

Consensus Statement on the Use of Insulin Pump Therapy in the Pediatric Age-Group

Moshe Phillip¹ Tadej Battelino², Henry Rodriguez³, Thomas Danne⁴, Francine Kaufman⁵, in collaboration with the participants in the Consensus Meeting, held in Berlin in April 2006, on the Use of Insulin Pumps Therapy in the Pediatric Age Group organized by the LoopClub on behalf of the European Society for Paediatric Endocrinology (ESPE), the Lawson Wilkins Pediatric Endocrine Society (LWPES) and the International Society for Pediatric and Adolescent Diabetes (ISPAD) and endorsed by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).

¹ Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Petah Tikva, Israel ²Department of Pediatric Endocrinology, Diabetes and Metabolism, University Children's Hospital, Ljubljana, Slovenia ³Section of Pediatric Endocrinology Indiana University School of Medicine, James Whitcomb Riley Hospital for Children, Indianapolis, IN, USA, ⁴Diabeteszentrum für Kinder und Jugendliche, Kinderkrankenhaus auf der Bult, Hannover, Germany ⁵Center for Diabetes, Endocrinology and Metabolism, Childrens Hospital, Los Angeles, California, USA

Corresponding Author:

Prof. Moshe Phillip

Institute for Endocrinology and Diabetes,
National Center for Childhood Diabetes,
Schneider Children's Medical Center of Israel
14 Kaplan Street, Petah Tikva, 49202, Israel

Tel: +972-3-9253731

Fax: +972-3-9253836

Email: mosheph@post.tau.ac.il

Approved for publication 7 March 2007.

Introduction

Young patients with diabetes, their families and their diabetes care providers continue to be faced with the challenge of striving to maintain blood glucose levels in the near-normal range. High blood glucose with elevated hemoglobin A1c (A1C) levels are associated with long-term microvascular and macrovascular complications. Recurrent episodes of hypoglycemia, especially at young ages, may cause short- and long-term adverse effects on cognitive function, lead to hypoglycemia unawareness, and may be associated with significant emotional morbidity for the child and parents. Fear of hypoglycemia, especially during the night, may compromise quality of life (QOL) for the family, and jeopardize efforts to achieve optimal metabolic control.

Over the past decade, continuous subcutaneous insulin infusion (CSII) has gained increasing popularity amongst patients with diabetes. CSII is the most physiologic method of insulin delivery currently available. It is able to closely simulate the normal pattern of insulin secretion; namely, continuous 24-hour adjustable “basal” delivery of insulin upon which are superimposed prandial “boluses”. In addition, CSII offers the possibility of more flexibility and more precise insulin delivery than multiple daily injections (MDI). However, there is still debate amongst diabetes care practitioners around the world as to whether CSII has advantages over MDI in terms of reduction in A1C levels, occurrence of severe hypoglycemic events, episodes of diabetic ketoacidosis (DKA) and frequency of hospitalizations in young patients. Furthermore, no clear criteria have been established to help the

physician choose the “appropriate” patient for CSII therapy.

In order to address these issues, the European Society for Pediatric Endocrinology (ESPE), the Lawson Wilkins Pediatric Endocrine Society (LWPES), and the International Society for Pediatric and Adolescent Diabetes (ISPAD) convened a panel of expert physicians for a consensus conference endorsed by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).

For each major topic area, clinical experts were chosen to review the literature and provide evidence-based recommendations according to criteria used by the ADA. Key citations identified for each topic were assigned a level of evidence (indicated in bold throughout the text) and verified by the expert panel (Table). This article summarizes the consensus recommendations of the expert panel and represents the current state of knowledge about CSII in pediatric and adolescent patients with type I diabetes mellitus (T1DM).

Benefits and risks of CSII in pediatric and adolescent patients—what we know so far

Since its introduction, there have been a number of real and perceived risks and benefits of CSII compared with conventional MDI. Ascertainment of the relative risk is hampered by limited data comparing CSII with MDI in toddlers, preschool-aged children and adolescents with T1DM [**C**: (1); **B**: (2)]. Despite this limitation, collective experience can help address questions regarding the relative

risks associated with the use of CSII in these age groups.

Impact on HbA1c

Treatment targets for blood glucose levels for children and adolescents are those that achieve a near-normal A1C (ISPAD 2000), which serves as a surrogate marker for a low risk of late complications. Most adequately powered randomized controlled trials (RCTs) in adults have demonstrated an average decrease in A1C of 0.5-1.2% with CSII compared with MDI (3), but their generalizability to the pediatric population has been questioned. Numerous observational studies, involving more than 760 pediatric patients with T1DM, have reported decreases in A1C with CSII [C: (4-27); B: (28)]. The mean A1C reported in these studies is comparable to, or lower than the mean A1C reported in the adolescent group in the Diabetes Control and Complications Trial (DCCT) [A: (29)]. However, most of these studies have been of limited duration (6-12 months) and only 4 of the studies reported a follow up period of 2-5 years (5,10,16, [C:(30)]. A recent, large 3-year observational study demonstrated a significant improvement in A1C after initiation of CSII [C: (31)] and another demonstrated the sustained benefit of CSII on glycemic control after in average almost four years of therapy [B: (28)].

Several RCTs have assessed the benefits of CSII compared with MDI. No significant difference in A1C was reported with CSII versus MDI using NPH as basal insulin in an open crossover RCT of children [B: (32)] and adolescents [B: (33)] with T1DM. In a study of preschool-age children with diabetes, A1C was slightly lower in the CSII group compared with the MDI group at 3 months, but not at 6 months [B: (34)]. In a 1-year RCT of

toddlers and preschool-age children, there was no difference in A1C between the CSII and MDI groups [B: (35)]. A 6-month RCT failed to demonstrate a significant decrease in A1C between groups of children aged 1 to 6 years treated with either CSII or MDI [B: (36)]. One RCT reported that after 16 weeks A1C was significantly lower in children and adolescents receiving CSII compared with their initial A1C level, as well as being significantly lower than the level observed in patients receiving MDI with glargine [B: (37)]. In addition, there was a statistically significant difference in the number of patients achieving the ADA treatment goal of A1C $\leq 7\%$, between the CSII group (8 out of 16 patients) and the MDI/glargine group (2 out of 16). Because all the RCT studies were of short duration (up to 1 year), it is difficult to determine if pump therapy per se was beneficial, or whether improved control resulted from increased motivation associated with the use of novel technology.

Recommendation: as only one short-term RCT have demonstrated improvement in A1c in pediatric patients treated with CSII vs. MDI, further well controlled trials are needed.

Severe hypoglycemia

Achieving optimal blood glucose control is especially challenging in younger patients with T1DM. Inadequate glucose control can lead to wide glycemic excursions or frequent hypoglycemia. Recurrent episodes of hypoglycemia at a very young age have been associated with neurocognitive dysfunction [E (38)]. Fear of hypoglycemia is prevalent in adolescents and the families of children with T1DM, and may pose a barrier to improved glycemic control [C: (39, 40)]. The threat of pump malfunction, resulting

in excessive insulin delivery, was an early concern after the introduction of CSII. This is not an issue with the current generation of pumps, which are equipped with numerous safety features.

