

ISPAD Clinical Practice Consensus Guidelines 2006–2007

Insulin treatment

Bangstad H-J, Danne T, Deeb LC, Jarosz-Chobot P, Urakami T, Hanas R. Insulin treatment. *Pediatric Diabetes* 2007; 8: 88–102.

Hans-Jacob Bangstad^a
Thomas Danne^b
Larry C Deeb^c
Przemyslaw Jarosz-Chobot^d
Tatsuhiko Urakami^e and
Ragnar Hanas^f

^aDepartment of Pediatrics, Ullevål University Hospital, Oslo, Norway

^bKinderkrankenhaus auf der Bult, Diabetes-Zentrum für Kinder und Jugendliche, Hannover, Germany

^cDepartment of Pediatrics, University of Florida College of Medicine, Tallahassee, FL, USA

^dDepartment of Pediatric Endocrinology and Diabetes, Katowice, Poland

^eDepartment of Pediatrics, Nihon University School of Medicine, Tokyo, Japan

^fDepartment of Pediatrics, Uddevalla Hospital, Uddevalla, Sweden

Corresponding author:
Ragnar Hanas, MD, PhD,
Department of Pediatrics,
Uddevalla Hospital,
S-451 80 Uddevalla,
Sweden.

Tel: +46 522 92000;
fax: +46 522 93149;
e-mail: ragnar.hanas@vgregion.se

Editors of the ISPAD Clinical Practice Consensus Guidelines 2006–2007: Ragnar Hanas, Kim Donaghue, Georgeanna Klingensmith, and Peter Swift

Insulin therapy started in 1922 using regular insulin before each main meal and one injection at night, usually at 1 AM. With the development of intermediate- and long-acting insulin, most patients moved to one or two injections per day after 1935. By 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 multiple daily injections (MDI) (61 vs. 9%) (1) (C).

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 analogues, rapid and long acting. These insulins represent some improvement in the care of diabetes, but the extent of benefit in a clinical long-term setting is not fully established.

Data in adults are not readily transferable to pediatric patients of different age-groups (2), but in children and adolescents, as in adults (3) (A), rapid-acting insulin (aspart) is rapidly absorbed and eliminated (4). Higher maximum insulin concentrations in adolescents vs. children were reported both for insulin aspart and for human regular insulin (5) (A) but not with glulisine (6) (A). The results from one study (5) are in-line with the relatively impaired insulin sensitivity

and higher insulin concentrations reported in healthy adolescents (7, 8) (B). Such findings highlight the necessity to study the effects of these new insulins in all age-groups separately.

The different rapid-acting analogues have different chemical properties, but no significant difference in time of action and duration has been reported (9). Their advantages compared with regular (soluble) insulin are still under debate. The Cochrane review from 2006 stated that in patients with type 1 diabetes mellitus (T1DM), the weighted mean difference (WMD) of hemoglobin A1c (HbA1c) was -0.1% in favor of insulin analogue [-0.2% when using continuous subcutaneous insulin infusion (CSII)] (10) (A). In children and adolescents, blood glucose control has not been shown to be significantly improved with these analogues (10–14) (A).

A reduction in hypoglycemia has been reported, both for lispro (11, 12, 15) (A) (B) and for aspart (17, 18) (A). In the Cochrane review, the WMD of the overall mean hypoglycemic episodes per patient per month was -0.2 (95% confidence interval: -1.1 to 0.7) (10) in favor of rapid-acting insulin analogues. In adolescents, a significantly reduced rate was found with analogues (14), but no difference was found in prepubertal children (11, 13). The median incidence of severe hypoglycemia for adults was 26.8 episodes/100 patient years vs. 46.1 for regular insulin (10) (A). In the

included pediatric studies, there was no difference found in prepubertal children (10, 11) or adolescents (14).

The basal insulin analogues 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 analogues have reduced day-to-day variability in absorption compared with neutral protamine Hagedorn (NPH) insulin, with detemir having the lowest within-subject variability in one study (19) (A). So far, the reduction in hypoglycemia but not in HbA1c is the most prominent feature (20) (A), both for glargine (21–24) (A) (25) (B) (26, 27) (C) and for detemir (28, 29) (A) (30) (B) (31) (C). Parental fear of severe hypoglycemia, especially at nighttime, is an impediment to achieving morning blood glucose control. Lower body mass index (z-score) has been reported for detemir (29) (C).

In randomized trials, better blood glucose control has been obtained using MDI and pumps compared with a twice daily treatment (32, 33). The Diabetes Control and Complications Trial (DCCT) proved convincingly that intensive insulin therapy, including a heavy multidisciplinary approach in adolescents with multiple injections or pumps, resulted in a lower rate of long-term complications (33) (A). A further analysis showed that even when comparing patients with the same HbA1c levels, intensive insulin therapy with MDIs or CSII resulted in fewer complications, especially at higher levels of HbA1c (34) (A). Although this has not been studied in the same way in younger children, there is reason to believe that the results apply also to them, limited only by the risk of increasing the risk of severe hypoglycemia (E). However, in a cross-sectional clinical setting, HbA1c, hypoglycemia, and diabetic ketoacidosis (DKA) were not associated with the number of injections per day in pediatric populations (35) (B).

