

ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Insulin treatment in children and adolescents with diabetes

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1-3).

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 (A).
- In all age groups, as close to physiological insulin replacement as possible and optimal glycemic control must be the aim (A). If available, an intensive insulin regimen is preferable [with analogs or regular/neutral protamine Hagedorn (NPH) insulin] (B). Although no insulin injection regimen satisfactorily mimics normal physiology, premixed 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 levels throughout 24 h to cover basal requirements and higher levels of insulin in an attempt to match the glycemic effect of meals (E).
- 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).
- Improvements in glycemic control, particularly when provided by intensive insulin treatment with

multiple daily injection (MDI) or pump therapy with dose adjustments, reduces the risks of vascular complications. There is no reason to believe that this is not the case also in younger children (A, E).

- 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 site (abdomen, thigh, buttocks, and 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 remains the responsibility of parents, care providers, and health professionals (E).
- The use of pumps requires special education for users, but does not need to be restricted to centers with 24 h access to pump expertise. The pump user or the family should be taught how to switch to multiple injections with pens or syringes in case of emergency (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).

Introduction

Since the last guidelines were published in 2009 (1) the changes have been modest with respect to insulin treatment, but the different modes have been refined especially when it comes to insulin pump treatment (continuous subcutaneous insulin infusion, CSII). Overall there has been a paradigm shift toward MDI and CSII over the last decade. While previously therapies have focused on avoiding painful injections in children, leading to regimens with little flexibility and dietary restrictions, nowadays intensive regimens with differential substitution of basal and prandial insulin are becoming the gold standard also in pediatric diabetology. As CSII has been proven to be safe in all ages and allows exact and flexible insulin dosing in small increments, multiple bolus dosing without need for injections, different prandial bolus options, and hourly adaptation of basal insulin, this form of therapy has become the insulin regimen of choice in many places particularly for the very young. However, there is wide variation in insulin regimens, both within regions as well as between pediatric diabetologists in the same country that are not related 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 hopefully more guidance of regimens associated with better long-term prognosis becomes available.

Insulin therapy started in 1922 using regular insulin before each main meal and one injection in the night, usually at 1:00 hour. With the development of intermediate- and long-acting insulin, most patients moved to one or two injections per day after 1935. Already in 1960 a study showed that patients who were diagnosed between 1935 and 1945 and using one or two injections per day had a much higher risk of retinopathy after 15 yr of diabetes compared with those diagnosed before 1935 using MDIs (61 vs. 9%) (2).

There are no randomized controlled studies comparing the longer term outcomes of 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 represent some improvement in the care of diabetes, but the extent in a clinical long-term setting is not fully established.

Adult data is not readily transferable to pediatric patients of different age groups (3), but in children and adolescents, as in adults (4), rapid-acting insulin (aspart) is rapidly absorbed and eliminated (5). Higher maximum insulin concentrations in adolescents vs. children were reported both for insulin aspart and human regular insulin (6), but not with glulisine (7). The results from reference (6) are in line with the relatively impaired insulin sensitivity and higher insulin concentrations reported in healthy adolescents (8, 9). Such findings highlight the necessity to study the effects of these new insulins in all age groups separately. The different rapid-acting analogs have different chemical properties, but no significant clinical difference in time of action and duration has been reported (10–12). Their advantages compared with regular (soluble) insulin are still under debate. The Cochrane review from 2006 (3) stated that in patients with type 1 diabetes, the weighted mean difference (WMD) of haemoglobin A1c (HbA1c) was -0.1% in favor of insulin analog (-0.2% when using CSII). In children and adolescents, blood glucose control has not been shown to be significantly improved with these analogs (13–17).

A reduction in hypoglycemia has been reported, both for lispro (14, 15, 18, 19) and aspart (20, 21). In the Cochrane review, the WMD of the overall mean hypoglycemic episodes per patient per month

was -0.2 [95% confidence interval (CI): $-1.1-0.7$] (3) in favor of rapid-acting insulin analogs. In adolescents, a significantly reduced rate was found with analogs (17), but in prepubertal children, no difference was found (14, 16). In the included pediatric studies, there was no difference found in prepubertal children (13, 14) or adolescents (17).

The basal insulin analogs 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 with NPH-insulin, with detemir having the lowest within-subject variability (22, 23). So far the reduction in hypoglycemia and not in HbA1c is the most prominent feature (24) [A], both for glargine (25–31) and detemir (32–35). Parental fear of severe hypoglycemia, especially during night time, is an impediment to achieving morning blood glucose control. Lower body mass index (z-score) has been reported for detemir (33).

In randomized trials, better blood glucose control has been obtained using MDIs and pumps compared with a twice daily treatment (36, 37). The Diabetes Control and Complications Trial (DCCT) proved convincingly that intensive insulin therapy including a heavy multidisciplinary approach concerning insulin dose adjustment, education in adolescents with multiple injections or pumps, resulted in a lower rate of long-term complications (37). Cognitive impairment 18 yr after the conclusion of the DCCT study was unrelated to the rate of hypoglycemia during intensive therapy (38, 39). 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 (40). A longitudinal Australian study showed a significant decrease in retinopathy and microalbuminuria and only a slight decrease in HbA1c (from 9.1 to 8.5%) during the years 1990–2009 when MDI/CSII increased from 17 to 88%. Both retinopathy and microalbuminuria were significantly associated with one to two injections per day (41).

Insulin pump therapy is at present the best way to imitate the physiological insulin profile. Insulin is infused subcutaneously at a preprogrammed basal rate and boluses are added to counterbalance the intake of carbohydrates. CSII has mostly been compared with MDI with NPH as the long-acting insulin (42–52). 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 (53), 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 (54). Several studies

have compared the use of analogs and regular insulin in pumps (55, 15). Insulin pumps from the onset have been found to result in superior metabolic control when compared with one to two injections per day (36) but not to MDI (53). In this study, diabetes treatment satisfaction was higher with CSII. In children <6 yr of age, pumps enabled better long-term metabolic control and lowered the risk of severe hypoglycemia better than MDI, especially when initiated at diagnosis (56). Data from a large pediatric survey showed a low incidence of acute complications at a mean HbA1c-level of 8.0% (57). An international consensus on pediatric indications and instructions for use has been published (58). 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 with MDI (mostly using NPH as basal insulin) (59).

Unequivocal evidence for the benefit of MDI, the analogs, and CSII-treatment in children is lacking. Carefully structured randomized studies are needed. The fact that these modalities are more expensive than conventional treatment has been an obstacle to the implementation of the use of them in many countries. However, the DCCT was performed with regular and NPH insulins, which are widely available in most countries. This implies that ISPAD's new practical recommendations have to be applicable for the total diabetes community worldwide.

The DCCT study and its follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study confirmed that an improvement in long-term glucose control, as obtained with intensified insulin therapy including heavy support and education, can reduce the incidence of complications and delay the progression of existing complications in type 1 diabetes, also in pediatric patients (37, 60, 61). A rapidly increasing numbers of centers around the world are introducing the basal/bolus concept of intensive insulin treatment already from the onset of diabetes.

Continuous glucose monitoring (CGM), both in patients using pump and MDI (age 6–70), has shown to give improved HbA1c without increasing the number of severe hypoglycemia, but the decrease in HbA1c was lower in the group that used the sensor $<70\%$ of the time (62) and the emerging results from recent studies with 'closed loop systems' are promising (63–65).

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.

Table 1. Types of insulin preparations and suggested action profiles according to manufacturers

Insulin type	Onset of action (h)	Peak of action (h)	Duration of action (h)
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
Intermediate acting Semilente (pork)	1–2	4–10	8–16
NPH	2–4	4–12	12–24
IZS Lente type	3–4	6–15	18–24
Basal long-acting analogs			
Glargine	2–4	None	24*
Detemir	1–2	6–12	20–24
Long-acting			
Degludec†	0.5–1.5	None	>24
Ultralente type	4–8	12–24	20–30

NPH, Neutral Protamine Hagedorn insulin; IZS, insulin zinc suspension.

All insulins used must be produced under 'Good Manufacturing Practice/Good Laboratory Practice' conditions.

*The duration of action may be shorter than 24 h (82).

†Not yet approved worldwide.

- ISPAD and IDF are working toward making insulin available for all children and adolescents with diabetes and promoting universal insulin labeling.

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) has been stopped.

The time of action of most insulins is dose-dependent in that a smaller dose has a shorter duration of effect and earlier (66, 67) peak and there is some evidence that lispro (68) and aspart (69) have the same time of 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.

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; or
- as premeal bolus injections in basal-bolus regimens (given 20–30 min before meals) together with intermediate-acting insulin once or twice daily or a basal analog given once or twice daily.

Rapid-acting insulin analogs

Several novel insulin analogs have been developed. Three rapid-acting types are currently available for children (aspart, glulisine, and 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 in the pediatric population (70).

The rapid-acting analogs:

- can when necessary 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 (14, 15, 18, 19);
- can in exceptional cases be given after food when needed (e.g., infants and toddlers who are reluctant to eat) (71);
- 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); and
- are most often used in insulin pumps (57).

Ultra-rapid-acting insulin

Ultra rapid-acting insulins are intended to better match the time–action profile of prandial insulins to cover the rapid increase in insulin meals and may be particularly 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. New formulations of excipients to modify the insulin hexamer complex resulting in

more rapid dissociation into dimers and monomers after s.c. injection are currently tested in clinical studies for human regular insulin (BIOD-090 to 123, Biondi, Danbury, CT, U.S.A.) and insulin aspart (FIAsp, NovoNordisk, Bagsvaerd, Denmark) (72).