In adults, RCTs have demonstrated a significant decrease in the rate of severe hypoglycemia with CSII [A: (41)]. In children, however, reports of the frequency of hypoglycemia on CSII are highly variable. Several observational pediatric trials, mostly of short-term duration (up to 1 year) have shown a decrease in the rate of severe hypoglycemia with CSII concomitant with a reduction in A1C [C: (1, 31, 42); B:(28)]. However, RCTs have not shown evidence of a significant difference in the frequency of severe hypoglycemia between CSII and MDI in children [B: (32-37)]. A possible explanation for this finding is that these studies were not powered to detect differences in hypoglycemia. Another explanation might be that in the short-term, patients are motivated to measure their BG more frequently and during the night therefore reducing the frequency and severity of hypoglycemia with CSII.

Recommendation: Pediatric observational studies, but not RCTs, have demonstrated that CSII decreases the frequency of severe hypoglycemia. Continuous glucose monitoring will undoubtedly improve the ability to monitor patients for hypoglycemia and future controlled studies will allow us to better characterize the hypoglycemic risk and benefits in young patients using CSII.

Blood glucose variability

Treatment targets for blood glucose levels in pediatric patients are the same whether they are using CSII or MDI, as published in guidelines from several organizations (ISPAD and ADA). Although A1C is the

most generally accepted marker for the risk of long-term complications, the adverse effect of glycemic variability is increasingly becoming recognized [C: (43)], although this has been questioned in the DCCT study [A: (44)].

In adults CSII has been shown to reduce blood glucose variability [C: (45)]. In children, CSII monitored with continuous glucose sensors, has shown a decrease in glucose variability in some, but not all trials [C: (15, 16, 46-51)].

Recommendations: the determination of the impact of glucose variability on the risk for complications must await the results of ongoing and future studies. More RCTs trials are needed to confirm if CSII reduces blood glucose variability in children.

Physical activity and exercise

Although children and adolescents with T1DM are encouraged to exercise regularly, plasma glucose concentrations are often difficult to manage during prolonged periods of physical activity. Recent studies from the Diabetes Research in Children Network (DirecNet) demonstrate that the risk of hypoglycemia is increased both during and on the night following a 75- min period of moderate intensity aerobic exercise in children and adolescents maintained on a fixed basal insulin replacement regimen [B: (52, 53)]. In a follow-up study [C: (54)], the DirecNet study group has shown that the risk of hypoglycemia with exercise can be markedly reduced with CSII by suspending the basal insulin infusion during exercise. Despite the cessation of insulin delivery during exercise, few subjects developed hyperglycemia and their blood ketone levels remained suppressed throughout the exercise period.

Another study compared prolonged standardized exercise in patients with CSII with either half of the regular basal rate (temporary basal) during the exercise or temporary interruption of insulin delivery. The rate of hypoglycemia during exercise was similar in both groups, but a trend towards an increased rate of late hypoglycemia was observed in the temporary basal group [**B**: (55)].

Conclusion: after subcutaneous injection, the action of long-acting insulin analogs cannot be interrupted, whereas with CSII, insulin delivery can be temporarily suspended during prolonged physical activity. This feature should decrease the risk of exercise-related hypoglycemia in patients using CSII.

Weight gain

Although concerns have been raised regarding CSII and weight gain, studies in pediatric patients have shown that CSII either decreases BMI SDS or results in no excess weight gain] over a study period of 3.5 -12 months. [**B**: (32); **C**: (7, 56)] and over 3 to 4 years of follow up [**C**: (31), **B**: (28)].

Conclusions: short-term studies have not shown weight gain with CSII, however, well controlled long-term trials are needed.

Metabolic deterioration

Individuals using CSII are potentially at increased risk of developing DKA, with DKA rates varying from 2.7-9 episodes per 100 patient years [**C**: (56)]. However, as with MDI, DKA is preventable in CSII using published DKA prevention guidelines [**E**: (57)] that recommend frequent monitoring of urine or serum ketones and blood glucose with appropriate intervention when ill. In Norwegian children with diabetes, the nationwide incidence of DKA

(approximately 4 per 100 patient years) did not change despite an increase in CSII use from 5% in 2001 to 38% in 2005 [**C**: (58)].

Recommendations: RCTs trials are needed to evaluate if young patients treated with CSII are more vulnerable to metabolic deterioration. However, DKA is should be preventable in CSII using published DKA prevention guidelines.

Infusion site reactions

Although few studies have systematically recorded the incidence of lipohypertrophy, skin irritation, infusion site infections, and scarring in children, more than 15 studies in adults have reported the frequency of episodes of infections and skin irritation at catheter sites. Rates of irritation and/or infection ranged from 0.06 to 12 per patient per year [**B**: (2)].

Conclusions: efforts to minimize the risk of irritation, scarring, and infection should include the strict adherence to proper infusion site preparation, catheter insertion, and site rotation.

Psychosocial issues

The adoption of CSII can weigh heavily on the patient and their family. Sources of familial stress may include the constant need to be accessible to other caregivers and the additional monetary costs of CSII. Furthermore, for the school-aged child, the additional skills and supervision required of school personnel can add stress and strain the relationship between the child's family and school personnel.

Evidence from studies using different assessment tools indicates that QOL, patient satisfaction and disease-related satisfaction are unchanged or improved with CSII therapy [**B**: (34, 36); **C**: (25, 59-65)]. A meta-analysis examining the metabolic and psychosocial impact of

CSII, which included five pediatric studies, reported no consistent differences in anxiety, depression, QOL, self-esteem and family functioning [**B**: (2)]. In qualitative studies using standardized interview techniques, on switching from MDI to CSII, parents of infants and toddlers reported more freedom, flexibility, and spontaneity in their lives as well as reduced parental stress and worry regarding their child's overall care [**C**: (66)]. Several other studies have found that CSII reduces parental anxiety [**C**: (61, 62, 67)]. In addition, adolescent patients using CSII report high levels of satisfaction due to a greater sense of control, independence, fewer physical complaints and increased flexibility in diet and daily schedule [**C**: (20)]. One nonrandomized study using Diabetes Quality of Life for Youth (DQOL), Children's Depression Inventory [**C**: (1)] and a second RCT of young children with diabetes using the Parenting Stress Index and Brief Symptom Inventory [**C**: (46)] did not find a significant improvement in QOL for children or their parents after initiation of CSII therapy. The authors commented, however, that the use of less objective and more open-ended questionnaires and interviews may have yielded different results.

Most of the studies evaluating QOL were done in infants and toddlers where the parents are completely in-charge, and very few of the studies were done with teenagers. Therefore, CSII may be helpful to the anxious parent however its benefits to the adolescent should be further studied.