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 (36, 37) (A) (38–40) (B) (41–46) (C). 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 (47) (B). Several studies have compared the use of analogues and regular insulin in pumps (48) (A) (12) (B). Insulin pumps from the onset have been found to result in superior metabolic control when compared with one to two injections per day (32) (A) but not with MDI (49) (C). However, in the study comparing MDI with CSII, diabetes treatment satisfaction was higher with CSII (50) (C).

Unequivocal evidence for the benefit of MDI, the analogues, 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. This implies that the new practical recommendations of the International Society for Pediatric and Adolescent Diabetes (ISPAD) 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 T1DM, also in pediatric patients (33, 50, 51) (A). 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.

Improvements in glycemic control, particularly when provided by intensive insulin treatment with MDI or pump therapy, reduce the risks of vascular complications (A). There is no reason to believe that this is not the case also in younger children (E). In all age-groups, as close to physiological insulin replacement as possible and optimal glycemic control must be the aim; the attainment of this aim should include the consideration of an intensive insulin regimen (E).

Insulin availability

- ◇ Children and adolescents with T1DM are dependent on insulin for survival and should have access to adequate amounts of at least regular and NPH insulin.
- ◇ ISPAD and the International Diabetes Federation are working towards making insulin available for all children and adolescents with diabetes and promoting universal insulin labeling.

Insulin treatment must be started as soon as possible after diagnosis (usually within 6 h if ketonuria is present) to prevent metabolic decompensation and DKA (A).

Insulin formulation and species

- ◇ Many formulations of insulin are available; most have some role in the management of T1DM (Table 1).
- ◇ Currently, children are prescribed human insulins instead of porcine or bovine insulin because of low immunogenicity, but in many countries, these are being superceded by analogues.

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

Insulin type	Onset of action (h)	Peak of action (h)	Duration of action (h)
Rapid-acting analogues (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 analogues			
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 analogues			
Glargine	2–4	None	24*
Detemir	1–2	6–12	20–24
Long-acting analogues			
Ultralente type	4–8	12–24	20–30

IZS, insulin zinc suspension; NPH, neutral protamine Hagedorn insulin.

*The duration of action may be shorter than 24 h (65) (A).

◇ Porcine or bovine preparations may be cheaper and more readily available in some parts of the world. They are not inferior in clinical efficacy to human insulins (52) (A). Some locally manufactured preparations have greater immunogenicity, and high titer antibodies may alter pharmacodynamics by acting as insulin-binding proteins. This is particularly relevant when using older bovine insulins. However, animal species insulins are being withdrawn from the market, and major manufacturers are moving towards production of analogue insulins only. At the same time, the production of zinc-containing insulin (lente) is about to be terminated by the largest insulin-producing companies.

The time action of most insulins is dose dependent in that a smaller dose has a shorter duration of effect and earlier peak (53, 54) (C) and (E). There is some evidence that lispro (55) and aspart (56) (C) have the same time action irrespective of dose. The results of these studies are obtained from a relatively small number of adult subjects, and the results in children may result in different profiles of action.

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 twice daily or a basal analogue given once or twice daily.

Rapid-acting insulin analogues

Several novel insulin **analogues** 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 (Table 1). The rapid-acting analogues:

- Can 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 (11, 12, 15) (A) (16) (B).
- Offer the useful option of being given after food when needed (e.g., infants and toddlers who are reluctant to eat) (57) (B).
- Give a quicker effect than regular insulin when treating hyperglycemia, with or without ketosis, including sick days (E).
- Are most often used as prandial or snack boluses in combination with longer acting insulins (see basal-bolus regimens).
- Are most often used in insulin pumps.

Intravenous insulin

Regular insulins are best suited for intravenous (i.v.) therapy and are used in the following **crisis situations**:

- DKA.
- Control of diabetes during surgical procedures.

Rapid-acting insulin can also be given i.v. (58) (C). However, the effect is not superior to that of regular insulin and it is more expensive.

All children should have rapid-acting or regular insulin available for crisis management.

Intermediate-acting insulins

The action profiles of these insulins make them suitable for twice daily regimens and for prebed dosage in basal-bolus regimens.

Two principal preparations exist:

- ◇ Isophane NPH insulins.
- ◇ Crystalline zinc acetate insulin (IZS or lente insulins).

Isophane insulins are mostly used in children, mainly because of their suitability for mixing with regular insulin in the same syringe, vial, or cartridge without interaction.

Note: When regular insulin is mixed with lente preparations, it reacts with excess zinc, blunting its short-acting properties (59) (B).

Basal insulin analogues

The new basal insulin analogues are glargine and detemir.