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* (73). 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* had indicated such possibility for glargine. In a new statement published online in May 2013 the European Medicines Agency (EMA) has concluded that insulin glargine-containing medicines (Lantus®, Optisulin®, Sanofi, Paris, France) 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 (74). Presently, there are no safety concerns that would preclude the use of insulin analogs in the pediatric age group.

IV insulin

Regular and rapid-acting insulins are equally suited for i.v. therapy in the following crisis situations (75):

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

However, regular insulin is less expensive.

Intermediate-acting insulins

The action profiles of the isophane NPH insulins make them suitable for twice daily regimens, tailored basal substitution, and for pre-bed dosage in basal-bolus regimens. As they are in suspension adequate preinjection mixing has to be ensured. Nevertheless they are associated with greater interindividual and intraindividual variability compared with soluble basal insulins (76).

Basal insulin analogs

The currently available basal insulin analogs are glargine, detemir, and degludec.

They show a more predictable insulin effect with less day-to-day variation, compared with NPH insulin (76) and no significant clinical difference (in adult) between detemir and glargine has been found (77). In

most countries, the two basal analogs are not formally approved for children below the age of 2 yr – there is a report of successful use of glargine in children from <1 to 5 yr of age (78). Basal analogs are more expensive (approximately +50 to 100%).

Glargine

A review of pediatric studies in the past 6 yr of once daily insulin glargine found a comparable or small improvement in HbA1c but a reduced rate of hypoglycemia, and a greater treatment satisfaction in adolescents compared with conventional basal insulins (79). However, in a Finnish retrospective study no difference concerning hypoglycemia and HbA1c was observed when glargine was compared to NPH as basal insulins (80). A randomized controlled trial in 125 preschool children aged 2–6 yr using CGM 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 (81).

The effect of glargine lasted for up to 24 h in adults, however, a waning effect can be seen approximately 20 h after injection (82). Lack of an accumulation effect of glargine given on consecutive days has been shown in one study (83). Some children report a burning sensation when injecting glargine due to the acid pH (84). Recently the EMA issued a positive opinion recommending approval for the investigational compound LY2963016 (Abrasia (R)), a new insulin glargine biosimilar product, for the treatment of type 1 and type 2 diabetes. The new insulin glargine product from Eli Lilly and Company (Indianapolis, U.S.A.) and Boehringer (Ingelheim, Germany) is the first biosimilar insulin recommended for approval in the European Union (EU). No pediatric data is available yet. Also, U300 is a new formulation of insulin glargine that is expected to last up to 40h. Preliminary data are showing positive outcomes with U300 performing the same in controlling blood glucose as insulin glargine but with less hypoglycemia during the day and night. U300 is based on the glargine molecule but requires a smaller volume of subcutaneous injection and U300 demonstrates a flatter and longer PK/PD profile than that of insulin glargine. Again, no pediatric data is available yet.

Detemir

A study with detemir in adults found the time of action to be between 6 and 23 h when doses between 0.1 and 0.8 U/kg were given (85). In a pediatric study, 70% of the patients used detemir twice daily (33). In adults, studies with detemir have shown weight reduction or

less weight gain (35), which has been observed also in children and adolescents (33).

Detemir is characterized by a more reproducible pharmacokinetic profile than glargine in children and adolescents with type 1 diabetes (23) and in a multicentre study the risk of nocturnal, severe hypoglycemia was reduced compared with glargine (86).

Long-acting insulins

Degludec

Degludec is a novel ultra-long-acting analog developed by NovoNordisk. It forms soluble multihexamers after subcutaneous administration, which then slowly dissociate and result in a slow and stable release of degludec monomers into the circulation extending the action for more than 40 initial results in pediatric patients, indicating that the long-acting properties of degludec are preserved in this age group also (87). The ultra-long action profile of degludec should allow less stringent timing of basal insulin administration from day-to-day 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. Currently it is only approved for adults as the pediatric regulatory trials are evaluated insulins.

PEGylated Lispro

LY2605541 is a novel long-acting insulin analog developed by Lilly, based on the polyethyleneglycol (PEG)-ylation principle. It has not yet received regulatory approval (88).

Ultralente

Ultralente™ (Eli Lilly) and Ultratard™ (NovoNordisk) insulins were designed to have a duration of more than 24 h to meet basal insulin requirements, and therefore could be used in basal-bolus injection regimens. Their action profile in children appears to be extremely variable (66), with dose accumulation effect. If available, basal insulin analogs are superior to traditional long-acting insulins.

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. 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 (89).

- There is no clear evidence that premixed insulins in young children are less effective, but there some evidence of poorer metabolic control when used in adolescents (40).
- Premixed insulins with regular (or rapid acting):NPH in different ratios, e.g., 10:90, 15:85, 20:80, 25:75, 30:70, 40:60, and 50:50 are available in various countries from different manufacturers.
- Premixed insulins are suitable for use in pen injector devices.
- Premixed insulins may be useful to reduce the number of injections when compliance (or adherence) to the regimen is a problem.

Inhaled insulin

This new form of insulin therapy has been investigated in children above 12 yr of age as part of a study in adults, but was not approved for clinical use in children. The sale of inhaled insulin was discontinued in 2007. Afrezza® (MannKind, Valencia, CA, U.S.A.) is a ultra rapid-acting mealtime insulin therapy being developed for type 1 and type 2 diabetes mellitus. It is a drug-device combination product, consisting of insulin inhalation powder and an inhaler which has received a conditional approval for adults by the Food and Drug Administration (FDA). No pediatric data is published yet.

Insulin concentrations

The most widely available insulin concentration is 100 IU/mL (U100). Treatment with U40 (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 (90, 91) 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 (92).

Storage of insulin

Regulatory requirements state that the labeled insulin product must retain at least 95% of its potency at expiry date (93). At room temperature (25°C, 77°F), insulin will lose <1.0% of its potency over 30 d. In contrast, insulin stored in a refrigerator will lose <0.1% of its potency over 30 d (93). Storage recommendations are more often based on regulatory requirements regarding sterility than loss of potency (93). 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) 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 (4–8°C).
- After first usage, an insulin vial should be discarded after 3 months if kept at 2–8°C or 4 wk if kept at room temperature. However, for some insulin preparations, manufacturers recommend only 10–14 d of use in room temperature.
- In hot climates where refrigeration is not available, cooling jars, earthenware pitcher (*matka*), (94) or a cool wet cloth around the insulin will help to preserve insulin activity.

In children on small doses of insulin, 3 mL cartridges instead of 10 mL vials should be chosen to avoid wasting of insulin.

Injection sites

The usual injection sites are:

- 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 in small children).
- 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 (95).

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 (96). Lipohypertrophy with the accumulation of fat in lumps underneath the skin are common in children (97). Lipoatrophy was said to be uncommon since the introduction of highly purified insulins and analogs (98). But a very recent report indicates that lipoatrophy is a growing problem in patients using insulin analogs and possibly mostly in patients on pumps (99, 100).

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 (101). Indwelling catheters (Insuflon[®], i-port[®]) can decrease injection pain (102).

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 have shown significantly less bleeding at the injection site (103).

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 (104).

Insulin absorption

Insulin activity profiles show substantial variability both day-to-day in the same individual and between individuals, particularly in children (6, 66). 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 (105), lipohypertrophy (106), also with rapid-acting analogs (107) → slower absorption).

- Dose of injection (larger dose → slower absorption (66))
- Site and depth of s.c. injection (abdomen faster than thigh (108); no good data exist on absorption from thigh vs. buttock).
- s.c. vs. i.m. injection (i.m. injection → faster absorption in thigh (109). Accidental i.m. injections can cause variable glucose control.
- Exercise (leg injection, leg exercise → faster absorption) (110).
- Insulin concentration, type, and formulation (lower concentration → faster absorption) (111).
- Ambient and body temperature (higher temperatures → faster absorption) (105).
- In general, the absorption speed of rapid-acting analogs is less affected by the above mentioned factors (112–114).
- There is no significant difference in the absorption of glargine from abdomen or thigh (115). Exercise does not influence glargine absorption (116). There is a risk of hypoglycemia if injecting glargine intramuscularly, particularly in young and lean individuals (117).

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') (118). Long-term effectivity and safety need to be established before this can be recommended for a pediatric population.

Insupad (R), (Insuline, Petach Tikva, Israel) is a device that warms an area $2 \times 4 \text{ cm}^2$ just prior to injection of bolus insulin. The device is resited daily. It has been shown to reduce the total daily insulin dose by 20%, and achieve a 75% reduction in hypoglycemic episode. The Insupatch (R) (Insuline, Peath Tkva, Israel) 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 min without heat and at 43 min with heat (119). With these new devices the insulin requirements are lower, and can achieve an earlier peak reducing area under curve (AUC) for glucose and also reduce the risk of hypoglycemia

Administration of insulin

Devices for insulin delivery

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 1 U per mark (e.g., 0.3 mL, 100 U/mL) available for small children.

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 reuse them without significant increase in risk of infection (120). Reuse should be discouraged if there is concern about hygiene or injection pain as they become blunted when reused (101).

Insulin syringes must have a measuring scale consistent with the insulin concentration (e.g., U100 syringes).