Concerns about the complexity of pump therapy and consequent problems in management of children by less knowledgeable and experienced caregivers have proven to be unfounded. On the contrary, children <7 years

utilizing CSII had greater A1C reduction and less severe hypoglycemia when daytime care was provided by paid providers rather than the mother [**C**: (10)]. Conclusions: in spite of the intensive nature of CSII, quality of life with CSII therapy is similar to or higher than that reported in youth treated with MDI.

Clinical experience has shown that instances of patient/family choice to discontinue CSII and return to MDI are not common in any of the pediatric age groups [**B**: (28, 35, 36); **C**: (64, 56)].

CSII use in the pediatric patient

The following summarizes the consensus recommendations convened by the expert panel.

Initiating CSII

The decision to begin pump therapy should be made jointly by the child, parent(s)/guardians and diabetes team.

All pediatric patients with T1DM are potential candidates for CSII and there is no lower age limit for initiating CSII [**E**]. The timing of pump initiation remains an important consideration for the family and health care team in optimizing the likelihood of successful implementation and outcomes [**B**: (28)]. CSII should be considered in the conditions listed below:

- 1) Recurrent severe hypoglycemia [**C**: (1, 4)].
- 2) Wide fluctuations in blood glucose levels regardless of A1C [**C**: (50)].
- 3) Suboptimal diabetes control (i.e., A1C exceeds target range for age) [**C**: (1)],
- 4) Microvascular complications and/or risk factors for macrovascular complications [**A**: (68, 69)].
- 5) Good metabolic control but insulin regimen that compromises lifestyle [**E**].

Other circumstances in which CSII may be beneficial include:

- 1) Young children and especially infants and neonates [**B**: (34-36); **C**: (10, 12, 13)],
- 2) Adolescents with eating disorders [**E**],
- 3) Children and adolescents with a pronounced dawn phenomenon [**E**],
- 4) Children with needle phobia [**E**],
- 5) Pregnant adolescents, ideally preconception [**A**: (70)],
- 6) Ketosis prone individuals [**C**: (71)]
- 7) Competitive athletes [**E**].

Recommendations

1. A pediatric multidisciplinary diabetes team experienced in insulin pump therapy is required to initiate CSII and supervise the ongoing management of a child on CSII [**E**].
2. Frequent contact between the family/child and diabetes team is required after initiating pump therapy, and 24-hour access to a diabetes team member is desirable [**E**].
3. CSII can be safely initiated at diagnosis [**A**: (72), **C**: (73), **B** (74)] or anytime thereafter [**A**: (70); **B**: (34-36)].
4. The child's parent/s, guardian and daytime care provider must be willing and able to provide the supportive care necessary for successful CSII implementation.
 - Psychosocial instability within the family or emotional problems in the child are reasons to consider postponing initiation of pump therapy [**E**].
 - Lack of an available parent during the day is not a contraindication to initiating CSII in the young child, as other caregivers can be taught to supervise and manage pump therapy [**C**: (10)].

CSII supportive care

The child and caregivers should be educated on the following concepts:

1. Nutrition therapy including carbohydrate counting/estimation
2. Principles of basal-bolus therapy
3. Insulin kinetics and pump failure
4. Recognition and management of hypoglycemia and hyperglycemia
5. The effects of activity and exercise on blood glucose
6. Sick day management.

Recommendations

1. Caregivers must be assessed to ensure proper supervision and responsibility for pump management and frequent blood glucose monitoring [**E**].
2. Children and their caregivers must receive initial and ongoing education regarding warning symptoms and strategies for prevention of DKA and problem-solving strategies for pump problems.
3. Children, adolescents and their caregivers must receive initial and ongoing education regarding pump functions, proper infusion set insertion, and pump catheter maintenance by a professional very knowledgeable about pumps [**E**].
 - Patients and families should be instructed to notify their diabetes care provider if pain, inflammation, purulent discharge or recurrent irritation occurs at the infusion site.
 - Adequate training for adolescents and young adults utilizing CSII should include a discussion about handling the pump in intimate situations.
4. Children and their caregivers should be counseled as to the possibility of weight gain with improved glycemic control.

Personalizing CSII

Selecting an insulin pump

The choice of a specific pump will be influenced by the experience and comfort of the diabetes team with a particular model, as well as by the personal preference of the patient and family. Pumps that automatically calculate meal or correction boluses based on insulin-to-carbohydrate ratios and insulin sensitivity factors are useful features that aid other caregivers, such as grandparents, nannies, and day care workers. The ability to review insulin boluses, carbohydrate intake used in bolus calculations and blood glucose levels from pump memory may be useful for counselling patients on their diabetes management, particularly for adolescents, who often omit boluses and have difficulty with manual record keeping [C: (19)].

Pump features requiring consideration include:

1. Small basal rate increments for infants and toddlers.
 - Some pumps allow for 0.025 or 0.05 unit /hour incremental changes, which is important when there is a low total daily insulin dose.
2. Sufficient reservoir volume.
 - May be important, particularly in teenagers, who may have high total daily insulin requirements.
3. Direct communication with a home blood glucose meter.
 - May be beneficial for pumps that assist with bolus dose calculation; however, the accuracy of the blood glucose meter must be considered.
4. Alarm features.
 - To remind a child that a meal bolus has been missed.

5. Water-proof casing
 - A consideration for youth active in water sports where inadvertent submersion is likely.

Determining which concentration and type of insulin to use

Rapid-acting insulin analogues result in a modest but significant reduction in A1C compared with soluble (regular) insulin when used in CSII, and are preferred by adult patients [B: (75)]. Both insulin lispro and insulin aspart are approved for CSII in most countries. Rapid-acting analogues are only available in a concentration of 100 IU per mL (U100).

Recommendations

1. Although there are no data from controlled studies in children, the use of rapid-acting insulin analogues for CSII is recommended (E).
 - Selected “ketosis-prone” patients may benefit from the longer lasting effect of regular insulin. Alternatively, one could add an injection of basal insulin, such as insulin glargine or levemir, to decrease the risk of DKA.
2. Particularly in neonates or toddlers, or during low insulin requirements such as the “honeymoon period,” insulin dilution with a compatible diluent may be required [E].
 - In a simulated continuous insulin infusion, U10 and U50 dilutions of U100 insulin aspart were found to be stable for seven days at 37°C [C: (76)].
 - Although similar studies with diluted insulin lispro (utilizing Sterile Diluent ND-800) are not yet published, diluted insulin lispro has been successfully used in single cases [B: (35); C: (77)].

- To avoid dosing errors or bacterial contamination, U50 or U10 dilutions should only be used in those cases requiring very low hourly insulin infusions (< 0.2 IU per h) [E].

Selecting a catheter

Selection of catheters, adhesives and tubing is dependent on age and individual circumstances. Children and adolescents involved in frequent physical exercise and outdoor activities prefer catheters that can be disconnected.

Several approaches have been utilized to minimize the discomfort of inserting infusion catheters, including topical anesthetics, application of ice, auto-insertion devices, distraction and insertion while the child is asleep.