- They show a more predictable insulin effect with less day-to-day variation compared with NPH insulin. (60) (A) (61) (B).
- In most countries, the two basal analogues have not been formally approved for children younger than 6 yr. However, there is a report on successful use of glargine in children aged from <1 to 5 yr (62) (C).
- Basal analogues are more expensive (approximately +50 to 100%).

Glargine

- Lack of an accumulation effect of glargine given on consecutive days has been shown in one study (63) (C).
- The effect of glargine lasts for up to 24 h; however, a waning effect can be seen approximately 20 h after injection (64) (A).
- Some children report a burning sensation when injecting glargine because of the acid pH (65) (C).

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 (66) (A). In a pediatric study, 70% of the patients used detemir twice or three times daily (29) (A).
- In adults, studies with detemir have shown weight reduction or less weight gain (31) (C), which has been observed also in children and adolescents (29) (C).

Traditional long-acting insulins

- ◇ Ultralente™ and Ultratard™ insulins were designed to have 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 (53), with dose accumulation effect

(E). If available, basal insulin analogues are superior to traditional long-acting insulins (E).

Premixed insulin preparations

Premixed insulins (fixed ratio mixtures of premeal and basal insulins) are popular 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 analogues. 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 (67).

- ◇ There is no clear evidence that premixed insulins in young children are less effective but some evidence of poorer metabolic control when used in adolescents (35).
- ◇ Premixed insulins with regular (or rapid-acting) insulin:NPH in different ratios, e.g., 10:90, 15:85, 20:80, 25:75, 30:70, 40:60, 50:50 are available in various countries from different manufacturers.
- ◇ Premixed insulins are suitable for use in pen injector devices.
- ◇ Premixed insulins may be useful to reduce the number of injections when compliance (or adherence) with the regimen is a problem.

Inhaled insulin

- ◇ This new form of insulin therapy has been investigated in children older than 12 yr as part of a study in adults (68) (B) but is not approved for clinical use in children.

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 are 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 (69, 70) (C) for use in pumps for infants or very young children.

Storage of insulin

Regulatory requirements state that the insulin product must retain at least 95% of its labeled potency at the expiration date (71). At room temperature (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 (71) (C). Storage recommendations are more often based on regulatory requirements regarding sterility than loss of potency (71). The individual manufacturer's storage recommendations and expiration 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 (71) (E).
- In hot climates where refrigeration is not available, cooling jars, earthenware pitcher (matka) (72) (C), 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.

It is essential that a small supply of spare insulin should be readily available to all children and adolescents so that the supply remains uninterrupted.

Injection sites

The usual injection sites are given below:

- ◇ 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);
- ◇ Buttocks (upper outer quadrant – may be useful in small children);
- ◇ Lateral aspect of the arm (in small children with little subcutaneous fat, intramuscular injection is more likely and it may cause unsightly bruising).

Cleaning or disinfection of skin is not necessary unless hygiene is a real problem. Infection at injection sites is rare (73) (C).

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.

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 (74) (C).
- ◇ **Lipohypertrophy** with the accumulation of fat in lumps underneath the skin are common in children (75).
- ◇ **Lipoatrophy** is now uncommon since the introduction of highly purified insulins but has been described also with the newer analogues (76, 77) (C).
- ◇ **Painful injections** are a common problem in children. Check angle, length of the needle, and depth of injection to ensure that injections are not being given intramuscularly and that the needle is sharp. Reused needles can cause more pain (78) (A). Indwelling catheters (Insuflon[®]) can decrease injection pain (79) (A).
- ◇ **Leakage of insulin** is common and cannot be totally avoided. Encourage slower withdrawal of needle from skin, stretching of the skin after the needle is withdrawn, or pressure with clean finger over the injection site.
- ◇ **Bruising and bleeding** are more common after intramuscular injection or tight squeezing of the skin. Use of thinner needles has shown significantly less bleeding at the injection site (80) (B).
- ◇ **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 (81) (C).

Insulin absorption

- ◇ Insulin activity profiles show substantial variability both day to day in the same individuals and between individuals, particularly in children (5, 53).
- ◇ The onset, peak effect, and duration of action depend on many factors that significantly affect the speed and consistency of absorption.

- ◇ Young people and care providers should know the factors that influence insulin absorption such as:
 - Age (young children, less subcutaneous fat→faster absorption) (E)
 - Fat mass (large subcutaneous fat thickness (82) (B) and lipohypertrophy (83) (B)→slower absorption).
 - Dose of injection (larger dose→slower absorption) (53) (C).
 - Site and depth of subcutaneous injection (abdomen faster than thigh (84) (A); no good data exist on absorption from thigh vs. buttock).
 - Subcutaneous vs. intramuscular injection (intramuscular injection→faster absorption in thigh), also with rapid-acting analogues (85) (B). Accidental intramuscular injections can cause variable glucose control (E).
 - Exercise (leg injection and leg exercise→faster absorption) (86) (B).
 - Insulin concentration, type, and formulation (lower concentration→faster absorption) (87) (B).
 - Ambient and body temperature (higher temperatures→faster absorption) (82) (B).
 - In general, the absorption speed of rapid-acting analogues is less affected by the above-mentioned factors (88–90) (B, B, A).
 - There is no significant difference in the absorption of glargine from abdomen or thigh (91) (B). Exercise does not influence glargine absorption (92) (A).
 - There is a risk of hypoglycemia if injecting glargine intramuscularly, particularly in young and lean individuals (93) (C).
- ◇ Syringes must never be shared with another person because of the risk of acquiring blood-borne infection (e.g., hepatitis, HIV).
- ◇ It is advisable that all children and adolescents with diabetes should know how to administer insulin by syringe because other injection devices may malfunction.