Syringes must never be shared with another person because of the risk of acquiring blood-borne infection [e.g., hepatitis and human immunodeficiency virus (HIV) infections].

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®, Becton Dickinson, Franklin lakes, NJ, U.S.A.) may be available to remove the needle and make it unusable. Without a 'sharps container', syringes with needles removed may be stored and disposed of in opaque plastic containers or tins for garbage collection.

Pen injector devices. 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.

Special pen injection needles of small size (4–6 mm) and diameter are available and may cause less discomfort on injection (103). Pen injectors of various sizes and types are available from the pharmaceutical companies. Some pens can be set to half 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 two- or three-dose regimen.

Needle length. The traditional needle length of 8–13 mm (27 G) has been replaced by thinner needles that are 4–8 mm long (30–32 G). There is no longer reason for needles longer than 6 mm (121). A two-finger pinch technique is recommended for all types of injections to ensure a strict subcutaneous injection, avoiding intramuscular injection (122).

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) (123). Lean boys, however, have a thinner subcutaneous fat layer, especially on the thigh (123, 124). 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.

Subcutaneous indwelling catheters. Such catheters (e.g., Insufion[®], Unomedical, Denmark, i-port[®], Medtronic, Northridge, CA, U.S.A.) inserted using topical local anesthetic cream, may be useful to overcome problems with injection pain at the onset of diabetes (102). The use of indwelling catheters do not affect metabolic control negatively (125). In children with injection problems, HbA1c has been lowered by using Insufion (126). 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. Indwelling catheters should be replaced every 2–4 d to prevent scarring and a negative effect on insulin absorption (127, 128).

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 (129).

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 (130), but problems with jet injectors have included a variable depth of penetration, delayed pain, and bruising (131). In a recent study, the insulin absorption was enhanced and

the duration of the glucose lowering action was reduced when using aspart insulin with a jet injector (132).

Continuous subcutaneous insulin infusion. The use of external pumps is increasing and is proving to be acceptable and successful (42–44, 46–52, 57), even in young infants (48, 133). Randomized studies in the pre-school group have failed to show better glycemic control (42, 134).

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 (135, 136). 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 (137, 138).

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 (139). A randomized study of CSII vs. MDI from the onset of diabetes in 7–17 yr olds also found a significant improvement in treatment satisfaction in spite of no difference in HbA1c (140).

Insulin pump use is increasing particularly in the younger age group during the 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 has been 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 (141).

CSII is used as a more physiological insulin replacement therapy (133). The newer generation of ‘smart’ pumps that automatically calculate meal or correction boluses based on insulin-to-carbohydrate ratios and insulin sensitivity factors have shown some benefits, i.e., reduced glucose variability (142) and a higher percentage of post-meal glucose readings within target level (143).

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 h in adult patients resulted in B-ketone (beta-hydroxybutyrate) levels of

approximately 1–1.5 mmol/L but not DKA. Results in children and adolescents seem to be similar (144). Short disconnection of the pump gives a blood glucose increment of ≈ 1 mg/dL, i.e., 1.5 mmol/L per 30 min (145).

The risk of DKA when using pumps comparing with MDI is unchanged in several studies (50, 146) and even lower in a recent long-term cohort study (147).

A literature review found an increased risk of DKA in pediatric pump patients in some studies (148). Data on national levels have shown both an unchanged (149) and an increased risk of DKA (150, 147).

Patients using insulin pumps, especially younger children, will benefit from being able to measure B-ketones.

The short interruption of insulin supply when changing infusion sets did not affect short-term glucose control. However, a 30-min interruption of basal insulin infusion resulted in significant glucose elevation; approximately 1 mg/dL for each minute basal insulin infusion was interrupted (i.e., 1.5 mmol/L per 30 min) (145). 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).

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 (28). 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 (151, 152).

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 hypoglycemia with insulin glulisine than with either of the other rapid-acting analogs (153). Lower percentage of basal insulin and more than seven daily boluses are an option for better metabolic control when using pumps (57). Motivation appears to be a crucial factor for the long-term success of this form of therapy (154).

Sensor-augmented pump therapy and 'closed loop'. In the Juvenile Diabetes Research Foundation (JDRF) study a significant improvement in HbA1c using sensor-augmented pump (SAP) compared with self-monitoring of blood glucose, but only in adults in the intention-to-treat-analysis (155). However, in a *post hoc* analysis the improvement in HbA1c was seen also in the non-adults who used the CGM at least 6 d/wk. Many children and adolescents find it difficult

to wear the sensor continuously (156), which may have prevented an overall positive effect on metabolic control in the JDRF study. In another randomized trial, an improvement was only seen when the device was worn for more than 60% of the time (157). In the STAR 3 1-yr study, which included both children and adolescents, they were reported to achieve treatment satisfaction (158), reduced HbA1c (159), and glycemic variability (160). Which patients are likely to profit from sensor-augmented therapy needs to be studied further.

An automatic shut-off of the pump to prevent hypoglycemia when the sensor has fallen below a preset threshold and the patient does not respond to alarms has been used successfully in children and adolescents (161). There was no evidence that this temporary shut-off may lead to a increased risk for DKA.

Short-term experiments in adolescents with a closed loop system where the sensor glucose level regulates the insulin delivery in the pump have been published (65). In 2011, a closed loop system used during the night in children and adolescents showed reduced risk of hypoglycemia compared with standard pump treatment (162). In 2013, a closed loop system used in a youth camp setting showed less nocturnal hypoglycemia and tighter glucose control than with SAP (64). Meanwhile studies have been also published using these systems safely and effectively in studies with pediatric patients in a home setting (163, 164).

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 wait of 15 s after pushing in the plunger helps to ensure complete expulsion of insulin through the needle (104).

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, Insufion (126), or insulin pump therapy may improve compliance.

There is great individual variation in the appropriate age for children to self-inject (165). The appropriate age relates to developmental maturity rather than chronological age. Most children over the age of 10 yr either give their own injections or help with them (165). 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 (e.g., buttocks) to avoid lipohypertrophy.

Self-mixing of insulin. When a mixture of two insulins is drawn up (e.g., 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 times, preferably 20 times (166), to mix the insulin suspension before carefully drawing it up into the clear insulin. If the cloudy insulin is of Lente type the mixture must be administered immediately, otherwise the regular component interacts with zinc which blunts the action (167, 168). 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 as NPH immediately before injections (169, 170). Immediate injection of a mixture of Ultralente and Humalog has been found not to diminish the Humalog effect (171). The manufacturer recommends that glargine should not be mixed with any other insulin before injection, but there is some evidence that it can be mixed with insulin lispro and aspart without affecting the blood glucose lowering effect (172) or HbA1c (173). The manufacturer recommends that detemir should not be mixed with any other insulin before injection. There are no available studies on this.

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 (i.e., a pump or intermediate-acting/long-acting insulin/basal analog once or twice daily and rapid-acting or regular boluses with meals and snacks (174) has the best possibility of imitating the physiological insulin profile with dose adjustments.
- At least two injections of insulin per day (mixing short-acting/rapid-acting and basal insulin) are advisable in most children.

- 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 (i.e., an HbA1c close to the normal range) on intermediate- or long-acting insulins or alternatively prandial insulin without basal alone.

Principles of insulin therapy

Frequently used regimens

Basal-bolus regimen

- Of the total daily insulin requirements, 40–60% should be basal insulin, the rest pre-prandial rapid-acting or regular insulin.
- Injection of regular insulin 20–30 min before each main meal (breakfast, lunch, and the main evening meal).
- Intermediate-acting insulin or basal/long-acting analog at bedtime or twice daily (mornings and evenings).
- Injection of rapid-acting insulin analog immediately before (or in exceptional cases after) (14, 71) each main meal (breakfast, lunch, and main evening meal) adjusted to glycemia, meal content, and daily activity. Rapid-acting analogs may need to be given 15–20 min before the meal to have full effect, especially at breakfast (175, 176).
- Intermediate-acting insulin or basal/long-acting analog at bedtime, probably before breakfast and occasionally at lunchtime or twice daily (mornings, evenings, preferable with small doses <10–15 U that do not have a 24-h duration).

Pump therapy (CSII)

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

Sensor-augmented therapies

- CGM systems used together with CSII or MDI is well tolerated in children with diabetes, but the usage over time declined in studies (155, 177).

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).

Note: None of these regimens can be optimized without frequent assessment by self-monitored blood glucose (SMBG)

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

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 in children's charts.

- During the partial remission phase, the total daily insulin dose is often <0.5 IU/kg/d.
- Prepubertal children (outside the partial remission phase) usually require 0.7–1.0 IU/kg/d.
- During puberty, requirements may rise substantially above 1.2 IU/kg/d and even up to 2 IU/kg/d.

Distribution of insulin dose

Children on twice daily regimens often require more (around two thirds) of their total daily insulin in the morning and less (around one third) in the evening. On this regimen, approximately one third of each insulin dose may be short- or rapid-acting insulin and approximately two thirds may be intermediate-acting insulin although these ratios change with greater age and maturity of the young person.

On basal-bolus regimens the night-time intermediate-acting 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 approximately 70%

as regular insulin is divided up between three and four 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 (29, 178). Glargine can be given before breakfast, before dinner, or at bedtime with equal effect, but nocturnal hypoglycemia occurs significantly less often after breakfast injection (82). When transferring to glargine as basal insulin, the total dose of basal insulin needs to be reduced by approximately 20% to avoid hypoglycemia (178). After that, the dose should be individually tailored.