Catheter features requiring consideration include:

- Needle length.
 - Children usually have significantly less subcutaneous fat than adults. Therefore, the preferred needle length is 6 to 8 mm.
 - If frequent catheter dislodgement occurs or if the overall success of CSII is less than expected, one should consider the use of longer needles/catheters or catheter insertion angles less than 90 degrees, especially in adolescents.
- Needle type.
 - Children fearful of an indwelling steel needle may prefer Teflon catheters; however, catheter obstruction may occur less frequently with steel needles (controlled studies are lacking).
- Tubing length.
 - The infusion set tubing length should be tailored for the individual child and his/her activities.

Recommendations

- Trials with different catheter tubing lengths may be necessary, and when in doubt, the shorter catheter length should be tried first [E].
- For infants and toddlers the tubing should not be so long that it could pose a risk of strangulation [E].
- To prevent accidental dislodgement of the pump catheter secondary to pulling, a catheter loop (pig tail) or a second piece of tape should be used to secure the tubing close to the insertion site [E].

Calculating the total daily insulin requirements when switching from MDI to CSII

The starting insulin dose is based on the pre-pump total daily dose and is guided by continued frequent blood glucose measurements, before and after meals and during the night. The higher the insulin dose required with MDI (in IU per kg), the more pronounced the insulin reduction should be when switching to CSII.

Recommendations

- In children with good glycemic control and a low frequency of hypoglycemia, the total dose may need to be reduced by 10% to 20% [C: (12, 42, 78)].
- In a patient who has been experiencing frequent hypoglycemia, the dose should be reduced by 20% [E].

Calculating the basal insulin rate

The basal rate of insulin delivery addresses the child's food-independent insulin requirement and regulates hepatic glucose production. As with MDI, this comprises 30% to 50% of the total daily dose. With the correct dose of basal insulin, all food intake (even small snacks) will necessitate a food bolus and,

conversely, skipping a meal will not lead to hypoglycemia.

Recommendations

1. The basal rate is typically 30%-50% of the total daily dose [E].
2. The total daily basal rate should be programmed in hourly intervals, according to the patient's circadian variation in insulin sensitivity [E].
 - The circadian variations in basal insulin are age-dependent. [C: (78), B: (79)].
 - Adolescents and young adults typically have a two-waved basal rate profile (decreased insulin sensitivity from approximately 5-9 a.m and, to a lesser extent, in the late afternoon [dawn-dusk phenomenon]).
 - Young children often need more basal insulin between 9 p.m. and midnight [C: (78, 80, 81)].
3. Extreme care is required if prandial boluses are programmed into the basal rate for meals that occur at the same time every day, as hypoglycemia will occur if this meal is missed or delayed [E].

Calculating and timing the prandial (bolus) insulin requirement

A method of accurately estimating the carbohydrate content of meals and snacks (carbohydrate counting) is a prerequisite for successfully determining the bolus insulin requirement [C: (82)]. Prandial boluses are dependent on carbohydrate intake as well as circadian variation of insulin sensitivity, current blood glucose levels, and planned physical activity. The amount of insulin per gram of carbohydrate usually is highest in the morning (breakfast).

Recommendations

1. Patients with CSII must have a method to calculate the appropriate insulin dose.
 - Various algorithms exist that assist in calculating insulin to carbohydrate ratios [C: (83)].
 - Receiving more than 7 daily boluses has been associated with a significantly lower A1C levels [C: (80)].
 - A dual wave bolus may be beneficial when eating foods that are gradually absorbed, such as pizza, beans, and meals with a high fat content [C: (84)].
2. The prandial bolus should be designed to preserve the physiological variation in postprandial blood glucose, i.e., blood glucose is approximately 30-40 mg/dL (1.67-2.2 mmol/L) higher 2 hours after a meal and returns to the preprandial level by 4 hours after a meal [E].
3. In very young children or fussy eaters, parents may prefer to administer the bolus after the meal [C: (85)] in order to choose an insulin dose that is appropriate for the amount of food actually eaten. However, if postprandial insulin doses are frequently forgotten, administration of the bolus after the meal should not be encouraged [C: (86)].

Calculating the correction dose

The correction insulin dose depends upon insulin sensitivity and the blood glucose target. It is calculated based on the difference between the current blood glucose and the desired target blood glucose level. As with meal boluses, formulae are available to calculate insulin sensitivity factors [C: (83)]. Some pump models offer calculation tools for this purpose, whereas, other models require

manual calculation or the use of other devices [C: (25, 87)].

Insulin analogues have a total duration of activity of 4 to 6 hours, with the main activity occurring during the first 3 hours after injection, followed by a prolonged tail of decreasing insulin effect. Many new pumps allow the user to set the “insulin on board” duration to a variable length, and most patients use between 3 to 6 hours. Subjects seeking very tight control prefer a shorter duration of action, whereas subjects concerned about hypoglycemia tend to choose a longer duration of insulin action.

Frequent administration of boluses is associated with better glycemic control (80). The putative benefits of different bolus modes and timing obtained with bolus calculators has yet to be established in the pediatric age group.

Recommendations

1. Infants and toddlers typically are more sensitive to insulin than older children and adolescents and, therefore, require less insulin to correct hyperglycemia [E].
2. “Active insulin” or “insulin on board” from a previous insulin bolus should be taken into consideration when determining the subsequent bolus dose to prevent “stacking” of correction insulin boluses [E].
 - The duration of action of large boluses is generally longer than small doses of insulin.
 - If the pump does not have an “insulin on board” function, a second correction dose should not be given within 2 hours of the first.
3. If a correction bolus fails to reduce the blood glucose within two hours, and particularly in the presence of ketosis, a correction dose with a pen or syringe

should be given immediately and the infusion set should be changed [E]. This is most important, since most episodes of DKA in pump users could have been avoided by this simple measure. Ketones should be tested whenever there are continued high blood glucose readings the patient feels unwell or has nausea/vomiting [E]. Blood ketone testing (measures betahydroxybutyrate) is more appropriate for preventing metabolic deterioration but urine ketones (measures acetoacetate) will be sufficient if this is not available [C:(88)].

Monitoring patients on CSII

Recommendations

After initiation of CSII, frequent contact with the diabetes team is required to review and optimize CSII [E]. Scheduled outpatient visits should address the following:

1. Glycemic control (A1C, blood glucose values and hypoglycemic episodes)
2. Weight gain
3. Average (7 days) total daily insulin dose - compared to body weight
4. Average total daily basal dose (should be roughly 0.2-0.4 IU/hr for toddlers, 0.4-0.6 IU/hr for pre-pubertal children and 0.8-1.2 IU/hr for adolescents)
5. Insulin:carbohydrate ratio
6. Correction dose and target blood glucose
7. Average number of boluses per day (to assess for missed boluses)
8. Basal:bolus ratio
9. Post-prandial and overnight blood glucose values
10. Are the total carbohydrates entered into the bolus calculator appropriate for the child’s age?

Terminating CSII

Recommendations

Discontinuation of CSII should be considered temporarily or permanently under the following circumstances [E].