Insulin must be administered by syringes (or other injection devices) calibrated to the concentration of insulin being used.

Disposal of syringes.

- ◇ Appropriate disposal procedures are mandatory.
 - Specifically designed and labeled ‘sharps containers’ may be available from pharmacies and diabetes centers.
 - Special needle clippers (e.g., Safeclip®) may be available to remove the needle and make it unusable.
 - Without a ‘sharps container’, syringes with needles removed may be stored and disposed of in opaque plastic containers or tins for garbage collection.

Pen injector devices.

- ◇ 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 (5–6 mm) and diameter are available and may cause less discomfort on injection (80) (B).
- ◇ Pen injectors of various sizes and types are available from the pharmaceutical companies. Some pens can be set to ½ unit increments. 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 (E).

Needle length.

- ◇ The traditional needle length of 12–13 mm (27 G) has been replaced by thinner needles that are 5–8 mm long (30–31 G). A two-finger pinch technique is recommended for all types of injections to ensure a strict subcutaneous injection, avoiding intramuscular injection (95) (C).

Note: Faster absorption usually results in shorter duration of action (see page 90).

Administration of insulin

Devices for insulin delivery

Insulin syringes.

- ◇ Plastic fixed-needle syringes with small dead space are preferable to glass 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) available for small children.
- ◇ Plastic fixed-needle syringes are designed for single use. However, many persons with diabetes successfully reuse them without significant increase in risk of infection (94) (B). Reuse should be discouraged if there is concern about hygiene or injection pain, as they become less sharp when reused (78) (A).
- ◇ Insulin syringes must have a measuring scale consistent with the insulin concentration (e.g., U100 syringes).

- ◇ With 5–6 mm needles, the injections can be given perpendicularly without lifting a skin fold if there is enough subcutaneous fat, which often is the case in girls (at least 8 mm as the skin layers often are compressed when injecting perpendicularly) (96) (C). Lean boys, however, have a thinner subcutaneous fat layer, especially on the thigh (96, 97) (C). 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 5–6 mm needles are not fully inserted into the skin.

Subcutaneous indwelling catheters.

- ◇ Such catheters (e.g., Insuflon) inserted using topical local anesthetic cream may be useful to overcome problems with injection pain at the onset of diabetes (79) (A).
- ◇ Insuflon is used in an increasing number of centers for introduction of MDI.
- ◇ The use of Insuflon does not affect metabolic control negatively (100) (B). In children with injection problems, HbA1c has been lowered by using Insuflon (99) (B).
- ◇ The use of a basal analogue and a short- or rapid-acting insulin at the same injection time in an Insuflon is not advisable in case of possible interaction of the two insulins (for mixing with glargine, see page 95).
- ◇ Insuflons should be replaced every 2–4 d to prevent scarring and a negative effect on insulin absorption (100) (B) (101) (C).

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 pen injectors are available (102) (B).

Jet injectors.

- ◇ High-pressure jet injection of insulin into the subcutaneous 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 similar to both conventional injections (103) and CSII (104), but problems with have included a variable depth of penetration, delayed pain, and bruising (105) (B).

Subcutaneous insulin infusion pumps.

- ◇ The use of external pumps is increasing and is proving to be acceptable and successful (36, 37) (A) (38, 40–46) (C) (39) (E), even in young infants (42) (C). Randomized studies in the preschool group have failed to show better glycemic control (36, 106) (A).
- ◇ 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 (107, 108). This highlights the importance of individualizing the decision of the method of therapy for every situation.
- ◇ An insulin pump is an alternative to treatment with MDI (including basal analogues) if HbA1c is persistently above the individual goal, hypoglycemia is a major problem, or quality of life needs be improved (109) (E).
- ◇ Insulin pump use is increasing in the younger age-group, as clinicians become more comfortable with CSII as a more physiological insulin replacement therapy (E).
- ◇ The newer generation of ‘smart’ pumps that automatically calculate meal- or correction-boluses based on insulin-to-carbohydrate ratios and insulin sensitivity factors have enabled alternate providers, such as grandparents, nannies, and daycare workers, to participate in diabetes management tasks (E).
- ◇ 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 β -ketone (beta-hydroxybutyrate) levels of approximately 1–1.5 mmol/L but not in DKA (110) (B). Results in children and adolescents seem to be similar (111) (C).
- ◇ Patients using insulin pumps, especially younger children, will benefit from being able to measure β -ketones (E).
- ◇ For patients using insulin pump, and prone to ketosis, it may help to give a small dose of basal insulin before bedtime (E).
- ◇ 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 analogue insulins are used in most pumps (E), and a meta-analysis has shown a 0.26% lower HbA1c level when comparing with human regular insulin (24) (A). Regular insulin is less often used in pumps but works well if rapid-acting insulin is not available.