Detemir is most commonly given twice daily in children (33). 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.

Insulin dose adjustments

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.
- If frequent SMBG is not possible, urinary tests are useful, especially in the assessment of nocturnal control.

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 may require postprandial BG tests approximately 2 h after meals to assess their efficacy. Frequently, insulin is dosed based on food consumption (carbohydrates) and the current SMBG reading. Pumps have the possibility of delivering the bolus dose in different ways in order to reduce the postprandial blood glucose excursions (179). 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.

Advice for persistent deviations of BG from target

- Elevated BG level before breakfast → increase pre-dinner or pre-bed 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 pre-breakfast basal insulin or increase dose of pre-breakfast 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 2–3 h after injection.
- When using carbohydrate counting, persistent elevations of postmeal 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 U of insulin will cover).
- The insulin to 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 2–3 mmol/L (20–30 mg/dL), the correction factor (see below) can be used to calculate out how much more (or less) insulin should have been ideally given for a certain meal.
- Some centers also count protein and fat for calculating insulin requirements when using a pump [fat-protein units (FPU)] (174). 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.
- Correction doses (also called insulin sensitivity factor, correction factor) can be used according to the ‘1800 rule’, i.e., divide 1800 by total daily insulin dose to get the mg/dL that 1 U of rapid-acting insulin will lower the blood glucose. For

mmol/L, use the ‘100 rule’, i.e., divide 100 by total daily insulin dose (180). For regular insulin, a ‘1500 rule’ can be used for results in mg/dL and a ‘83-rule’ for results in mmol/L. However, correction doses should always be adjusted individually before administration, depending on other factors affecting insulin resistance like exercise.

- Rise in BG level after evening meal → increase pre-evening meal regular/rapid-acting insulin.

In addition

- Unexplained hypoglycemia requires re-evaluation of insulin therapy.
- Hyperglycemia or hypoglycemia occurring in the presence of intercurrent illness requires a knowledge of ‘sick day management’.
- 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 (e.g., 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 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.

Dawn phenomenon

Blood glucose levels tend to rise in the hours of the morning (usually after 05:00 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 (181–183) 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).

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 with MDI (184). 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, and
- change to insulin pump treatment.

Conflicts of interest

RH has received lecture honoraria from NovoNordisk, Lilly, Sanofi, Medtronic, Johnson & Johnson, and Roche. PJ-C has received lecture fees from Eli Lilly, Novo-Nordisk, Sanofi, Abbott, Bayer, Medtronic, and Roche. TD has received honoraria from NovoNordisk, Lilly, Sanofi, Medtronic, Biodel, Bekton Dickinson, Boehringer, and Roche. TB has received honoraria from NovoNordisk, Lilly, Sanofi, and Medtronic. HJB has received honoraria and lecture fees from Novo Nordisk, Lilly, Sanofi, Medtronic, and Roche. LD has received research support from Novo Nordisk and Advisory Groups for Sanofi. The remaining authors (TU, BS, and LM) have declared no potential conflicts. Editors of the ISPAD Clinical Practice Consensus Guidelines 2014 Compendium: Carlo Acerini, Maria Craig, David Maahs, and Ragnar Hanas.

References

1. BANGSTAD HJ, DANNE T, DEEB L, JAROSZ-CHOBOT P, URAKAMI T, HANAS R. Insulin treatment in children and adolescents with diabetes. *Pediatr Diabetes* 2009; 10 (Suppl. 12): 82–99.
2. JOHNSON S. Retinopathy and nephropathy in diabetes mellitus: comparison of the effects of two forms of treatment. *Diabetes* 1960; 9: 1–8.
3. SIEBENHOFER A, PLANK J, BERGHOLD A et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. *Cochrane Database Syst Rev* 2006: CD003287.
4. BRUNNER GA, HIRSCHBERGER S, SENDLHOFER G et al. Post-prandial administration of the insulin analogue insulin aspart in patients with type 1 diabetes mellitus. *Diabet Med* 2000; 17: 371–375.
5. DANNE T, DEISS D, HOPFENMULLER W, VON SCHUTZ W, KORDONOURI O. Experience with insulin analogues in children. *Horm Res* 2002; 57 (Suppl. 1): 46–53.
6. MORTENSEN HB, LINDHOLM A, OLSEN BS, HYLLEBERG B. Rapid appearance and onset of action of insulin aspart in paediatric subjects with type 1 diabetes. *Eur J Pediatr* 2000; 159: 483–488.
7. DANNE T, BECKER RH, HEISE T, BITTNER C, FRICK AD, RAVE K. Pharmacokinetics, prandial glucose control, and safety of insulin glulisine in children and adolescents with type 1 diabetes. *Diabetes Care* 2005; 28: 2100–2105.
8. ACERINI CL, CHEETHAM TD, EDGE JA, DUNGER DB. Both insulin sensitivity and insulin clearance in children and young adults with type I (insulin-dependent) diabetes vary with growth hormone concentrations and with age. *Diabetologia* 2000; 43: 61–68.
9. AMIEL SA, SHERWIN RS, SIMONSON DC, LAURITANO AA, TAMBORLANE WV. Impaired insulin action in puberty. A contributing factor to poor glycemic control in adolescents with diabetes. *N Engl J Med* 1986; 315: 215–219.
10. PLANK J, WUTTE A, BRUNNER G et al. A direct comparison of insulin aspart and insulin lispro in patients with type 1 diabetes. *Diabetes Care* 2002; 25: 2053–2057.
11. CEMEROGLU AP, KLEIS L, WOOD A, PARKES C, WOOD MA, DAVIS AT. Comparison of the effect of insulin glulisine to insulin aspart on breakfast postprandial blood glucose levels in children with type 1 DM on multiple daily injections. *Endocr Pract* 2013; 19:614–619.
12. HEISE T, NOSEK L, SPITZER H et al. Insulin glulisine: a faster onset of action compared with insulin lispro. *Diabetes Obes Metab* 2007; 9: 746–753.
13. FORD-ADAMS ME, MURPHY NP, MOORE EJ et al. Insulin lispro: a potential role in preventing nocturnal hypoglycaemia in young children with diabetes mellitus. *Diabet Med* 2003; 20: 656–660.
14. DEEB LC, HOLCOMBE JH, BRUNELLE R et al. Insulin lispro lowers postprandial glucose in prepubertal children with diabetes. *Pediatrics* 2001; 108: 1175–1179.
15. TUBIANA-RUFI N, COUTANT R, BLOCH J et al. Special management of insulin lispro in continuous subcutaneous insulin infusion in young diabetic children: a randomized cross-over study. *Horm Res* 2004; 62: 265–271.
16. TUPOLA S, KOMULAINEN J, JAASKELAINEN J, SIPILA I. Post-prandial insulin lispro vs. human regular insulin in prepubertal children with type 1 diabetes mellitus. *Diabet Med* 2001; 18: 654–658.
17. HOLCOMBE JH, ZALANI S, ARORA VK, MAST CJ. Comparison of insulin lispro with regular human insulin for the treatment of type 1 diabetes in adolescents. *Clin Ther* 2002; 24: 629–638.
18. RENNER R, PFUTZNER A, TRAUTMANN M, HARZER O, SAUTER K, LANDGRAF R. Use of insulin lispro in continuous subcutaneous insulin infusion treatment. Results of a multicenter trial. German Humalog-CSII Study Group. *Diabetes Care* 1999; 22: 784–788.
19. RUTLEDGE KS, CHASE HP, KLINGENSMITH GJ, WALRAVENS PA, SLOVER RH, GARG SK. Effectiveness of postprandial Humalog in toddlers with diabetes. *Pediatrics* 1997; 100: 968–972.
20. HELLER SR, COLAGIURI S, VAALER S et al. Hypoglycaemia with insulin aspart: a double-blind, randomised, crossover trial in subjects with type 1 diabetes. *Diabet Med* 2004; 21: 769–775.
21. HOME PD, LINDHOLM A, RIIS A, European Insulin Aspart Study Group. Insulin aspart vs. human insulin in the management of long-term blood glucose control in type 1 diabetes mellitus: a randomized controlled trial. *Diabet Med* 2000; 17: 762–770.
22. HEISE T, NOSEK L, RONN BB et al. Lower within-subject variability of insulin detemir in comparison to

