INSULIN TREATMENT IN CHILDREN AND ADOLESCENTS WITH DIABETES

Bangstad H-J, Danne T, Deeb LC, Jarosz-Chobot P, Urakami T, Hanas R. Insulin treatment in children and adolescents with diabetes

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Introduction
Insulin therapy started in 1922 using regular insulin before each main meal and one injection in the night, usually at 1 a.m. 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/day had a much higher risk of retinopathy after 15 years of diabetes compared to those diagnosed before 1935 using multiple daily injections (61% vs. 9%) \cite{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 lead 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 \cite{2} [A], but in children and adolescents, as in adults \cite{3} [A], rapid acting insulin (aspart) is rapidly absorbed and eliminated \cite{4} [C]. Higher maximum insulin concentrations in adolescents vs. children were reported both for insulin aspart and human regular insulin \cite{5} [A], but not with glulisine \cite{6} [A]. The results from reference \cite{5} are in line with the relatively impaired insulin sensitivity and higher insulin concentrations reported in healthy adolescents \cite{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 analogs have different chemical properties, but no significant difference in time of action and duration has been reported \cite{9}. Their advantages compared to regular (soluble) insulin are still
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under debate. The Cochrane review from 2006 stated that in patients with type 1 diabetes, the weighted mean difference (WMD) of HbA1c was −0.1% in favour of insulin analog (−0.2% when using CSII, continuous subcutaneous insulin infusion) (2) [A]. In children and adolescents, blood glucose control has not been shown to be significantly improved with these analogs (10–14) [A].

A reduction in hypoglycemia has been reported, both for lispro (11, 12, 15) [A] (16) [B] and aspart (17, 18) [A]. In the Cochrane review, the WMD of the overall mean hypoglycemic episodes per patient per month was −0.2 (95% CI: −1.1 to 0.7) (2) in favor of rapid acting insulin analogs. In adolescents, a significantly reduced rate was found with analogs (14), but in prepubertal children, no difference was found (11, 13). The median incidence of severe hypoglycemia for adults was 26.8 episodes/100 patient years vs. 46.1 for regular insulin. In the included pediatric studies, there was no difference found in prepubertal children (10, 11) or adolescents (14).

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 to NPH-insulin, with detemir having the lowest within-subject variability (19, 20) [A]. So far the reduction in hypoglycemia and not in HbA1c is the most prominent feature (21) [A], both for glargine (22–25) [A] (26) [B] (27, 28) [C] and detemir (29,30) [A] (31) [B] (32) [C]. Parental fear of severe hypoglycemia, especially night time, is an impediment to achieving morning blood glucose control. Lower body mass index (z-score) has been reported for detemir (30) [C].

In randomized trials, better blood glucose control has been obtained using multiple daily injections (MDI) and pumps compared to a twice daily treatment (33, 34). 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 (34) [A]. Cognitive impairment 18 years after the conclusion of the DCCT study was unrelated to the rate of hypoglycemia during intensive therapy (35–36) [B]. 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 (37) [B].

Insulin pump therapy is at present the best way to imitate the physiological insulin profile. Insulin is infused subcutaneously at a pre-programmed basal rate and boluses are added to counterbalance the intake of carbohydrates. CSII has mostly been compared to MDI with NPH as the long-acting insulin (38–39) [A] (40–42) [B] (43–48) [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 (49) [B]. Several studies have compared the use of analogs and regular insulin in pumps (50) [A] (12) [B]. Insulin pumps from the onset have been found to result in superior metabolic control when compared to 1–2 injections/day (33) [A] but not to MDI (51) [C]. However, in the study comparing MDI vs. CSII, diabetes treatment satisfaction was higher with CSII. Data from a large pediatric survey showed a low incidence of acute complications at a mean HbA1c-level of 8.0% (52) [C]. An international consensus on pediatric indications and instructions for use has been published (53) [E]. The most recent metanalysis of six pediatric randomized controlled trials with 165 patients showed a reduction of HbA1c by 0.24% with CSII compared to MDI (54) [A].

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. This implies that ISPAD’s new practical recommendations have to be applicable for the total diabetes community world wide.

The DCCT study and its follow-up EDIC (Epidemiology of Diabetes Interventions and Complications) study confirmed that an improvement in long-term glucose control, as obtained with intensified insulin therapy including 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 (34, 55, 56) [A]. A rapidly increasing numbers of centres around the world are introducing the basal/bolus concept of intensive insulin treatment already from the onset of diabetes.