- ◇ There is no difference in action effect (112), pump stops or catheter cloggings when using insulin lispro or aspart in pumps (113).
- ◇ Lower percentage of basal insulin and more than seven daily boluses are an option for better metabolic control when using pumps (114) (C).

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.

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 (see page 94).
- ◇ **Pen injector technique** requires a 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 (81) (B).

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 (E). For these individuals, an injection aid, Insuflon (99) (B), or insulin pump therapy may improve compliance (E).
- ◇ There is great individual variation in the appropriate age for children to self-inject (115) (B).
- ◇ The appropriate age relates to developmental maturity rather than to chronological age.
- ◇ Most children older than 10 yr either give their own injections or help with them (115) (B)
- ◇ Younger children sharing injection responsibility with a parent or other care provider may help prepare the device or help push the plunger and, subsequently, under supervision, be able to perform the whole task successfully.
- ◇ Self-injection is sometimes triggered by an external event such as 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., the buttocks) to avoid lipohypertrophy.

Regular checking of injection sites, injection technique, and skills remain a responsibility of parents, care providers, and health professionals.

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, preferably 20, times (116) (B) 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 (59, 117) (C).
- ◇ Insulins from different manufacturers should be used together with caution, as there may be interaction between the buffering agents.
- ◇ NPH and lente insulins should never be mixed.
- ◇ Rapid-acting insulin analogues may be mixed in the same syringe as NPH immediately before injections (118) (B) (119) (C). Immediate injection of a mixture of Ultralente and Humalog has been found not to diminish the Humalog effect (120) (C).
- ◇ 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 (121) (B) or HbA1c (122) (C).
- ◇ The manufacturer recommends that detemir should not be mixed with any other insulin before injection. There are no available studies on this.

Insulin regimens

No insulin injection regimen satisfactorily mimics normal physiology.

- ◇ The choice of insulin regimen will depend on many factors including age, duration of diabetes, life-style (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 insulin/long-acting insulin/basal analogue once or twice daily and rapid-acting or regular boluses with meals and snacks) has the best possibility of imitating the physiological insulin profile.
- ◇ At least two injections of insulin per day (mixing short/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, long-acting or basal analogue, but some children may, during the partial remission phase, maintain satisfactory metabolic control on intermediate- or long-acting insulins alone (i.e., an HbA1c close to the normal range).

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.

Principles of insulin therapy

Aim for appropriate insulin levels throughout the 24 h to cover basal requirements and higher levels of insulin in an attempt to match the glycemic effect of meals.

Frequently used regimens

- ◇ **Two injections daily** of a mixture of short- or rapid- and intermediate-acting insulins (before breakfast and the main evening meal).
- ◇ **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 the main evening meal; intermediate-acting insulin before bed or variations of this.
- ◇ **Basal-bolus regimen**
 - of the total daily insulin requirements, 40–60% should be basal insulin, the rest preprandial 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 analogue at bedtime or twice daily (mornings and evenings).
 - injection of rapid-acting insulin analogue immediately before (or after) (11, 57) (A) each main meal (breakfast, lunch, and main evening meal); intermediate-acting insulin or basal/long-acting analogue at bedtime, probably before breakfast and occasionally at lunchtime or twice daily (mornings and evenings).

- **Insulin pump** regimens are regaining popularity with a fixed or a variable basal dose and bolus doses with meals.

Note: None of these regimens can be optimized without frequent assessment by blood glucose monitoring (BGM).

Daily insulin dosage

Daily insulin dosage varies greatly between individuals and changes over time. It, therefore, requires regular review and reassessment.

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 BGM (and glycated hemoglobin);
- ◇ Intercurrent illness.

Guidelines on dosage:

- ◇ During the partial remission phase, the total daily insulin dose is often <0.5 IU/kg/day.
- ◇ Prepubertal children (outside the partial remission phase) usually require insulin of 0.7–1.0 IU/kg/day.
- ◇ During puberty, requirements may rise substantially above 1 and even up to 2 U/kg/day.

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

Distribution of insulin dose

The distribution of insulin dose across the day shows great individual variation. Regardless of mode of insulin therapy, doses should be adapted based on the daily pattern of blood glucose.

- ◇ Children on twice daily regimens often require more (perhaps 2/3) of their total daily insulin in the morning and less (perhaps 1/3) in the evening.
- ◇ On this regimen, approximately 1/3 of the insulin dose may be short-acting insulin and approximately 2/3 may be intermediate-acting insulin although these ratios change with greater age and maturity of the young person.