- NPH insulin and insulin glargine in people with type 1 diabetes. *Diabetes* 2004; 53: 1614–1620.
23. DANNE T, DATZ N, ENDAHL L et al. Insulin detemir is characterized by a more reproducible pharmacokinetic profile than insulin glargine in children and adolescents with type 1 diabetes: results from a randomized, double-blind, controlled trial. *Pediatr Diabetes* 2008; 9: 554–560.
 24. HERMANSEN K, FONTAINE P, KUKOLJA KK, PETERKOVA V, LETH G, GALL MA. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. *Diabetologia* 2004; 47: 622–629.
 25. SCHOBER E, SCHOENLE E, VAN DYK J, WERNICKE-PANTEN K. Comparative trial between insulin glargine and NPH insulin in children and adolescents with type 1 diabetes. *Diabetes Care* 2001; 24: 2005–2006.
 26. DEBRAH K, SHERWIN RS, MURPHY J, KERR D. Effect of caffeine on recognition of and physiological responses to hypoglycaemia in insulin-dependent diabetes. *Lancet* 1996; 347: 19–24.
 27. PORCELLATI F, ROSSETTI P, PAMPANELLI S et al. Better long-term glycaemic control with the basal insulin glargine as compared with NPH in patients with type 1 diabetes mellitus given meal-time lispro insulin. *Diabet Med* 2004; 21: 1213–1220.
 28. NICE. (National Institute of Clinical Excellence). Guidance on the Use of Long-Acting Insulin Analogues for the Treatment of Diabetes-Insulin Glargine. Technology Appraisal Guidance No 53 2002 (available from <http://guidance.nice.org.uk/TA53/guidance/pdf/English>).
 29. CHASE HP, DIXON B, PEARSON J et al. Reduced hypoglycemic episodes and improved glycemic control in children with type 1 diabetes using insulin glargine and neutral protamine Hagedorn insulin. *J Pediatr* 2003; 143: 737–740.
 30. HATHOUT EH, FUJISHIGE L, GEACH J, ISCHANDAR M, MARUO S, MACE JW. Effect of therapy with insulin glargine (lantus) on glycemic control in toddlers, children, and adolescents with diabetes. *Diabetes Technol Ther* 2003; 5: 801–806.
 31. ALEMZADEH R, BERHE T, WYATT DT. Flexible insulin therapy with glargine insulin improved glycemic control and reduced severe hypoglycemia among preschool-aged children with type 1 diabetes mellitus. *Pediatrics* 2005; 115: 1320–1324.
 32. MOHN A, STRANG S, WERNICKE-PANTEN K, LANG AM, EDGE JA, DUNGER DB. Nocturnal glucose control and free insulin levels in children with type 1 diabetes by use of the long-acting insulin HOE 901 as part of a three-injection regimen. *Diabetes Care* 2000; 23: 557–559.
 33. ROBERTSON KJ, SCHOENLE E, GUCEV Z, MORDHORST L, GALL MA, LUDVIGSSON J. Insulin detemir compared with NPH insulin in children and adolescents with type 1 diabetes. *Diabet Med* 2007; 24: 27–34.
 34. DANNE T, LUPKE K, WALTE K, VON SCHUETZ W, GALL MA. Insulin detemir is characterized by a consistent pharmacokinetic profile across age-groups in children, adolescents, and adults with type 1 diabetes. *Diabetes Care* 2003; 26: 3087–3092.
 35. VAGUE P, SELAM JL, SKEIE S et al. Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. *Diabetes Care* 2003; 26: 590–596.
 36. DE BEAUFORT CE, HOUTZAGERS CM, BRUINING GJ et al. Continuous subcutaneous insulin infusion (CSII) versus conventional injection therapy in newly diagnosed diabetic children: two-year follow-up of a randomized, prospective trial. *Diabet Med* 1989; 6: 766–771.
 37. DCCT. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group. *J Pediatr* 1994; 125: 177–188.
 38. JACOBSON AM, MUSEN G, RYAN CM et al. Long-term effect of diabetes and its treatment on cognitive function. *N Engl J Med* 2007; 356: 1842–1852.
 39. MUSEN G, JACOBSON AM, RYAN CM et al. Impact of diabetes and its treatment on cognitive function among adolescents who participated in the Diabetes Control and Complications Trial. *Diabetes Care* 2008; 31: 1933–1938.
 40. MORTENSEN HB, ROBERTSON KJ, AANSTOOT HJ et al. Insulin management and metabolic control of type 1 diabetes mellitus in childhood and adolescence in 18 countries. Hvidore Study Group on Childhood Diabetes. *Diabet Med* 1998; 15: 752–759.
 41. DOWNIE E, CRAIG ME, HING S, CUSUMANO J, CHAN AK, DONAGHUE KC. Continued reduction in the prevalence of retinopathy in adolescents with type 1 diabetes: role of insulin therapy and glycemic control. *Diabetes Care* 2011; 34: 2368–2373.
 42. DiMEGLIO LA, POTTORFF TM, BOYD SR, FRANCE L, FINEBERG N, EUGSTER EA. A randomized, controlled study of insulin pump therapy in diabetic preschoolers. *J Pediatr* 2004; 145: 380–384.
 43. PICKUP J, MATTOCK M, KERRY S. Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomised controlled trials. *BMJ* 2002; 324: 705.
 44. WILLI SM, PLANTON J, EGEDE L, SCHWARZ S. Benefits of continuous subcutaneous insulin infusion in children with type 1 diabetes. *J Pediatr* 2003; 143: 796–801.
 45. KAUFMAN FR. Intensive management of type 1 diabetes in young children. *Lancet* 2005; 365: 737–738.
 46. HANAS R, ADOLFSSON P. Insulin pumps in pediatric routine care improve long-term metabolic control without increasing the risk of hypoglycemia. *Pediatr Diabetes* 2006; 7: 25–31.
 47. BOLAND EA, GREY M, OESTERLE A, FREDRICKSON L, TAMBORLANE WV. Continuous subcutaneous insulin infusion. A new way to lower risk of severe hypoglycemia, improve metabolic control, and enhance coping in adolescents with type 1 diabetes. *Diabetes Care* 1999; 22: 1779–1784.
 48. LITTON J, RICE A, FRIEDMAN N, ODEN J, LEE MM, FREEMARK M. Insulin pump therapy in toddlers and preschool children with type 1 diabetes mellitus. *J Pediatr* 2002; 141: 490–495.

49. AHERN JAH, BOLAND EA, DOANE R et al. Insulin pump therapy in pediatrics: a therapeutic alternative to safely lower HbA1c levels across all age groups. *Pediatr Diabetes* 2002; 3: 10–15.
50. PLOTNICK LP, CLARK LM, BRANCATI FL, ERLINGER T. Safety and effectiveness of insulin pump therapy in children and adolescents with type 1 diabetes. *Diabetes Care* 2003; 26: 1142–1146.
51. SAHA ME, HUUPPONE T, MIKAEL K, JUUTI M, KOMULAINEN J. Continuous subcutaneous insulin infusion in the treatment of children and adolescents with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab* 2002; 15: 1005–1010.
52. SULLI N, SHASHAJ B. Continuous subcutaneous insulin infusion in children and adolescents with diabetes mellitus: decreased HbA1c with low risk of hypoglycemia. *J Pediatr Endocrinol Metab* 2003; 16: 393–399.
53. SKOGSBERG L, FORS H, HANAS R, CHAPLIN JE, LINDMAN E, SKOGSBERG J. Improved treatment satisfaction but no difference in metabolic control when using continuous subcutaneous insulin infusion vs. multiple daily injections in children at onset of type 1 diabetes mellitus. *Pediatr Diabetes* 2008; 9: 472–479.
54. BOLLI GB, KERR D, THOMAS R et al. Comparison of a multiple daily insulin injection regimen (basal once-daily glargine plus mealtime lispro) and continuous subcutaneous insulin infusion (lispro) in type 1 diabetes: a randomized open parallel multicenter study. *Diabetes Care* 2009; 32: 1170–1176.
55. COLQUITT J, ROYLE P, WAUGH N. Are analogue insulins better than soluble in continuous subcutaneous insulin infusion? Results of a meta-analysis. *Diabet Med* 2003; 20: 863–866.
56. SULMONT V, SOUCHON PF, GOUILLARD-DARNAUD C et al. Metabolic control in children with diabetes mellitus who are younger than 6 years at diagnosis: continuous subcutaneous insulin infusion as a first line treatment? *J Pediatr* 2010; 157: 103–107.
57. DANNE T, BATTELLINO T, JAROSZ-CHOBOT P et al. Establishing glycaemic control with continuous subcutaneous insulin infusion in children and adolescents with type 1 diabetes: experience of the PedPump Study in 17 countries. *Diabetologia* 2008; 51: 1594–1601.
58. PHILLIP M, BATTELLINO T, RODRIGUEZ H, DANNE T, KAUFMAN F. Use of insulin pump therapy in the pediatric age-group: consensus statement from the European Society for Paediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes, endorsed by the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2007; 30: 1653–1662.
59. PANKOWSKA E, BLAZIK M, DZIECHCIARZ P, SZYPOWSKA A, SZAJEWSKA H. Continuous subcutaneous insulin infusion vs. multiple daily injections in children with type 1 diabetes: a systematic review and meta-analysis of randomized control trials. *Pediatr Diabetes* 2009; 10: 52–58.
60. DCCT. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; 329: 977–986.
61. WHITE NH, CLEARY PA, DAHMS W, GOLDSTEIN D, MALONE J, TAMBORLANE WV. Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after the conclusion of the Diabetes Control and Complications Trial (DCCT). *J Pediatr* 2001; 139: 804–812.
62. BATTELLINO T, CONGET I, OLSEN B et al. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. *Diabetologia* 2012; 55: 3155–3162.
63. ELLERI D, ALLEN JM, KUMARESWARAN K et al. Closed-loop basal insulin delivery over 36 hours in adolescents with type 1 diabetes: randomized clinical trial. *Diabetes Care* 2013; 36: 838–844.
64. PHILLIP M, BATTELLINO T, ATLAS E et al. Nocturnal glucose control with an artificial pancreas at a diabetes camp. *N Engl J Med* 2013; 368: 824–833.
65. WEINZIMER SA, STEIL GM, SWAN KL, DZIURA J, KURTZ N, TAMBORLANE WV. Fully automated closed-loop insulin delivery versus semiautomated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. *Diabetes Care* 2008; 31: 934–939.
66. LAURITZEN T. Pharmacokinetic and clinical aspects of intensified subcutaneous insulin therapy. *Dan Med Bull* 1985; 32: 104–118.
67. BECKER R, FRICK A, HEINEMANN L, NOSEK L, RAVE K. Dose response relation of insulin glulisine (GLU) in subjects with type 1 diabetes (T1DM). *Diabetes* 2005; 54 (Suppl. 1): Abstract 1367-P.
68. WOODWORTH J, HOWEY D, BOWSHER R, LUTZ S, SANAT P, BRADY P. Lys(B28), Pro(B29) human insulin (K): dose ranging vs. humulin R (H). *Diabetologia* 1993; 42 (Suppl. 1): 54A.
69. NOSEK L, HEINEMANN L, KAISER M, ARNOLDS S, HEISE T. No increase in the duration of action with rising doses of insulin aspart. *Diabetes* 2003; 52 (Suppl. 1): Abstract 551-P.
70. PHILOTHEOU A, ARSLANIAN S, BLATNICZKY L, PETERKOVA V, SOUHAMI E, DANNE T. Comparable efficacy and safety of insulin glulisine and insulin lispro when given as part of a Basal-bolus insulin regimen in a 26-week trial in pediatric patients with type 1 diabetes. *Diabetes Technol Ther* 2011; 13: 327–334.
71. DANNE T, AMAN J, SCHOBER E et al. A comparison of postprandial and preprandial administration of insulin aspart in children and adolescents with type 1 diabetes. *Diabetes Care* 2003; 26: 2359–2364.
72. KRASNER A, POHL R, SIMMS P, PICHOTTA P, HAUSER R, DE SOUZA E. A review of a family of ultra-rapid-acting insulins: formulation development. *J Diabetes Sci Technol* 2012; 6: 786–796.
73. KURTZHALS P, SCHAFFER L, SORENSEN A et al. Correlations of receptor binding and metabolic and mitogenic potencies of insulin analogs designed for clinical use. *Diabetes* 2000; 49: 999–1005.
74. European Medicines Agency (EMA) Statement 2013 (available from http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2013/05/WC500143823.pdf).
75. STILLER R, KOTHNY T, GUDAT U et al. Intravenous administration of insulin lispro versus regular insulin

