) can be used to calculate out how much more (or less) insulin that ideally should have been given for a certain meal.
- Some centers also count protein and fat for calculating insulin requirements when using a pump (FPU, fat-protein units).[198] One 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 postmeal hypoglycemia, and more recent studies have found a lower need of insulin for protein, around 200 kcal equaling 10 g of carbs.[212]
- Correction doses (also called insulin sensitivity factor, 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 rapid-acting insulin will lower the blood glucose. For mol/L, use the "100 rule," that is, divide 100 by total daily insulin dose.[213] For regular insulin, a "1500 rule" can be used for results in mg/dL and a "83-rule" for results in moll/L. However, correction doses follow the same circadian variation of insulin sensitivity as seen for the insulin: carbohydrate ratio.
- Rise in BG level after evening meal → increase preevening meal regular/rapid acting insulin.

In addition

- Unexplained hypoglycemia requires re-evaluation of insulin therapy.

- Unexplained hyperglycemia may be caused by a "rebound phenomenon," that is, hypoglycemia followed by hyperglycemia that is potentiated by excessive eating to cure the hypoglycemia along with hormonal counter-regulation, especially if the premeal dose is decreased.
- Hyper- or hypoglycemia occurring in the presence of intercurrent illness requires a knowledge of "sick day management." See chapter 13 on sick days.
- Day-to-day insulin adjustments may be necessary for variations in lifestyle routines, especially exercise or dietary changes.
- Various levels of exercise require adjustment of diabetes management.
- 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.
- During periods of regular change in consumption of food (eg, Ramadan), the total amount of insulin should not be reduced but redistributed according to the amount and timing of carbohydrate intake. However, if total calorie/carbohydrate intake is reduced during Ramadan, the daily amount of bolus insulin for meals usually needs to be reduced, for example to two-thirds or three-quarters of the usual dose.

29 | DAWN PHENOMENON

Blood glucose levels tend to rise in the hours of the morning (usually after 0500 hours) prior to waking. This is called the dawn phenomenon. In non-diabetic individuals the mechanisms include increased nocturnal growth hormone secretion, increased resistance to insulin action and increased hepatic glucose production. These mechanisms are more potent in puberty.

Pump studies[214–216] have shown that younger children often need more basal insulin before midnight than after (reversed dawn phenomenon). With a basal/bolus analog regimen this can be achieved by giving regular instead of rapid acting insulin for the last bolus of the day (night time blood glucose levels need to be checked).[210]

In individuals with type 1 diabetes, fasting hyperglycemia is predominantly caused by waning insulin levels, thus exaggerating the dawn phenomenon. Morning hyperglycemia can in some cases be preceded by nighttime hypoglycemia (so called Somogyi phenomenon), being seen less often in pump therapy compared to MDI.[217] Correction of fasting hyperglycemia is likely to require an adjustment of the insulin regimen to provide effective insulin levels throughout the night and the early morning by the use of:

- Intermediate acting insulin later in the evening or at bedtime a longer acting evening insulin/basal insulin analog.
- Change to insulin pump treatment.

By the time of the next update of the ISPAD guidelines in 2022, we will have celebrated the centenary of the discovery of insulin (1921) and its revolutionary impact on the lives of people with diabetes mellitus. The quality of insulins in terms of purity, non-contamination with spurious proteins, the use of human insulin for

humans, the variety of chemical alterations to provide rapid short acting or variably longer acting forms of insulin, and the various means of insulin delivery were unimaginable to early investigators and caregivers. These advances have revolutionized the lives of those affected by diabetes at all ages-for children this has meant near-normal life spans and far fewer micro-and macro vascular complications. The dawn of closed-loop systems-the so-called artificial pancreas, offers even better futures for our patients. At the core of all these advances insulin remains the pillar of treatment. This chapter has attempted to detail how to use insulin appropriately and wisely in each individual based on current knowledge.

Conflict of interest

T.D. has received speaker honoraria and research support and has consulted for Abbott, Bayer, BMS, AstraZeneca, Boehringer Ingelheim, Dexcom, Eli Lilly, Medtronic, Novo Nordisk, Sanofi, and Roche. He is a shareholder of DreaMed Ltd. T.B. served on advisory boards of Novo Nordisk, Sanofi, Eli Lilly, Boehringer, Medtronic and Bayer Health Care. TB's Institution received research grant support, with receipt of travel and accommodation expenses in some cases, from Abbott, Medtronic, Novo Nordisk, GluSense, Sanofi, Sandoz and Diamyd. T.B. received honoraria for participating on the speaker's bureaux of Eli Lilly, Bayer, Novo Nordisk, Medtronic, Sanofi and Roche. T.B. owns stocks of DreamMed. B.A.B. has received research support from Medtronic, Dexcom, Insulet, Roche, Tandem, and Bigfoot Biomedical, is on advisory boards for Sanofi, NovoNordisk and Becton Dickinson and Company, and was a consultant for Dexcom. R.H. has received speaker honoraria from Novo Nordisk, Eli Lilly, Sanofi, Roche, Medtronic, DexCom, Menarini and Abbott, taken part in advisory boards for Novo Nordisk, Eli Lilly, Sanofi, Roche, Medtronic, DexCom, Menarini and Abbott and received research support from Sanofi. P.J.-C. has received speaker honoraria and research support and has consulted for Abbott, Bayer/Ascentia, BMS/AstraZeneca, Boehringer Ingelheim, DexCom, Eli Lilly, Medtronic, Novo Nordisk, Sanofi, and Roche. M.P.'s institute has received grants or research support from Medtronic, Novo Nordisk, Roche, Eli Lilly, Merck, Sanofi, Bristol-Myers Squibb, Kamada, AstraZeneca, and Lexicon. M.P. has received honoraria or consultation fees from Sanofi, Medtronic, Novo Nordisk, and Eli Lilly; has participated in advisory boards for Sanofi, Medtronic, AstraZeneca, and Eli Lilly; and is a stock shareholder in DreaMed Diabetes. The remaining authors have no relevant disclosure.

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APPENDIX

Limited care

1. Insulin should be available in sufficient amounts, being consistent in quality and type.

2. Use syringes and vials for insulin administration (or pens, if available).

3. The principles of insulin use including professional support, are as for Recommended care, but a combination of NPH and Regular insulin may give acceptable blood glucose control.

4. Regular and NPH insulin may be mixed in the same syringe, given as premixed insulin or given as separate injections.

5. A basal bolus regimen with Regular and NPH is preferred to premixed insulin preparations. NPH insulin should be given twice daily in most cases, in addition, Regular insulin needs to be given 2-4 times daily to match carbohydrate intake.

6. Premixed insulins may be convenient (ie, few injections), but limit the individual tailoring of the insulin regimen, and can be difficult in cases where regular food supply is not available.

7. Insulin storage as for Recommended care.

8. In hot climates where refrigeration is not available, cooling jars, earthenware pitcher (matka) or a cool wet cloth around the insulin will help to preserve insulin activity.

9 In children on small doses of insulin, 3 mL cartridges instead of 10 mL vials should be chosen for use with syringes to avoid wastage of insulin.