- ◇ On basal-bolus regimens, the nighttime 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 daytime basal insulin coverage (25, 123) (C).
- ◇ Glargine can be given before breakfast, before dinner or at bedtime with equal effect, but nocturnal hypoglycemia occurs significantly less often after breakfast injection (64) (A, adult study).
- ◇ When transferring to glargine as basal insulin, the total dose of basal insulin needs to be reduced by approximately 20% to avoid hypoglycemia (123) (C). After that, the dose should be individually tailored.
- ◇ Detemir is most commonly given twice daily in children (29) (A) and (E).
- ◇ When transferring to detemir from NPH, the same doses can be used to start with (E).

Insulin dose adjustments

Soon after diagnosis:

- ◇ Frequent advice by members of the diabetes care 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 blood glucose levels and target HbA1c are achieved.
- ◇ If frequent BGM 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 for a number of days or on 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 BGM. In addition, the daily blood glucose pattern should be taken into account. The rapid-acting analogues may require postprandial blood glucose tests approximately 2 h after meals to assess their efficacy. Frequently, insulin is dosed based on food consumption (carbohydrates) and on deviation from a target glucose. Many newer

insulin pumps allow programming algorithms for these automatic adjustments for ambient blood glucose and carbohydrate intake.

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.

Advice for persistent deviations of blood glucose from target

- ◇ Elevated blood glucose level before breakfast→increase predinner or prebed intermediate- or long-acting insulin. (Blood glucose tests during the night are needed to ensure that this change does not result in nocturnal hypoglycemia.)
- ◇ Rise in blood glucose level after a meal→increase premeal rapid-acting/regular insulin.
- ◇ Elevated blood glucose level before lunch/dinner meal→increase prebreakfast basal insulin or increase dose of prebreakfast regular/rapid-acting insulin if on basal-bolus regimen. When using rapid-acting insulin for basal-bolus regimen, the dose or type of basal insulin may need to be adjusted in this situation.
- ◇ When using carbohydrate counting, persistent elevations of blood glucose may require adjustment in ratios for carbohydrate (insulin-to-carbohydrate ratio).
- ◇ Correction doses can be used according to the '1800 rule', i.e., divide 1800 by total daily insulin dose to get the results in mg/dL that 1 U of rapid-insulin will lower the blood glucose. For the results in mmol/L, use the '100 rule', i.e. divide 100 by total daily insulin dose (C) and (E). 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, such as exercise.
- ◇ Rise in blood glucose level after evening meal →increase pre-evening meal regular/rapid-acting insulin.

In addition:

- ◇ Unexplained hypoglycemia requires re-evaluation of insulin therapy.
- ◇ Hyper- 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 routine, especially exercise or dietary changes.

- ◇ Various levels of exercise require adjustment of diabetes management.
- ◇ Special advice may be helpful when there are changes in routine, travel, school outings, educational holidays/diabetes camps, or other activities that 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, e.g., to 2/3 or 3/4 of the usual dose (E).

Dawn phenomenon

- ◇ Blood glucose levels tend to rise in the hours of the morning (usually after 5 AM) prior to waking. This is called the dawn phenomenon. In individuals without diabetes, 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 (124) (B) (125) (C) have shown that younger children often need more basal insulin before midnight than after (reversed dawn phenomenon). With a basal-bolus analogue regimen, this can be achieved by giving regular instead of rapid-acting insulin for the last bolus of the day (nighttime blood glucose levels need to be checked) (E).
- ◇ In individuals with T1DM, 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, being seen less often in pump therapy compared with MDI (126) (B).
- ◇ 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 analogue;
 - changeover to insulin pump treatment.

This article is a Chapter in the ISPAD Clinical Practice Consensus Guidelines 2006–2007 of the ISPAD (www.ispad.org). The complete set of these Guidelines will later be published as a compendium. Additional comments, clarifications, or corrections should be directed to the corresponding author (R.H.).

The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See the Introduction of the ISPAD Clinical Practice Consensus Guidelines in *Pediatric Diabetes* 2006; 7: 341–342.