1. Child wishes to return to injection therapy
2. Conditions that put the child at undue risk.
 - Recurrent DKA due to pump mismanagement
 - Ineffective pump management (e.g., recurrent missed boluses, inadequate frequency of blood glucose monitoring or set changes)
 - Intentional insulin overdosing to cause hypoglycemia.
 - Recurrent site infections.

Cost-Effectiveness

There are no published cost-effectiveness analyses or cost-benefit studies comparing CSII with MDI in children or adolescents with T1DM and such analyses are needed. Studies performed in adults have calculated the expense of insulin pumps, infusion sets, batteries, and insulin cartridges compared with that of insulin (vials and cartridges) and syringes used in MDI. In most countries, the cost of a pump and related supplies is higher than the cost of MDI therapy. Furthermore, the diabetes care team should anticipate additional personnel costs for time spent in the initial education and training, and subsequent support of pump users.

Two meta-analyses in adults [A: (89); B: (2)] found that in comparison with MDI therapy, CSII is associated with a significant reduction in mean A1C. Using an A1C reduction of 0.5% with CSII, Scuffham et al. (90) constructed a Markov model to estimate the cost and outcomes

of CSII compared with MDI. The primary outcome measure was quality-adjusted life years (QALYs). Using Monte Carlo simulations for 10,000 hypothetical patients over 8 years of monthly cycles (considered to be the expected life of a pump), the average patient using CSII could expect to gain 0.48 ± 0.2 QALYs compared with MDI, at an incremental cost of $\pounds 11,461 \pm 3656$ ($\sim 22,800 \pm 7200$ US \$) per QALY. Using the CORE diabetes model to describe the incidence and progression of diabetes-related complications, Roze et al. [C: (91)] found that treatment with CSII was associated with an improvement in mean quality adjusted life expectancy (QALE) of 0.76 ± 0.19 years compared with MDI, and an incremental cost-effectiveness ratio of $\pounds 25,648$ ($\sim 51,000$ US \$) per QALY gained. It must be noted, however, that many of the studies included in these meta-analyses and for calculating cost-effectiveness were published several years before the introduction of currently available pumps, and, more importantly, these models have never been validated against real long term prospective controlled trials, so their value is questionable. Furthermore, more recent studies show that CSII therapy is associated with fewer severe hypoglycemic events [A: (89); C: (92-94)]. Even if these models were accurate, what is cost-effective in adults may not be cost-effective in children given the additional health team interventions required for children and their families.

The following variables should be considered in analyzing the cost-benefit of CSII: acute complications, i.e., the frequency of severe hypoglycemia and DKA (including emergency department visits and hospitalizations; [C: (58)]), chronic complications, both micro- and

macrovascular (EDIC macrovascular study [B: (95)], direct costs of supplies, indirect costs related to lost earnings of parents and costs of other caregivers and additional care team resources.

Conclusions: there are insufficient data at this time to make a definitive statement about cost-effectiveness of CSII in pediatric patients.

Conclusions

There are very few published long-term studies on pump use in children and adolescents, and almost all of those are observational studies.

The vast majority of the studies cited utilize a multidisciplinary trained team that usually is not available to the general pediatrician or non-academic pediatric endocrinologist. This may be a caveat to prescribing CSII. However, based on the available evidence and the experience of the expert panel, CSII therapy may be appropriate for children and youth of all ages provided that appropriate support personnel are available. CSII use in children and adolescents may be associated with improved glycemic control and improved QOL and poses no greater, and possibly less, risk than MDI. Minimizing risks of CSII entails the same interventions that promote safety in all patients with T1DM, including proper education, frequent blood glucose monitoring, attention to diet and exercise and the maintenance of communication with a diabetes team. Additional risk reduction may be possible with current continuous glucose sensors and will almost certainly decline further with advances in this technology and the eventual development of “closed-loop” insulin delivery systems.

Acknowledgments

The European Society for Paediatric Endocrinology (ESPE), the Lawson Wilkins Pediatric Endocrine Society (LWPES) and the International Society for Pediatric and Adolescent Diabetes (ISPAD) gratefully acknowledge the support for the consensus meeting from Medtronic Minimed, Animas Corporation, Novo Nordisk A/S, Abbott Diabetes Care, Eli Lilly & Company, Amylin Pharmaceuticals, Inc, Roche Diagnostics GmbH, Sooil Development Co Ltd and Smith Medical Deutschland GmbH.

The following experts were co-authors in the production of the Consensus document:

Holley Allen (Springfield, MA, USA), Shin Amemiya (Saitama, Japan), Bruce Buckingham (Stanford, CA, USA), Fergus Cameron (Parkville, Victoria, Australia), Francesco Chiarelli (Chiety, Italy), Nathaniel Clark (Alexandria, VA, USA), Carine de Beaufort (Luxembourg), Dorothee Deiss (Berlin, Germany), Knut Dahl-Joergensen, (Oslo, Norway), Larry Fox (Jacksonville, FL, USA), Ragnar Hanas, (Uddevalla, Sweden), Przemyslaw Jarosz-Chobot (Katowice, Poland), Lori Laffel (Boston, MA, USA), Margaret Lawson (Ottawa, Ont, Canada) Johnny Ludvigsson (Linköping, Sweden), Michel Polak (Paris, France), Kenneth Robertson (Glasgow, UK), Shlomit Shalitin (Petah Tikva, Israel), William Tamborlane (New Haven, CT, USA), Joseph Wolfsdorf (Boston, MA, USA).

References

- (1) 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.
- (2) Weissberg-Benchell J, Antisdell-Lomaglio J, Seshadri R. Insulin Pump Therapy: A meta-analysis. *Diabetes Care* 2003;26(4):1079-87.
- (3) Hanaire-Broutin H, Melki V, Bessieres-Lacombe S, Tauber JP. Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens using insulin lispro in type 1 diabetic patients on intensified treatment: a randomized study. The Study Group for the Development of Pump Therapy in Diabetes. *Diabetes Care* 2000;23(9):1232-5.
- (4) Maniatis AK, Klingensmith GJ, Slover RH, Mowry CJ, Chase HP. Continuous subcutaneous insulin infusion therapy for children and adolescents: an option for routine diabetes care. *Pediatrics* 2001; 107: 351-356.
- (5) 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.
- (6) 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.
- (7) 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.
- (8) Liberatore R Jr, Perlman K, Buccino J, Artiles-Sisk A, Daneman D. Continuous subcutaneous insulin infusion pump treatment in children with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab* 2004; 17: 223-226.
- (9) Mack-Fogg JE, Orłowski CC, Jospe N. Continuous subcutaneous insulin infusion in toddlers and children with type 1 diabetes mellitus is safe and effective. *Pediatr Diabetes* 2005; 6: 17-21.
- (10) Weinzimer SA, Ahern JH, Doyle EA, Vincent MR, Dziura J, Steffen AT, Tamborlane WV. Persistence of benefits of continuous subcutaneous insulin infusion in very young children with type 1 diabetes: a follow-up report. *Pediatrics* 2004; 114: 1601-1605.
- (11) Tubiana-Rufi N, de Lonlay P, Bloch J, Czernichow P. Remission of severe hypoglycemic incidents in young diabetic children treated with subcutaneous infusion. *Arch Pediatr* 1996; 3: 969-976.