Insulin availability

♦ Children and adolescents with type 1 diabetes are dependent on insulin for survival and should have access to adequate amounts of at least regular and NPH-insulin.
♦ ISPAD and IDF are working towards 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).
Table 1. Types of insulin preparations and suggested action profiles according to manufacturers

<table>
<thead>
<tr>
<th>Insulin type</th>
<th>Onset of action (h)</th>
<th>Peak of action (h)</th>
<th>Duration of action (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid acting analogs (aspart, glulisine, lispro)</td>
<td>0.15-0.35</td>
<td>1-3</td>
<td>3-5</td>
</tr>
<tr>
<td>Regular/soluble (short acting)</td>
<td>0.5-1</td>
<td>2-4</td>
<td>5-8</td>
</tr>
<tr>
<td>Intermediate acting Semilente (pork)</td>
<td>1-2</td>
<td>4-10</td>
<td>8-16</td>
</tr>
<tr>
<td>NPH*</td>
<td>2-4</td>
<td>4-12</td>
<td>12-24</td>
</tr>
<tr>
<td>Lente type</td>
<td>3-4</td>
<td>6-15</td>
<td>18-24</td>
</tr>
<tr>
<td>Basal long-acting analogs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine</td>
<td>2-4</td>
<td>None</td>
<td>24**</td>
</tr>
<tr>
<td>Detemir</td>
<td>1-2</td>
<td>6-12</td>
<td>20-24</td>
</tr>
<tr>
<td>Long-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultralente type</td>
<td>4-8</td>
<td>12-24</td>
<td>20-30</td>
</tr>
</tbody>
</table>

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

**Footnote: All insulins used must be produced under “Good Manufacturing Practice/Good Laboratory Practice” conditions.

Diamond: Currently, children are prescribed human insulins instead of porcine or bovine insulin because of low immunogenicity, but in many countries these are being superseded by analogs.

Diamond: 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 (57) [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 analog insulins only. At the same time the production of zinc-containing insulins (Lente) is stopped 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 (58, 59) [C] and [E]. There is some evidence that lispro (60) and aspart (61) [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.
  - As pre-meal bolus injections in basal-bolus regimens (given 20–30 min before meals) together with intermediate-acting insulin 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, lispro). They have a rapid onset and shorter duration of action than regular insulin (see Table 1). 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 (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) (62) [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.

Safety of insulin analogs

As insulin analogs are molecules with modified structure compared to human insulin, safety concerns have been raised due to changes in mitogenicity in vitro (63) [C]. Studies in primary human cultures have not revealed altered proliferative effects (64) [C]. In 2009, four epidemiologic studies were published using large diabetes and cancer databases, investigating the risk of malignancy in patients treated with...
insulin glargine. A small, but significant increased risk of cancer, specifically breast cancer, was identified in patients treated with insulin glargine alone, a population of mostly older adults with type 2 diabetes mellitus (65–67) [C]. A fourth study was negative and did not identify a link between cancer and glargine (68) [C]. In addition, there was no clear evidence of harm in type 1 diabetes or in patients taking insulin glargine in combination with other insulin analogs. The authors of the studies and the accompanying editorial caution against over-interpretation of the limited data available to date, and state that no firm conclusions can be drawn (69). Presently, there are not safety concerns that would preclude the use of insulin analogs in the pediatric age group.

**IV insulin**

Regular insulins are best suited for IV therapy and are used in the following crisis situations:

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

Rapid-acting insulin can also be given IV (70) [C]. However, the effect is not superior to that of regular insulin and it is more expensive.

**Intermediate acting insulins**

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

Two principal preparations exist:

- Isophane NPH (neutral protamine Hagedorn) insulins.
- Crystalline zinc acetate insulin (insulin zinc suspensions, 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. Lente insulins are discontinued in many countries.

**NOTE:** When regular insulin is mixed with lente preparations it reacts with excess zinc, blunting its short acting properties (71) [B].

**Basal insulin analogs**

The new basal insulin analogs are glargine and detemir

- They show a more predictable insulin effect with less day to day variation, compared to NPH insulin (30) [A] (72) [B].

- In most countries, the two basal analogs have not been formally approved for children below the age of 6 years. However, there is a report of successful use of glargine in children from < 1 to 5 years of age (73) [C].

- Basal analogs are more expensive (approximately +50 to100%).

**Glargine**

- Lack of an accumulation effect of glargine given on consecutive days has been shown in one study (74) [C].
- The effect of glargine lasted for up to 24 hours in adults, however, a waning effect can be seen approximately 20 hours after injection (75) [A].
- Some children report a burning sensation when injecting glargine due to the acid pH (76) [C].
- A review of pediatric studies in the past six years 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 to conventional basal insulins (77) [C].