References

1. JOHANSSON S. Retinopathy and nephropathy in diabetes mellitus: comparison of the effects of two forms of treatment. *Diabetes* 1960; 9: 1–8.
2. SIEBENHOFER A, PLANK J, BERGHOLD A, NARATH M, GFRERER R, PIEBER TR. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. *Cochrane Database Syst Rev* 2004: CD003287.
3. 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.
4. 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.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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.
10. 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.
11. DEEB LC, HOLCOMBE JH, BRUNELLE R et al. Insulin lispro lowers postprandial glucose in prepubertal children with diabetes. *Pediatrics* 2001; 108: 1175–1179.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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.
 17. 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.
 18. HOME PD, LINDHOLM A, RIIS A. Insulin aspart vs. human insulin in the management of long-term blood glucose control in type 1 diabetes mellitus: a randomized controlled trial. European Insulin Aspart Study Group (In Process Citation). *Diabet Med* 2000; 17: 762–770.
 19. 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.
 20. 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.
 21. 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.
 22. MURPHY NP, KEANE SM, ONG KK et al. Randomized cross-over trial of insulin glargine plus lispro or NPH insulin plus regular human insulin in adolescents with type 1 diabetes on intensive insulin regimens. *Diabetes Care* 2003; 26: 799–804.
 23. 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.
 24. 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 2002; 53: <http://guidance.nice.org.uk/TA53/guidance/pdf/English>
 25. 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.
 26. 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.
 27. 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.
 28. 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.
 29. 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.
 30. 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.
 31. 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.
 32. 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.
 33. DCCT RESEARCH GROUP. 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.
 34. DCCT RESEARCH GROUP. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. *Diabetes* 1995; 44: 968–983.
 35. 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. Hvidovre Study Group on Childhood Diabetes. *Diabet Med* 1998; 15: 752–759.
 36. 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.
 37. 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.
 38. 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.
 39. KAUFMAN FR. Intensive management of type 1 diabetes in young children. *Lancet* 2005; 365: 737–738.
 40. 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.
 41. 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.
 42. 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.
 43. 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.
 44. 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.
 45. 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.
46. 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.
 47. DOYLE EA, WEINZIMER SA, STEFFEN AT, AHERN JA, VINCENT M, TAMBORLANE WV. A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. *Diabetes Care* 2004; 27: 1554–1558.
 48. 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.
 49. 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: 65 (Abstract).
 50. DCCT Research Group. 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.
 51. 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.
 52. RICHTER B, NEISES G. 'Human' insulin versus animal insulin in people with diabetes mellitus. *Cochrane Database Syst Rev* 2005; CD003816.
 53. LAURITZEN T. Pharmacokinetic and clinical aspects of intensified subcutaneous insulin therapy. *Dan Med Bull* 1985; 32: 104–118.
 54. 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): A332 (Abstract 1367-P).
 55. WOODWORTH J, HOWEY D, BOWSER 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.
 56. 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): A128 (Abstract 551-P).
 57. 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.
 58. 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): A115 (Abstract 0497).
 59. 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.
 60. ROBERTSON K, SCHOENLE E, GUCEV Z et al. Benefits of insulin detemir over NPH insulin in children and adolescents with type 1 diabetes: lower and more predictable fasting plasma glucose and lower risk of nocturnal hypoglycemia. *Diabetes* 2004; 51 (Suppl. 2): A144 (Abstract).
 61. 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.
 62. 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.
 63. 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.
 64. 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.
 65. 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.
 66. 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.
 67. 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.
 68. SKYLER JS, WEINSTOCK RS, RASKIN P et al. Use of inhaled insulin in a basal/bolus insulin regimen in type 1 diabetic subjects: a 6-month, randomized, comparative trial. *Diabetes Care* 2005; 28: 1630–1635.
 69. 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.
 70. 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): A102 (Abstract).
 71. 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 2266–2669.
 72. 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): 347 (Abstract).
 73. MCCARTHY JA, COVARRUBIAS B, SINK P. Is the traditional alcohol wipe necessary before an insulin injection? Dogma disputed. *Diabetes Care* 1993; 16: 402.
 74. 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.
 75. KORDONOURI O, LAUTERBORN R, DEISS D. Lipohypertrophy in young patients with Type 1 diabetes. *Diabetes Care* 2002; 25: 634.
 76. ARRANZ A, ANDIA V, LOPEZ-GUZMAN A. A case of lipoatrophy with Lispro insulin without insulin pump therapy. *Diabetes Care* 2004; 27: 625–626.
 77. BELTRAND J, GUILMIN-CREPON S, CASTANET M, PEUCHMAUR M, CZERNICHOV P, LEVY-MARCHAL C. Insulin allergy and extensive lipoatrophy in child with type 1 diabetes. *Horm Res* 2006; 65: 253–260.