- in patients with type 1 diabetes. *Diabetes* 1999; 48 (Suppl. 1): Abstract 0497.
76. LEPORE M, PAMPANELLI S, FANELLI C et al. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes* 2000; 49: 2142–2148.
 77. HELLER S, KOENEN C, BODE B. Comparison of insulin detemir and insulin glargine in a basal-bolus regimen, with insulin aspart as the mealtime insulin, in patients with type 1 diabetes: a 52-week, multinational, randomized, open-label, parallel-group, treat-to-target noninferiority trial. *Clin Ther* 2009; 31: 2086–2097.
 78. DIXON B, PETER CHASE H, BURDICK J et al. Use of insulin glargine in children under age 6 with type 1 diabetes. *Pediatr Diabetes* 2005; 6: 150–154.
 79. THISTED H, JOHNSEN SP, RUNGBY J. An update on the long-acting insulin analogue glargine. *Basic Clin Pharmacol Toxicol* 2006; 99: 1–11.
 80. PÄIVÄRINTA M, TAPANAINEN P, VEIJOLA R. Basal insulin switch from NPH to glargine in children and adolescents with type 1 diabetes. *Pediatr Diabetes* 2008; 9: 83–90.
 81. DANNE T, PHILOTHEOU A, GOLDMAN D et al. A randomized trial comparing the rate of hypoglycemia – assessed using continuous glucose monitoring – in 125 preschool children with type 1 diabetes treated with insulin glargine or NPH insulin (the PRESCHOOL study). *Pediatr Diabetes* 2013; 14: 593–601.
 82. HAMANN A, MATTHAEI S, ROSAK C, SILVESTRE L. A randomized clinical trial comparing breakfast, dinner, or bedtime administration of insulin glargine in patients with type 1 diabetes. *Diabetes Care* 2003; 26: 1738–1744.
 83. HEISE T, BOTT S, RAVE K, DRESSLER A, ROSSKAMP R, HEINEMANN L. No evidence for accumulation of insulin glargine (LANTUS): a multiple injection study in patients with Type 1 diabetes. *Diabet Med* 2002; 19: 490–495.
 84. RATNER RE, HIRSCH IB, NEIFING JL, GARG SK, MECCA TE, WILSON CA. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes. *Diabetes Care* 2000; 23: 639–643.
 85. PLANK J, BODENLENZ M, SINNER F et al. A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir. *Diabetes Care* 2005; 28: 1107–1112.
 86. CARLSSON A, FORSANDER G, LUDVIGSSON J, LARSEN S, ORTQVIST E, GROUP SP-YS. A multicenter observational safety study in Swedish children and adolescents using insulin detemir for the treatment of type 1 diabetes. *Pediatr Diabetes* 2013; 14: 358–365.
 87. BIESTER T, BLAESIG S, REMUS K et al. Insulin degludec's ultra-long pharmacokinetic properties observed in adults are retained in children and adolescents with type 1 diabetes. *Pediatr Diabetes* 2014; 15: 27–33.
 88. ROSENSTOCK J, BERGENSTAL RM, BLEVINS TC et al. Better glycemic control and weight loss with the novel long-acting basal insulin LY2605541 compared with insulin glargine in type 1 diabetes: a randomized, crossover study. *Diabetes Care* 2013; 36: 522–528.
 89. MORTENSEN H, KOCOVA M, TENG LY, KEIDING J, BRUCKNER I, PHILOTHEOU A. Biphasic insulin aspart vs. human insulin in adolescents with type 1 diabetes on multiple daily insulin injections. *Pediatr Diabetes* 2006; 7: 4–10.
 90. STICKELMEYER MP, GRAF CJ, FRANK BH, BALLARD RL, STORMS SM. Stability of U-10 and U-50 dilutions of insulin lispro. *Diabetes Technol Ther* 2000; 2: 61–66.
 91. JORGENSEN D, SOLBECK H. Dilution of insulin aspart with NPH medium for small dose use in continuous subcutaneous insulin infusion does not affect in vitro stability. *Diabetes* 2005; 54 (Suppl. 1): Abstract A102.
 92. DATZ N, WESTERGAARD L, NESTORIS C et al. Increase of insulin requirements after changing from U40 to U100 insulin in children and adolescents with type 1 diabetes without effect on the metabolic status. *Pediatr Diabetes* 2008; 9: Abstract 59.
 93. GRAJOWER MM, FRASER CG, HOLCOMBE JH et al. How long should insulin be used once a vial is started? *Diabetes Care* 2003; 26: 2665–2666 discussion 266-9.
 94. RANGAWALA S, SHAH P, HUSSAIN S, GOENKA S, PILLAI K. Insulin stored in matka (earthen pitcher) with water for 60 days does not reduce in bio-activity. *J Pediatr Endocrinol Metab* 1997; 10 (Suppl. 2): Abstract 347.
 95. MCCARTHY JA, COVARRUBIAS B, SINK P. Is the traditional alcohol wipe necessary before an insulin injection? Dogma disputed. *Diabetes Care* 1993; 16: 402.
 96. LOEB JA, HEROLD KC, BARTON KP, ROBINSON LE, JASPAN JB. Systematic approach to diagnosis and management of biphasic insulin allergy with local anti-inflammatory agents. *Diabetes Care* 1989; 12: 421–423.
 97. KORDONOURI O, LAUTERBORN R, DEISS D. Lipohypertrophy in young patients with type 1 diabetes. *Diabetes Care* 2002; 25: 634.
 98. HOLSTEIN A, STEGE H, KOVACS P. Lipoatrophy associated with the use of insulin analogues: a new case associated with the use of insulin glargine and review of the literature. *Expert Opin Drug Saf* 2010; 9: 225–231.
 99. FORSANDER GA, MALMODIN OC, KORDONURI O, LUDVIGSSON J, KLINGENSMITH G, BEAUFORT CD. An ISPAD survey insulin-induced lipoatrophy. *Pediatr Diabetes* 2013; 14: 1.
 100. SCHNELL K, BIESTER T, TSIOLI C, DATZ N, DANNE T, KORDONURI O. Lipoatrophy in a large pediatric diabetes outpatient service. *Pediatr Diabetes* 2013; 14: 20.
 101. CHANTELAU E, LEE DM, HEMMANN DM, ZIPFEL U, ECHTERHOFF S. What makes insulin injections painful? *BMJ* 1991; 303: 26–27.
 102. HANAS R, ADOLFSSON P, ELFVIN-AKESSON K et al. Indwelling catheters used from the onset of diabetes decrease injection pain and pre-injection anxiety. *J Pediatr* 2002; 140: 315–320.
 103. ARENDT-NIELSEN L, EGEKVIST H, BJERRING P. Pain following controlled cutaneous insertion of needles with different diameters. *Somatosens Mot Res* 2006; 23: 37–43.
 104. GINSBERG BH, PARKES JL, SPARACINO C. The kinetics of insulin administration by insulin pens. *Horm Metab Res* 1994; 26: 584–587.