- (12) 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.
- (13) Shehadeh N, Battelino T, Galatzer A, Naveh T, Hadash A, de Vries L, Phillip M. Insulin pump therapy for 1-6 year old children with type 1 diabetes. *Isr Med Assoc J* 2004; 6: 284-286.
- (14) Battelino T, Ursic-Bratina N, Bratanic N, Zerjav-Tansek M, Avbelj M, Krzisnik C. The use of continuous subcutaneous insulin infusion (CSII) as the treatment of choice in children and adolescents with type 1 diabetes. *Pediatr Endocrinol Rev* 2004;Suppl 3:537-9.
- (15) Deiss D, Hartmann R, Hoeffe J, Kordonouri O. Assessment of glycemic control by continuous glucose monitoring system in 50 children with type 1 diabetes starting on insulin pump therapy. *Pediatr Diabetes* 2004;5:117-21.
- (16) 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;15:1005-10.
- (17) Schiaffini R, Ciampalini P, Spera S, Cappa M, Crino A. An observational study comparing continuous subcutaneous insulin infusion (CSII) and insulin glargine in children with type 1 diabetes. *Diabetes Metab Res Rev* 2005;21:347-52.
- (18) Doyle Boland EA, Steffen AT, Tamborlane WV. Case study: contrasting challenges of insulin pump therapy in a toddler and adolescent with type 1 diabetes. *Diabetes Educ* 2005;31:584-90.
- (19) Pankowska E, Skorka A, Szypowska A, Lipka M. Memory of insulin pumps and their record as a source of information about insulin therapy in children and adolescents with type 1 diabetes. *Diabetes Technol Ther* 2005;7:308-14.
- (20) Low KG, Massa L, Lehman D, Olshan JS. Insulin pump use in young adolescents with type 1 diabetes: a descriptive study. *Pediatr Diabetes* 2005; 6: 22-31.
- (21) Grylli V, Hafferl-Gattermayer A, Wagner G, Schober E, Karwautz A. Eating disorders and eating problems among adolescents with type 1 diabetes: exploring relationships with temperament and character. *J Pediatr Psychol* 2005;30:197-206.
- (22) Grylli V, Wagner G, Hafferl-Gattermayer A, Schober E, Karwautz A. Disturbed eating attitudes, coping styles, and subjective quality of life in adolescents with Type 1 diabetes. *J Psychosom Res* 2005a;59:65-72.

- (23) Mannucci E, Rotella F, Ricca V, Moretti S, Placidi GF, Rotella CM. Eating disorders in patients with type 1 diabetes: a meta-analysis. *J Endocrinol Invest* 2005;28:417-9.
- (24) Peveler RC, Bryden KS, Neil HA, Fairburn CG, Mayou RA, Dunger DB, Turner HM. The relationship of disordered eating habits and attitudes to clinical outcomes in young adult females with type 1 diabetes. *Diabetes Care* 2005;28:84-8.
- (25) Glaser NS, Iden SB, Green-Burgeson D, Bennett C, Hood-Johnson K, Styne DM, Goodlin-Jones B. Benefits of an insulin dosage calculation device for adolescents with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab* 2004;17:1641-51.
- (26) Moreland EC, Tovar A, Zuehlke JB, Butler DA, Milaszewski K, Laffel LM. The impact of physiological, therapeutic and psychosocial variables on glycaemic control in youth with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab* 2004;17:1533-44.
- (27) Tamborlane WV, Fredrickson LP, Ahern JH. Insulin pump therapy in childhood diabetes mellitus: guidelines for use. *Treat Endocrinol* 2003;2:11-21.
- (28) Wood JR, Moreland EC, Volkening LK, Svoren BM, Butler DA, Laffel LMB. Durability of insulin pump use in pediatric patients with type 1 diabetes. *Diab Care* 2006; 29:2355-2360.
- (29) Diabetes Control and Complications Trial 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. *J Pediatr* 1994; 125: 177-188.
- (30) 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 (1): 25-31.
- (31) Nimri R, Weintrob N, Benzaquen H, Ofan R, Fayman G, Phillip M. Insulin pump therapy in youth with type 1 diabetes: a retrospective paired study. *Pediatrics* 2006 Jun;117(6):2126-31.
- (32) Weintrob N, Benzaquen H, Galatzer A, Shalitin S, Lazar L, Fayman G, Lilos P, Dickerman Z, Phillip M. Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens in children with type 1 diabetes: a randomized open crossover trial. *Pediatrics* 2003; 112: 559-564.
- (33) Cohen D, Weintrob N, Benzaquen H, Galatzer A, Fayman G, Phillip M. Continuous subcutaneous insulin infusion versus multiple daily injections in adolescents with type I diabetes mellitus: a randomized open crossover trial. *J Pediatr Endocrinol Metab*. 2003;16(7):1047-50.

- (34) 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.
- (35) 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.
- (36) Fox LA, Buckloh LM, Smith SD, Wysocki T, Mauras N. A randomized controlled trial of insulin pump therapy in young children with type 1 diabetes. *Diabetes Care* 2005;28:1277-81.
- (37) 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.
- (38) Bober E, Buyukgebiz A. Hypoglycemia and its effects on the brain in children with type 1 diabetes mellitus. *Pediatr Endocrinol Rev* 2005;2(3):378-82.
- (39) Marrero DG, Guare JC, Vandagriff JL, Fineberg NS: Fear of hypoglycemia in the parents of children and adolescents with diabetes: maladaptive or healthy response? *Diabetes Educ* 1997; 23:281–286.
- (40) Nordfeldt S, Ludvigsson J. Fear and other disturbances of severe hypoglycaemia in children and adolescents with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab* 2005 Jan;18(1):83-91.
- (41) Hoogma RP, Hammond PJ, Gomis R, Kerr D, Bruttomesso D, Bouter KP, Wiefels KJ, de la Calle H, Schweitzer DH, Pfohl M, Torlone E, Krinelke LG, Bolli GB; on behalf of the 5-Nations Study Group. Comparison of the effects of continuous subcutaneous insulin infusion (CSII) and NPH-based multiple daily insulin injections (MDI) on glycaemic control and quality of life: results of the 5-nations trial. *Diabet Med* 2006;23:141-7.
- (42) Ahern JA, Boland EA, Doane R, Ahern JJ, Rose P, Vincent M, Tamborlane WV. Insulin pump therapy in pediatrics: a therapeutic alternative to safely lower HbA1c levels across all age groups. *Pediatr Diabetes* 2002; 3: 10-15.
- (43) Hirsch IB, Brownlee M. Should minimal blood glucose variability become the gold standard of glycemic control? *J Diabetes Complications* 2005;19:178-181
- (44) Kilpatrick ES, Rigby AS, Atkin SL. The effect of glucose variability on the risk of microvascular complications in type 1 diabetes. *Diabetes Care* 2006 Jul;29(7):1486-90