**Detemir**

- A study with detemir in adults found the time of action to be between 6 and 23 hours when doses between 0.1U/kg and 0.8 U/kg were given (78) [A]. In a pediatric study, 70% of the patients used detemir twice daily (30) [A].
- In adults, studies with detemir have shown weight reduction or less weight gain (32) [A], which has been observed also in children and adolescents (30) [C].

Detemir is characterized by a more reproducible pharmacokinetic profile than glargine in children and adolescents with type 1 diabetes (20) [A].

**Traditional long acting insulins**

- Ultralente™ and Ultratard™ insulins were designed to have a duration of more than 24 hours 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 (58), with dose accumulation effect [E]. If available, basal insulin analogs are superior to traditional long-acting insulins [E].
Pre-mixed insulin preparations

Pre-mixed insulins (fixed ratio mixtures of pre-meal 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 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 (79) [B].

There is no clear evidence that pre-mixed insulins in young children are less effective, but some evidence of poorer metabolic control when used in adolescents (37).

Pre-mixed insulins with regular (or rapid acting):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) to the regimen is a problem.

Inhaled insulin

This new form of insulin therapy has been investigated in children above 12 years of age as part of a study in adults (80) [B], but was not approved for clinical use in children. The sale of inhaled insulin was discontinued in 2007.

Insulin concentrations

The most widely available insulin concentration is 100 IU/ml (U 100).

Treatment with U 40 (40 IU/ml), U50 or other concentrations such as U500 is also acceptable, subject to availability and special needs.

Care must be taken to ensure that the same concentration is supplied each time new supplies are received.

Very young children occasionally require insulin diluted with diluent obtained from the manufacturer, but special care is needed in dilution and drawing up the insulin into the syringe. Rapid-acting insulin can be diluted to U10 or U50 with sterile NPH diluent and stored for 1 month (81, 82) [C] for use in pumps for infants or very young children.

Changing 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 (83) [C].

Storage of insulin

Regulatory requirements state that the insulin product must retain at least 95% of its labeled potency at expiry date (84). At room temperature (25°C, 77°F), insulin will lose <1.0% of its potency over 30 days. In contrast, insulin stored in a refrigerator will lose <0.1% of its potency over 30 days (84) [C]. Storage recommendations are more often based on regulatory requirements regarding sterility than loss of potency (84). 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 insulins that have 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 weeks if kept at room temperature. However, for some insulin preparations, manufacturers recommend only 10 – 14 days of use in room temperature (84) [E].
- In hot climates where refrigeration is not available, cooling jars, earthenware pitcher (matka) (85) [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.

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).
- buttocks (upper outer quadrant—may be 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).
- Cleaning or disinfection of skin is not necessary unless hygiene is a real problem. Infection at injection sites is rare (86) [C].
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 (87) [C].
- **Lipoatrophy** with the accumulation of fat in lumps underneath the skin are common in children (88).
- **Lipohypertrophy** is now uncommon since the introduction of highly purified insulins, but has been described also with the newer analogs (89, 90) [C].
- **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 (91) [A]. Indwelling catheters (Insuflon) can decrease injection pain (92) [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 have shown significantly less bleeding at the injection site (93) [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 (94) [C].

Insulin absorption

- Insulin activity profiles show substantial variability both day to day in the same individuals and between individuals, particularly children (5, 58) [C,C].
- 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) [E].
  - **Fat mass** (large subcutaneous fat thickness (95) [B], lipohypertrophy (96) [B], also with rapid-acting analogs (97) [B] → slower absorption).
  - **Dose of injection** (larger dose → slower absorption) (58) [C].
  - **Site and depth** of sc injection (abdomen faster than thigh (98) [A]; no good data exist on absorption from thigh vs. buttock).
  - **Sc versus im injection** (im injection → faster absorption in thigh (99) [B]. Accidental im injections can cause variable glucose control [E].
  - **Exercise** (leg injection, leg exercise → faster absorption) (100) [B].
  - **Insulin concentration**, type and formulation (lower concentration → faster absorption) (101) [B].
  - **Ambient and body temperature** (higher temperatures → faster absorption) (95) [B].
- In general, the absorption speed of rapid-acting analogs is less affected by the above mentioned factors (102–104) [B,B,A].
- There is no significant difference in the absorption of glargine from abdomen or thigh (105) [B]. Exercise does not influence glargine absorption (106) [A].
- There is a risk of hypoglycemia if injecting glargine intramuscularly, particularly in young and lean individuals (107) [C].