105. SINDELKA G, HEINEMANN L, BERGER M, FRENCK W, CHANTELAU E. Effect of insulin concentration, subcutaneous fat thickness and skin temperature on subcutaneous insulin absorption in healthy subjects. *Diabetologia* 1994; 37: 377–380.
106. YOUNG RJ, HANNAN WJ, FRIER BM, STEEL JM, DUNCAN LJ. Diabetic lipohypertrophy delays insulin absorption. *Diabetes Care* 1984; 7: 479–480.
107. JOHANSSON UB, AMSBERG S, HANNERZ L et al. Impaired absorption of insulin aspart from lipohypertrophic injection sites. *Diabetes Care* 2005; 28: 2025–2027.
108. BANTLE JP, NEAL L, FRANKAMP LM. Effects of the anatomical region used for insulin injections on glycemia in type I diabetes subjects. *Diabetes Care* 1993; 16: 1592–1597.
109. FRID A, GUNNARSSON R, GUNTNER P, LINDE B. Effects of accidental intramuscular injection on insulin absorption in IDDM. *Diabetes Care* 1988; 11: 41–45.
110. FRID A, OSTMAN J, LINDE B. Hypoglycemia risk during exercise after intramuscular injection of insulin in thigh in IDDM. *Diabetes Care* 1990; 13: 473–477.
111. Frid A. Injection and absorption of insulin. PhD Thesis: Faculty of Medicine, Karolinska Institute, Stockholm, Sweden; 1992.
112. MUDALIAR SR, LINDBERG FA, JOYCE M et al. Insulin aspart (B28 asp-insulin): a fast-acting analog of human insulin: absorption kinetics and action profile compared with regular human insulin in healthy nondiabetic subjects. *Diabetes Care* 1999; 22: 1501–1506.
113. TER BRAAK EW, WOODWORTH JR, BIANCHI R et al. Injection site effects on the pharmacokinetics and glucodynamics of insulin lispro and regular insulin. *Diabetes Care* 1996; 19: 1437–1440.
114. RAVE K, HEISE T, WEYER C et al. Intramuscular versus subcutaneous injection of soluble and lispro insulin: comparison of metabolic effects in healthy subjects. *Diabet Med* 1998; 15: 747–751.
115. OWENS DR, COATES PA, LUZIO SD, TINBERGEN JP, KURZHALS R. Pharmacokinetics of ¹²⁵I-labeled insulin glargine (HOE 901) in healthy men: comparison with NPH insulin and the influence of different subcutaneous injection sites. *Diabetes Care* 2000; 23: 813–819.
116. PETER R, LUZIO SD, DUNSEATH G et al. Effects of exercise on the absorption of insulin glargine in patients with type 1 diabetes. *Diabetes Care* 2005; 28: 560–565.
117. KARGES B, BOEHM BO, KARGES W. Early hypoglycaemia after accidental intramuscular injection of insulin glargine. *Diabet Med* 2005; 22: 1444–1445.
118. MORROW L, MUCHMORE DB, HOMPESCH M, LUDINGTON EA, VAUGHN DE. Comparative pharmacokinetics and insulin action for three rapid-acting insulin analogs injected subcutaneously with and without hyaluronidase. *Diabetes Care* 2013; 36: 273–275.
119. CENGIZ E, WEINZIMER SA, SHERR JL et al. Faster in and faster out: accelerating insulin absorption and action by insulin infusion site warming. *Diabetes Technol Ther* 2014; 16: 20–25.
120. SCHULER G, PELZ K, KERP L. Is the reuse of needles for insulin injection systems associated with a higher risk of cutaneous complications? *Diabetes Res Clin Pract* 1992; 16: 209–212.
121. FRID A, HIRSCH L, GASPAR R et al. New injection recommendations for patients with diabetes. *Diabetes Metab* 2010; 36 (Suppl. 2): S3–S18.
122. HOFMAN PL, LAWTON SA, PEART JM et al. An angled insertion technique using 6-mm needles markedly reduces the risk of intramuscular injections in children and adolescents. *Diabet Med* 2007; 24: 1400–1405.
123. BIRKEBAEK NH, JOHANSEN A, SOLVIG J. Cutis/subcutis thickness at insulin injection sites and localization of simulated insulin boluses in children with type 1 diabetes mellitus: need for individualization of injection technique? *Diabet Med* 1998; 15: 965–971.
124. SMITH CP, SARGENT MA, WILSON BP, PRICE DA. Subcutaneous or intramuscular insulin injections. *Arch Dis Child* 1991; 66: 879–882.
125. HANAS SR, LUDVIGSSON J. Metabolic control is not altered when using indwelling catheters for insulin injections. *Diabetes Care* 1994; 17: 716–718.
126. BURDICK P, COOPER S, HORNER B, COBRY E, MCFANN K, CHASE HP. Use of a subcutaneous injection port to improve glycemic control in children with type 1 diabetes. *Pediatr Diabetes* 2009; 10: 116–119.
127. HANAS SR, CARLSSON S, FRID A, LUDVIGSSON J. Unchanged insulin absorption after 4 days' use of subcutaneous indwelling catheters for insulin injections. *Diabetes Care* 1997; 20: 487–490.
128. HANAS R, LUDVIGSSON J. Side effects and indwelling times of subcutaneous catheters for insulin injections: a new device for injecting insulin with a minimum of pain in the treatment of insulin-dependent diabetes mellitus. *Diabetes Res Clin Pract* 1990; 10: 73–83.
129. DIGLAS J, FEINBÖCK C, WINKLER F et al. Reduced pain perception with an automatic injection device for use with an insulin pen. *Horm Res* 1998; 50: Abstract A30.
130. CHIASSEON JL, DUCROS F, POLIQUIN-HAMET M, LOPEZ D, LECAVALIER L, HAMET P. Continuous subcutaneous insulin infusion (Mill-Hill Infuser) versus multiple injections (Medi-Jector) in the treatment of insulin-dependent diabetes mellitus and the effect of metabolic control on microangiopathy. *Diabetes Care* 1984; 7: 331–337.
131. HOUTZAGERS CM, VISSER AP, BERNTZEN PA, HEINE RJ, VAN DER VEEN EA. The Medi-Jector II: efficacy and acceptability in insulin-dependent diabetic patients with and without needle phobia. *Diabet Med* 1988; 5: 135–138.
132. ENGERDA EE, ABBINK EJ, TACK CJ, DE GALAN BE. Improved pharmacokinetic and pharmacodynamic profile of rapid-acting insulin using needle-free jet injection technology. *Diabetes Care* 2011; 34: 1804–1808.
133. BERGHAUSER MA, KAPELLEN T, HEIDTMANN B, HABERLAND H, KLINKERT C, HOLL RW. Continuous subcutaneous insulin infusion in toddlers starting at diagnosis of type 1 diabetes mellitus. A multicenter analysis of 104 patients from 63 centres in Germany and Austria. *Pediatr Diabetes* 2008; 9: 590–595.
134. WILSON DM, BUCKINGHAM BA, KUNSELMAN EL, SULLIVAN MM, PAGUNTALAN HU, GITELMAN SE. A two-center randomized controlled feasibility trial of insulin pump therapy in young children with diabetes. *Diabetes Care* 2005; 28: 15–19.