78. CHANTELAU E, LEE DM, HEMMANN DM, ZIPFEL U, ECHTERHOFF S. What makes insulin injections painful? *BMJ* 1991; 303: 26–27.
79. 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.
80. ARENDT-NIELSEN L, EGEKVIST H, BJERRING P. Pain following controlled cutaneous insertion of needles with different diameters. *Somatosens Mot Res* 2006; 23: 37–43.
81. GINSBERG BH, PARKES JL, SPARACINO C. The kinetics of insulin administration by insulin pens. *Horm Metab Res* 1994; 26: 584–587.
82. 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.
83. YOUNG RJ, HANNAN WJ, FRIER BM, STEEL JM, DUNCAN LJ. Diabetic lipohypertrophy delays insulin absorption. *Diabetes Care* 1984; 7: 479–480.
84. 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.
85. FRID A, GUNNARSSON R, GUNTNER P, LINDE B. Effects of accidental intramuscular injection on insulin absorption in IDDM. *Diabetes Care* 1988; 11: 41–45.
86. 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.
87. FRID A. Injection and absorption of insulin. PhD Thesis, Faculty of Medicine, Karolinska Institute, Stockholm, Sweden, 1992.
88. 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.
89. 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.
90. 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.
91. 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.
92. 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.
93. KARGES B, BOEHM BO, KARGES W. Early hypoglycaemia after accidental intramuscular injection of insulin glargine. *Diabet Med* 2005; 22: 1444–1445.
94. 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.
95. HOFMAN P, PEART J, HOLT J et al. Angled 6 mm needles and a pinch technique dramatically reduce intramuscular injections in children. *J Pediatr Endocrinol Metab* 2002; 15 (Suppl. 4): 1079 (Abstract).
96. 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.
97. SMITH CP, SARGENT MA, WILSON BP, PRICE DA. Subcutaneous or intramuscular insulin injections. *Arch Dis Child* 1991; 66: 879–882.
98. HANAS SR, LUDVIGSSON J. Metabolic control is not altered when using indwelling catheters for insulin injections. *Diabetes Care* 1994; 17: 716–718.
99. BURDICK P, COOPER S, HORNER B et al. Use of the InsufloTM injection port to improve glycemic control in children with type 1 diabetes. *Diabetes* 2006; 56 (Suppl. 1): A55 (Abstract 236).
100. 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.
101. 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.
102. 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: A30 (Abstract).
103. WORTH R, ANDERSON J, TAYLOR R, ALBERTI KG. Jet injection of insulin: comparison with conventional injection by syringe and needle. *Br Med J* 1980; 281: 713–714.
104. CHIASSON 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.
105. 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.
106. 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.
107. BLACKETT PR. Insulin pump treatment for recurrent ketoacidosis in adolescence. *Diabetes Care* 1995; 18: 881–882 (Letter).
108. 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.
109. NICE (NATIONAL INSTITUTE OF CLINICAL EXCELLENCE). Clinical and cost effectiveness of continuous subcutaneous insulin infusion for diabetes. Technology Appraisal 2003; 57: <http://www.nice.org.uk/guidance/TA57>
110. GUERCI B, BENICHOU M, FLORIOT M et al. Accuracy of an electrochemical sensor for measuring capillary blood ketones by fingerstick samples during metabolic deterioration after continuous subcutaneous insulin infusion interruption in type 1 diabetic patients. *Diabetes Care* 2003; 26: 1137–1141.
111. 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): 35 (Abstract).

112. 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.
113. SIEGMUND T, AMELUNXEN S, KAISER M, SCHUMM-DRAEGER P. Pump compatibility of insulin aspart compared to insulin Lispro with respect to catheter complications and dermal/subcutaneous irritations in patients (P) with type 1 diabetes (T1D) undergoing continuous subcutaneous insulin infusion (CSII) therapy. *Diabetes* 2005; 54 (Suppl. 1): A105 (Abstract).
114. JAROSZ-CHOBOT P, BATTELINO T, KORDONOURI O, PANKOWSKA E, DANNE T, GROUP PS. The PedPump survey: indication for CSII and number of daily boluses are associated with HbA1c in 1086 children with T1 DM from 17 countries. *Pediatr Diabetes* 2005; 6 (Suppl. 3): 14 (Abstract).
115. 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.
116. JEHLE PM, MICHELER C, JEHLE DR, BREITIG D, BOEHM BO. Inadequate suspension of neutral protamine Hagedorn (NPH) insulin in pens. *Lancet* 1999; 354: 1604–1607 (See comments).
117. 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.
118. 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): A104 (Abstract 448).
119. JOSEPH SE, KORZON-BURAKOWSKA A, WOODWORTH JR, EVANS M, HOPKINS D, JANES JM, AMIEL SA. The action profile of lispro is not blunted by mixing in the syringe with NPH insulin. *Diabetes Care* 1998; 21: 2098–2012.
120. BASTYR EJ III, HOLCOMBE JH, ANDERSON JH, CLORE JN. Mixing insulin lispro and ultralente insulin. *Diabetes Care* 1997; 20: 1047–1048.
121. 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.
122. FIALLO-SCHARER R, CHASE P, HORNER B, MCFANN K, WALRAVENS P, GARG S. The mixing of rapid-acting insulin (RAI) analogues (Humalog[®] or NovoLog[®]) with insulin glargine (IG) in youth with type 1 diabetes (T1D). *Diabetes* 2005; 54 (Suppl. 1): A451 (Abstract 1879-P).
123. TAN CY, WILSON DM, BUCKINGHAM B. Initiation of insulin glargine in children and adolescents with type 1 diabetes. *Pediatr Diabetes* 2004; 5: 80–86.
124. 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.
125. BOLAND E, AHERN J, VINCENT M. Pumps and kids: basal requirements for excellent metabolic control. *Diabetes* 2002; 51 (Suppl. 2): A3 (Abstract).
126. 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.