Note: Faster absorption usually results in shorter duration of action (see page 83).
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 (93) [B].
- Pen injectors of various sizes and types are available from the pharmaceutical companies. Some pens can be set to 1/2 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 2 or 3-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 (30–32 G). A two-finger pinch technique is recommended for all types of injections to ensure a strict subcutaneous injection, avoiding intramuscular injection (109) [C].
- 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) (110) [C]. Lean boys, however, have a thinner subcutaneous fat layer, especially on the thigh (110, 111) [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 (92) [A].
- Insuflon is used in an increasing number of centers for introduction of MDI.
- The use of Insuflon does not affect metabolic control negatively (112) [B]. In children with injection problems, HbA1c has been lowered by using Insuflon (113) [B].
- The use of a basal analog 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 89).
- Insuflons should be replaced every 2-4 days to prevent scarring and a negative effect on insulin absorption (114) [B], (115) [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 (116) [B].

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 (117) and CSII (118), but problems with have included a variable depth of penetration, delayed pain and bruising (119) [B].

Continuous subcutaneous insulin infusion (CSII).

- The use of external pumps is increasing and is proving to be acceptable and successful (38, 39) [A] (40, 42–48, 52) [C] (41) [E], even in young infants (44) [C] (120) [C]. Randomized studies in the pre-school group have failed to show better glycemic control (38, 121) [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 (122, 123) [C]. 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 (124) [C] (125) [E].

♦ Pump therapy is an option for many patients to improve treatment satisfaction. In a review of 5 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 (126) [E]. A randomized study of CSII vs. MDI from the onset of diabetes in 7–17 year olds also found a significant improvement in treatment satisfaction in spite of no difference in HbA1c (49) [A].

♦ Insulin pump use is increasing in the younger age group, as clinicians become more comfortable with CSII as a more physiological insulin replacement therapy (120) [C,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 hours in adult patients resulted in B-ketone (beta-hydroxybutyrate) levels of ~1 – 1.5 mmol/l but not DKA (127) [B]. Results in children and adolescents seem to be similar (128) [C].

♦ The risk of DKA when using pumps comparing with MDI is unchanged in several studies (46, 129) [C]. A literature review found an increased risk of DKA in pediatric pump patients in some studies (130) [C]. Data on national levels have shown both an unchanged (131) [C] and an increased risk of DKA (132) [C].

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

♦ For patients using insulin pumps, and are 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 analog insulins are used in most pumps [E], and a meta-analysis has shown a 0.26% lower HbA1c when comparing with human regular insulin (25) [A]. Regular insulin is less often used in pumps but works well if rapid acting insulin is not available.

♦ Longer age of the infusion site may yield a faster peak of insulin of and a shorter duration of insulin effect (133) [B].

♦ There is no difference in action effect (134) [A], pump stops or catheter cloggings when using insulin lispro or aspart in pumps (135) [C].

♦ Lower percentage of basal insulin and more than seven daily boluses are an option for better metabolic control when using pumps (52) [C].

♦ Motivation appears to be a crucial factor for the long-term success of this form of therapy (136) [C].

Sensor-augmented pump therapy.

♦ The first generation of retrospective, physician-oriented devices for continuous glucose measurement did not show a benefit for glycemic control in children and adolescents (137, 138) [A].

♦ Devices with real-time display were associated with a significant improvement of HbA1c compared to convention blood glucose self monitoring when worn continuously. This was shown in studies of 3 – 6 months including both pediatric and adult patients (139) [A]. Therefore, only devices with real-time display should be used for sensor-augmented therapy [E].

♦ However, in the Juvenile Diabetes Research Foundation (JDRF) Study a significant improvement of HbA1c was seen only in adults in the Intention-to-treat-analysis (140) [A]. Many children and adolescents find it difficult to wear the sensor continuously (141) [C], which may have prevented a 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 (142) [A]. Which patients are likely to profit from sensor-augmented therapy needs to be studied further.

♦ An automatic shut-off of the pump when the sensor has detected nighttime hypoglycemia has been used successfully in children (143) [C]. 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 (144) [C].

Injection technique.

♦ Injections by syringe are usually given into the deep subcutaneous tissue through a two-finger pinch of
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Skin at a 45° angle. A 90° angle can be used if the s.c. fat is thick enough (see page 7).