- (45) Pickup JC, Kidd J, Burmiston S, Yemane N. Determinants of glycaemic control in type 1 diabetes during intensified therapy with multiple daily insulin injections or continuous subcutaneous insulin infusion: importance of blood glucose variability. *Diabetes Metab Res Rev* 2006;[Epub ahead of print]
- (46) Jeha GS, Karaviti LP, Anderson B, Smith EO, Donaldson S, McGirk TS, Haymond MW. Insulin pump therapy in preschool children with type 1 diabetes mellitus improves glycemic control and decreases glucose excursions and the risk of hypoglycemia. *Diabetes Technol Ther* 2005;7:876-84.
- (47) Alemzadeh R, Palma-Sisto P, Parton EA, Holzum MK. Continuous subcutaneous insulin infusion and multiple dose of insulin regimen display similar patterns of blood glucose excursions in pediatric type 1 diabetes. *Diabetes Technol Ther* 2005;7:587-96.
- (48) Heptulla RA, Allen HF, Gross TM, Reiter EO. Continuous glucose monitoring in children with type 1 diabetes: before and after insulin pump therapy. *Pediatr Diabetes* 2004;5(1):10-5.
- (49) Lepore G, Dodesini AR, Nosari I, Trevisan R. Effect of continuous subcutaneous insulin infusion vs multiple daily insulin injection with glargine as basal insulin: an open parallel long-term study. *Diabetes Nutr Metab* 2004 Apr;17(2):84-9.
- (50) Weintrob N, Schechter A, Benzaquen H, Shalitin S, Lilos P, Galatzer A, Phillip M. Glycemic patterns detected by continuous subcutaneous glucose sensing in children and adolescents with type 1 diabetes mellitus treated by multiple daily injections vs continuous subcutaneous insulin infusion. *Arch Pediatr Adolesc Med* 2004;158:677-84.
- (51) Schaepelynck-Belicar P, Vague P, Simonin G, Lassmann-Vague V. Improved metabolic control in diabetic adolescents using the continuous glucose monitoring system (CGMS). *Diabetes Metab* 2003;29:608-12.
- (52) The DirecNet Study Group. Impact of exercise on overnight glycemic control in children with type 1 diabetes. *J Pediatr* 2005; 147:528-534.
- (53) The DirecNet Study Group. The effects of aerobic exercise on glucose and counter-regulatory hormone levels in children with type 1 diabetes. *Diabetes Care* 2006; 29: 20-25.
- (54) Tansey M, Tsalikian E, Beck RW, Fiallo-Scharer R, Janz K, Fox L, Wilson D, Weinzimer S, Tamborlane W, Steffes M, Xing D, Ruedy K and the Diabetes Research in Children Network (DirecNet) Study Group. Stopping Basal Insulin during Exercise Markedly Reduces the Risk of Hypoglycemia in Children with Type 1 Diabetes on Insulin Pump Therapy. *Diabetes* 2006 (ADA abstract)

- (55) Admon G, Weinstein Y, Falk B, Weintrob N, Benzaquen H, Ofan R, Fayman G, Zigel L, Constantini N, Phillip M. Exercise with and without an insulin pump among children and adolescents with type 1 diabetes mellitus. *Pediatrics* 2005; 116: e348-355.
- (56) Hanas R, Ludvigsson J. Hypoglycemia and ketoacidosis with insulin pump therapy in children and adolescents. *Pediatr Diabetes* 2006 Aug; 7 Suppl 4:32-8.
- (57) Wolfsdorf J, Glaser N, Sperling MA; American Diabetes Association. Diabetic ketoacidosis in infants, children, and adolescents: A consensus statement from the American Diabetes Association. *Diabetes Care* 2006;29(5):1150-9.
- (58) Margeirsdottir HD, Larsen JR, Brunborg C, Dahl-Jorgensen K. Nationwide improvement in HbA1c and complication screening in a benchmarking project in childhood diabetes. *Pediatr Diabetes* 2006; 7 (Suppl. 5):18 .
- (59) McMahon SK, Airey FL, Marangou DA, McElwee KJ, Carne CL, Clarey AJ, Davis EA, Jones TW. Insulin pump therapy in children and adolescents: improvements in key parameters of diabetes management including quality of life. *Diabetic Medicine* 22: 92-6, 2005
- (60) Hoogma RP, Spijker AJ, van Doorn-Scheele M, van Doorn TT, Michels RP, van Doorn RG, Levi M, Hoekstra JB. Quality of life and metabolic control in patients with diabetes mellitus type 1 treated by continuous subcutaneous insulin infusion or multiple daily insulin injections. *Neth J Med* 2004;62:383-7.
- (61) Kamoi K, Miyakoshi M, Maruyama R. A quality-of-life assessment of intensive insulin therapy using insulin lispro switched from short-acting insulin and measured by an ITR-QOL questionnaire: a prospective comparison of multiple daily insulin injections and continuous subcutaneous insulin infusion. *Diabetes Res Clin Pract* 2004;64:19-25.
- (62) Peyrot M, Rubin RR. Validity and reliability of an instrument for assessing health-related quality of life and treatment preferences: the Insulin Delivery System Rating Questionnaire. *Diabetes Care* 2005;28:53-8.
- (63) Rudolph JW, Hirsch IB. Assessment of therapy with continuous subcutaneous insulin infusion in an academic diabetes clinic. *Endocr Pract* 2002;8(6):401-5.
- (64) Weintrob N, Shalitin S, Phillip M. Why pumps? Continuous subcutaneous insulin infusion for children and adolescents with type 1 diabetes. *Isr Med Assoc J* 2004;6:271-5.
- (65) Rizvi AA, Petry R, Arnold MB, Chakraborty M. Beneficial effects of continuous subcutaneous insulin infusion in older patients with long-standing type 1 diabetes. *Endocr Pract* 2001;7:364-9.