135. BLACKETT PR. Insulin pump treatment for recurrent ketoacidosis in adolescence [letter]. *Diabetes Care* 1995; 18: 881–882.
136. STEINDEL BS, ROE TR, COSTIN G, CARLSON M, KAUFMAN FR. Continuous subcutaneous insulin infusion (CSII) in children and adolescents with chronic poorly controlled type 1 diabetes mellitus. *Diabetes Res Clin Pract* 1995; 27: 199–204.
137. KAPELLEN TM, HEIDTMANN B, BACHMANN J, ZIEGLER R, GRABERT M, HOLL RW. Indications for insulin pump therapy in different age groups: an analysis of 1,567 children and adolescents. *Diabet Med* 2007; 24: 836–842.
138. NICE. (National Institute of Clinical Excellence). Clinical and Cost Effectiveness of Continuous Subcutaneous Insulin Infusion for Diabetes. Technology Appraisal No 57 2003 (available from <http://www.nice.org.uk/guidance/TA57>).
139. NAHATA L. Insulin therapy in pediatric patients with type I diabetes: continuous subcutaneous insulin infusion versus multiple daily injections. *Clin Pediatr (Phila)* 2006; 45: 503–508.
140. SKOGSBERG L, LINDMAN E, FORS H. To compare metabolic control and quality of life (QoL) of CSII with multiple daily injections (MDI) in children/adolescents at onset of T1DM. *Pediatr Diabetes* 2006; 7: Abstract 65.
141. KORDONOURI O, PANKOWSKA E, RAMI B et al. Sensor-augmented pump therapy from the diagnosis of childhood type 1 diabetes: results of the Paediatric Onset Study (ONSET) after 12 months of treatment. *Diabetologia* 2010; 53: 2487–2495.
142. ENANDER R, GUNDEVALL C, STROMGREN A, CHAPLIN J, HANAS R. Carbohydrate counting with a bolus calculator improves post-prandial blood glucose levels in children and adolescents with type 1 diabetes using insulin pumps. *Pediatr Diabetes* 2012; 13: 545–551.
143. ZISSER H, ROBINSON L, BEVIER W et al. Bolus calculator: a review of four "smart" insulin pumps. *Diabetes Technol Ther* 2008; 10: 441–444.
144. HANAS R, LUNDQVIST K, WINDELL L. Blood glucose and beta-hydroxybutyrate responses when the insulin pump is stopped in children and adolescents. *Pediatr Diabetes* 2006; 7 (Suppl. 5): Abstract 35.
145. ZISSER H. Quantifying the impact of a short-interval interruption of insulin-pump infusion sets on glycemic excursions. *Diabetes Care* 2008; 31: 238–239.
146. SULLI N, SHASHAJ B. Long-term benefits of continuous subcutaneous insulin infusion in children with type 1 diabetes: a 4-year follow-up. *Diabet Med* 2006; 23: 900–906.
147. JOHNSON SR, COOPER MN, JONES TW, DAVIS EA. Long-term outcome of insulin pump therapy in children with type 1 diabetes assessed in a large population-based case-control study. *Diabetologia* 2013; 56: 2392–2400.
148. HANAS R, LUDVIGSSON J. Hypoglycemia and ketoacidosis with insulin pump therapy in children and adolescents. *Pediatr Diabetes* 2006; 7 (Suppl. 4): 32–38.
149. MARGEIRSDOTTIR H, LARSEN J, BRUNBORG C, DAHL-JORGENSEN K. Nationwide improvement in HbA1c and complication screening in a benchmarking project in childhood diabetes. *Pediatr Diabetes* 2006; 7 (Suppl. 5): Abstract 18.
150. HANAS R, LINDGREN F, LINDBLAD B. A 2-yr national population study of pediatric ketoacidosis in Sweden: predisposing conditions and insulin pump use. *Pediatr Diabetes* 2009; 10: 33–37.
151. LIU D, MOBERG E, WREDLING R, LINS PE, ADAMSON U. Insulin absorption is faster when keeping the infusion site in use for three days during continuous subcutaneous insulin infusion. *Diabetes Res Clin Pract* 1991; 12: 19–24.
152. BODE B, WEINSTEIN R, BELL D et al. Comparison of insulin aspart with buffered regular insulin and insulin lispro in continuous subcutaneous insulin infusion: a randomized study in type 1 diabetes. *Diabetes Care* 2002; 25: 439–444.
153. VAN BON AC, BODE BW, SERT-LANGERON C, DEVRIES JH, CHARPENTIER G. Insulin glulisine compared to insulin aspart and to insulin lispro administered by continuous subcutaneous insulin infusion in patients with type 1 diabetes: a randomized controlled trial. *Diabetes Technol Ther* 2011; 13: 607–614.
154. WOOD JR, MORELAND EC, VOLKENING LK, SVOREN BM, BUTLER DA, LAFFEL LM. Durability of insulin pump use in pediatric patients with type 1 diabetes. *Diabetes Care* 2006; 29: 2355–2360.
155. TAMBORLANE WV, BECK RW, BODE BW et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 2008; 359: 1464–1476.
156. WEINZIMER S, XING D, TANSEY M et al. FreeStyle navigator continuous glucose monitoring system use in children with type 1 diabetes using glargine-based multiple daily dose regimens: results of a pilot trial Diabetes Research in Children Network (DirecNet) Study Group. *Diabetes Care* 2008; 31: 525–527.
157. HIRSCH IB, ABELSETH J, BODE BW et al. Sensor-augmented insulin pump therapy: results of the first randomized treat-to-target study. *Diabetes Technol Ther* 2008; 10: 377–383.
158. PEYROT M, RUBIN RR, GROUP SS. Treatment satisfaction in the sensor-augmented pump therapy for A1C reduction 3 (STAR 3) trial. *Diabet Med* 2013; 30: 464–467.
159. SLOVER RH, WELSH JB, CRIEGO A et al. Effectiveness of sensor-augmented pump therapy in children and adolescents with type 1 diabetes in the STAR 3 study. *Pediatr Diabetes* 2012; 13: 6–11.
160. BUSE JB, KUDVA YC, BATTELINO T, DAVIS SN, SHIN J, WELSH JB. Effects of sensor-augmented pump therapy on glycemic variability in well-controlled type 1 diabetes in the STAR 3 study. *Diabetes Technol Ther* 2012; 14: 644–647.
161. BUCKINGHAM B, COBRY E, CLINTON P et al. Preventing hypoglycemia using predictive alarm algorithms and insulin pump suspension. *Diabetes Technol Ther* 2009; 11: 93–97.
162. ELLERI D, ALLEN JM, NODALE M et al. Automated overnight closed-loop glucose control in young children with type 1 diabetes. *Diabetes Technol Ther* 2011; 13: 419–424.
163. NIMRI R, MULLER I, ATLAS E et al. Night glucose control with MD-Logic artificial pancreas in home setting: a single blind, randomized crossover trial-interim analysis. *Pediatr Diabetes* 2014; 15: 91–99.

164. HOVORKA R, ELLERI D, THABIT H et al. Overnight closed-loop insulin delivery in young people with type 1 diabetes: a free-living, randomized clinical trial. *Diabetes Care* 2014; 37: 1204–1211.
165. WYSOCKI T, HARRIS MA, MAURAS N et al. Absence of adverse effects of severe hypoglycemia on cognitive function in school-aged children with diabetes over 18 months. *Diabetes Care* 2003; 26: 1100–1105.
166. JEHLER PM, MICHELER C, JEHLER DR, BREITIG D, BOEHM BO. Inadequate suspension of neutral protamine Hagedorn (NPH) insulin in pens [see comments]. *Lancet* 1999; 354: 1604–1607.
167. HEINE RJ, BILO HJ, FONK T, VAN DER VEEN EA, VAN DER MEER J. Absorption kinetics and action profiles of mixtures of short- and intermediate-acting insulins. *Diabetologia* 1984; 27: 558–562.
168. PERRIELLO G, TORLONE E, DI SANTO S et al. Effect of storage temperature of insulin on pharmacokinetics and pharmacodynamics of insulin mixtures injected subcutaneously in subjects with type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 1988; 31: 811–815.
169. HALBERG I, JACOBSEN L, DAHL U. A study on self-mixing insulin aspart with NPH insulin in the syringe before injection. *Diabetes* 1999; 48 (Suppl. 1): Abstract 448.
170. JOSEPH SE, KORZON-BURAKOWSKA A, WOODWORTH JR et al. The action profile of lispro is not blunted by mixing in the syringe with NPH insulin. *Diabetes Care* 1998; 21: 2098–2102.
171. BASTYR EJ III, HOLCOMBE JH, ANDERSON JH, CLORE JN. Mixing insulin lispro and ultralente insulin. *Diabetes Care* 1997; 20: 1047–1048.
172. KAPLAN W, RODRIGUEZ LM, SMITH OE, HAYMOND MW, HEPTULLA RA. Effects of mixing glargine and short-acting insulin analogs on glucose control. *Diabetes Care* 2004; 27: 2739–2740.
173. FIALLO-SCHARER R, HORNER B, MCFANN K, WALRAVENS P, CHASE HP. Mixing rapid-acting insulin analogues with insulin glargine in children with type 1 diabetes mellitus. *J Pediatr* 2006; 148: 481–484.
174. PANKOWSKA E, BLAZIK M, GROELE L. Does the fat-protein meal increase postprandial glucose level in type 1 diabetes patients on insulin pump: the conclusion of a randomized study. *Diabetes Technol Ther* 2012; 14: 16–22.
175. COBRY E, MCFANN K, MESSER L et al. Timing of meal insulin boluses to achieve optimal postprandial glycemic control in patients with type 1 diabetes. *Diabetes Technol Ther* 2010; 12: 173–177.
176. LUIJF YM, VAN BON AC, HOEKSTRA JB, DEVRIES JH. Premeal injection of rapid-acting insulin reduces postprandial glycemic excursions in type 1 diabetes. *Diabetes Care* 2010; 33: 2152–2155.
177. WEINZIMER S, XING D, TANSEY M et al. Prolonged use of continuous glucose monitors in children with type 1 diabetes on continuous subcutaneous insulin infusion or intensive multiple-daily injection therapy. *Pediatr Diabetes* 2009; 10: 91–96.
178. TAN CY, WILSON DM, BUCKINGHAM B. Initiation of insulin glargine in children and adolescents with type 1 diabetes. *Pediatr Diabetes* 2004; 5: 80–86.
179. O'CONNELL MA, GILBERTSON HR, DONATH SM, CAMERON FJ. Optimizing postprandial glycemia in pediatric patients with type 1 diabetes using insulin pump therapy: impact of glycemic index and prandial bolus type. *Diabetes Care* 2008; 31: 1491–1495.
180. DAVIDSON PC, HEBBLEWHITE HR, STEED RD, BODE BW. Analysis of guidelines for basal-bolus insulin dosing: basal insulin, correction factor, and carbohydrate-to-insulin ratio. *Endocr Pract* 2008; 14: 1095–1101.
181. CONRAD SC, MCGRATH MT, GITELMAN SE. Transition from multiple daily injections to continuous subcutaneous insulin infusion in type 1 diabetes mellitus. *J Pediatr* 2002; 140: 235–240.
182. NICOLAJSSEN T, SAMUELSSON A, HANAS R. Insulin doses before and one year after pump start: children have a reversed dawn phenomenon. *J Diabetes Sci Technol* 2012; 6: 589–594.
183. SZYPOWSKA A, LIPKA M, BLAZIK M, GROELE L, PANKOWSKA E. Insulin requirement in preschoolers treated with insulin pumps at the onset of type 1 diabetes mellitus. *Acta Paediatr* 2009; 98: 527–530.
184. LUDVIGSSON J, HANAS R. Continuous subcutaneous glucose monitoring improved metabolic control in pediatric patients with type 1 diabetes: a controlled crossover study. *Pediatrics* 2003; 111: 933–938.