♦ **Pen injector technique** requires careful education including the need to ensure that no airlock or blockage forms in the needle. A wait of 15 seconds after pushing in the plunger helps to ensure complete expulsion of insulin through the needle (94) [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 persons, an injection aid, Insuflon (113) [B] or insulin pump therapy may improve compliance [E].
♦ There is great individual variation in the appropriate age for children to self-inject (145) [B].
♦ The appropriate age relates to developmental maturity rather than chronological age.
♦ Most children over the age of ten years either give their own injections or help with them (145) [B].
♦ 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, preferably 20 times (146) [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 (71, 147) [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 analogs may be mixed in the same syringe as NPH immediately before injections (148) [B] (149) [C]. Immediate injection of a mixture of Ultralente and Humalog has been found not to diminish the Humalog effect (150) [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 (151) [B] or HbA1c (152) [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.**

♦ 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) 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 analog, 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).

**Principles of insulin therapy**

**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.
Insulin treatment

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 minutes 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, evenings).
- injection of rapid acting insulin analog immediately before (or after) (11, 62) each main meal (breakfast, lunch and main evening meal). Rapid-acting analogs may need to be given 15 minutes before the meal to have full effect, especially at breakfast [E].
- intermediate-acting insulin or basal/long-acting analog at bedtime, probably before breakfast and occasionally at lunchtime or twice daily (mornings, evenings).
- Insulin pump regimes are regaining popularity with a fixed or variable basal dose and bolus doses with meals.
- Continuous glucose monitoring systems (CGMS) used together with CSII or MDI is well tolerated in children with diabetes, but the usage over time declined in studies (140, 153) [A].

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

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

- During the partial remission phase, the total daily insulin dose is often <0.5 IU/kg/day.
- Prepubertal children (outside the partial remission phase) usually require 0.7–1.0 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

- Children on twice daily regimens often require more (perhaps two-thirds) of their total daily insulin in the morning and less (perhaps 1/3) in the evening.
- On this regimen approximately one-third of the insulin dose may be short-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 ~ 70% as regular insulin is divided up between 3–4 pre-meal boluses. When using rapid-acting insulin for pre-meal boluses, the proportion of basal insulin is usually higher, as short-acting 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 (26, 154) [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 (75) [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 (154) [C]. After that, the dose should be individually tailored.
- Detemir is most commonly given twice daily in children (30) [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 BG 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 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 BGM. In addition the daily blood glucose pattern should be taken into account. The rapid acting analogs may require postprandial BG tests approx. 2 hours after meals to assess their efficacy. Frequently, insulin is dosed based on food consumption (carbohydrates) and on deviation from a target glucose. Pumps have the property of delivering the bolus dose in different ways in order to reduce the postprandial blood glucose excursions (155) [C]. Many newer insulin pumps allow programming algorithms for these automatic adjustments for ambient blood glucose and carbohydrate intake.

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 pre-meal 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.

◊ When using carbohydrate counting, persistent elevations of BG may require adjustment in ratios for carbohydrate (insulin to carb ratio).

◊ Correction doses can be used according to the “1800 rule”, i.e. divide 1800 by total daily insulin dose to get the mg/DL that 1 unit of rapid-acting insulin will lower the blood glucose. For mmol/L, use the “100 rule”, i.e. divide 100 by total daily insulin dose (156) [C, 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 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.

◊ 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 of routine, 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 [E].

Dawn phenomenon

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

◊ Pump studies (157) [B] (158) [C] 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) [E].

◊ 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, being seen less often in pump therapy compared to MDI (159) [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 analog.
• changeover to insulin pump treatment.

Recommendations

• Insulin treatment must be started as soon as possible after diagnosis (usually within 6 hours if ketonuria is present) to prevent metabolic decompensation and diabetic ketoacidosis.
• In all age groups, as close to physiological insulin replacement as possible and optimal glycemic control must be the aim, which should include the consideration of an intensive insulin regimen. However, no insulin injection regimen satisfactorily mimics normal physiology.
• 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.
• Aim for appropriate insulin levels throughout the twenty-four hours to cover basal requirements and higher levels of insulin in an attempt to match the glycemic effect of meals.
• Daily insulin dosage varies greatly between individuals and changes over time. It therefore requires regular review and reassessment.
• 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.
• Improvements in glycemic control, particularly when provided by intensive insulin treatment with MDI or pump therapy, reduces the risks of vascular complications. There is no reason to believe that this is not the case also in younger children.
• All children should have rapid-acting or regular insulin available for crisis management.
• 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.
• Children and adolescents should be encouraged to inject consistently within the same site (abdomen, thigh, buttocks, arm) at a particular time in the day, but must avoid injecting repeatedly into the same spot to prevent lipohypertrophy.
• Insulins need to be administered by insulin syringes (or other injection devices) calibrated to the concentration of insulin being used.
• Regular checking of injection sites, injection technique and skills remain a responsibility of parents, care providers and health professionals.
• The use of pumps requires special education for users, but does not need to be restricted to centers with 24 hour 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.
• 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.

References


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