- (66) Sullivan-Bolyai S, Knafl K, Tamborlane W, Grey M. Parents' reflections on managing their children's diabetes with insulin pumps. *J Nurs Scholarsh* 2004; 36: 316-323.
- (67) Maniatis AK, Toig SR, Klingensmith GJ, Fay-Itzkowitz E, Chase HP. Life with continuous subcutaneous insulin infusion (CSII) therapy: child and parental perspectives and predictors of metabolic control. *Pediatr Diabetes* 2001a;2:51-7.
- (68) Beneficial effects of intensive therapy of diabetes during adolescence: Outcomes after the conclusion of the Diabetes Control and Complications Trial (DCCT). *J Pediatr* 139:804-812, 2001.
- (69) The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group: Intensive Diabetes Treatment and Cardiovascular Disease in Patients with Type 1 Diabetes. *N Engl J Med* 353:2643-2653, 2005.
- (70) Burkart W, Hanker JP, Schneider HPG: Complications and fetal outcome in diabetic pregnancy. Intensified conventional versus insulin pump therapy. *Gynecol Obstet Invest* 26:104-112, 1998
- (71) 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.
- (72) Pozzilli P, Crino A, Schiaffini R, Manfrini S, Fioriti E, Coppolino G, Pitocco D, Visalli N, Corbi S, Spera S, Suraci C, Cervoni M, Matteoli MC, Patera IP, Ghirlanda G, The IMDIAB Group: A 2-Year Pilot Trial of Continuous Subcutaneous Insulin Infusion Versus Intensive Insulin Therapy in Patients with Newly Diagnosed Type 1 Diabetes (IMDIAB 8). *Diabetes Technology & Therapeutics* 2003;5:965-974.
- (73) De Beaufort CE, Houtzagers CM 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.
- (74) Skogsberg, L. Lindman, E., Fors H. Comparison in metabolic control and quality of life of continuous subcutaneous insulin infusion and multiple daily injections in children at onset of type 1 diabetes mellitus, ISPAD 2006.
- (75) 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; 20:863-6.
- (76) Jorgensen D, Solbeck H, Harboe E. Dilution of Novolog (insulin aspart 100 U/ml) with NPH medium for small dose use in continuous subcutaneous insulin infusion does not affect in-vitro stability (Abstract). *Diabetes* 2005; 54 (Suppl. 1): A 102

- (77) Bharucha T, Brown J, McDonnell C, Gebert R, McDougall P, Cameron F, Werther G, Zacharin M. Neonatal diabetes mellitus: Insulin pump as an alternative management strategy. *J Paediatr Child Health* 2005;41:522-6.
- (78) Conrad SC, McGrath MT, Gitelman SE. Transition from multiple daily injections to continuous subcutaneous insulin infusion in type 1 diabetes mellitus. *J Pediatr* 2002;140:235-40.
- (79) Danne T, Battelino T, Kordonouri O, Hanas R, Klinkert C, Ludvigsson J, Barrio R, Aebi C, Gschwend S, Mullis PE, Schumacher U, Zumsteg U, Morandi A, Rabbone I, Cherubini V, Toni S, de Beaufort C, Hindmarsh P, Sumner A, van Waarde WM, van den Berg N, Phillip M. A cross-sectional international survey of continuous subcutaneous insulin infusion in 377 children and adolescents with type 1 diabetes mellitus from 10 countries. *Pediatr Diabetes* 2005;6:193-8
- (80) Danne T, Battelino T, Jarosz-Chobot P, Kordonouri O, Pankowska E, Phillip M and the PedPump Study Group. The PedPump Study: A Low Percentage of Basal Insulin and More Than Five Daily Boluses Are Associated with Better Centralized HbA1c in 1041 Children on CSII from 17 Countries (Abstract). *Diabetes* 2005a; 54 (Suppl. 1): A 453
- (81) Boland E, Ahern J, WV Tamborlane. Pumps in kids: basal requirements for excellent metabolic control (Abstract). *Diabetes* 2002; 51 (Suppl 2): A3
- (82) Waldron S, Hanas R, Palmvig B. How do we educate young people to balance carbohydrate intake with adjustments of insulin? *Horm Res* 2002;57 (Suppl 1):62-5.
- (83) Davidson PC (1995). *The Insulin Pump Therapy Book: Insights from the Experts*, Fredrickson L, ed. Sylmar, Calif.
- (84) Chase HP, Saib SZ, MacKenzie T, Hansen MM, Garg SK. Post-prandial glucose excursions following four methods of bolus insulin administration in subjects with type 1 diabetes. *Diabet Med* 2002;19:317-321
- (85) Rutledge KS, Chase HP, Klingensmith GJ, Walravens PA, Slover RH, Garg SK. Effectiveness of postprandial Humalog in toddlers with diabetes. *Pediatrics* 1997 Dec;100(6):968-72.
- (86) Burdick J, Chase HP, Slover RH, Knieval K, Scrimgeour L, Maniatis AK, Klingensmith GJ. Missed insulin meal boluses and elevated hemoglobin A1c levels in children receiving insulin pump therapy. *Pediatrics* 2004; 113: e221-224.
- (87) Kaufman FR, Halvorson M, Carpenter S. Use of a plastic insulin dosage guide to correct blood glucose levels out of the target range and for carbohydrate counting in subjects with type 1 diabetes. *Diab Care* 1999; 8:1252-7.

- (88) Laffel LM, Wentzell K, Loughlin C, Tovar A, Motltz K, Brink S. Sick day management using blood 3-hydroxybutyrate (3-OHB) compared with urine ketone monitoring reduces hospital visits in young people with T1DM: a randomized clinical trial. *Diabet Med* 2006; 23 (3): 278-284.
- (89) 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(7339):705.
- (90) Scuffham P, Carr L. The cost-effectiveness of continuous subcutaneous insulin infusion compared with multiple daily injections for the management of diabetes. *Diabet Med* 2003;20:586-93.
- (91) Roze S, Valentine WJ, Zakrzewska KE, Palmer AJ. Health-economic comparison of continuous subcutaneous insulin infusion with multiple daily injection for the treatment of Type 1 diabetes in the UK. *Diabet Med* 2005;22:1239-45.
- (92) Bode BW, Sabbah HT, Gross TM, Fredrickson LP, Davidson PC. Diabetes management in the new millennium using insulin pump therapy. *Diabetes Metab Res Rev* 2002;18 Suppl 1:S14-20.
- (93) Linkeschova R, Raoul M, Bott U, Berger M, Spraul M. Less severe hypoglycaemia, better metabolic control, and improved quality of life in Type 1 diabetes mellitus with continuous subcutaneous insulin infusion (CSII) therapy; an observational study of 100 consecutive patients followed for a mean of 2 years. *Diabet Med* 2002;19(9):746-51.
- (94) DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. *JAMA* 2003;289(17):2254-64.
- (95) Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353(25):2643-53.

Table: ADA evidence grading system for clinical recommendations*

Level of evidence	Criteria
A	Clear evidence from well conducted, generalisable, randomised controlled trials (RCTs) that are adequately powered, including: <ul style="list-style-type: none"> • Multicenter trial • Meta-analysis incorporating quality ratings • Compelling non-experimental evidence (i.e., "all or none" rule) developed by the Centre for Evidence Based Medicine at Oxford† • Supportive evidence from well conducted RCTs that are adequately powered, including: <ul style="list-style-type: none"> • Well conducted trials at one or more institutions
B	Supportive evidence from well conducted cohort studies, including: <ul style="list-style-type: none"> • Prospective cohort studies or registry • Meta-analysis of cohort studies Supportive evidence from a well conducted case-control study
C	Supportive evidence from poorly controlled or uncontrolled studies including: <ul style="list-style-type: none"> • RCTs with one or more major or three or more minor methodological flaws that could invalidate the results • Observational studies with high potential for bias • Case series or case reports Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience
*Diabetes Care 2003;26(suppl 1):S1. †Either all patients died before therapy and at least some survived with therapy or some patients died without therapy and none died with therapy. Example: use of insulin in the treatment of diabetic ketoacidosis.	