Use of Insulin Pump Therapy in the Pediatric Age-Group

Consensus statement from the European Society for Paediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes, endorsed by the American Diabetes Association and the European Association for the Study of Diabetes

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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 levels with elevated 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 and 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 among 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-h 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 injection (MDI). However, there is still debate among 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.

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 1). 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 1 diabetes.

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*A complete list of the participants in the forum can be found in the ACKNOWLEDGMENTS.

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Abbreviations: ADA, American Diabetes Association; CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Control and Complications Trial; DKA, diabetic ketoacidosis; EASD, European Association for the Study of Diabetes; ESPE, European Society for Paediatric Endocrinology; ISPAD, International Society for Pediatric and Adolescent Diabetes; LWPES, Lawson Wilkins Pediatric Endocrine Society; MDI, multiple daily injection; QALY, quality-adjusted life year; QOL, quality of life; RCT, randomized controlled trial.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*ADA evidence grading system for clinical practice recommendations [reprinted from* Diabetes Care *26 (Suppl. 1):S1, 2003]*

Level of evidence	Description
A	Clear evidence from well-conducted, generalizable, randomized controlled trials that are adequately powered, including: • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis • Compelling nonexperimental evidence, i.e., "all or none" rule developed by the Center for Evidence Based Medicine at Oxford* Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including: • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis
B	Supportive evidence from well-conducted cohort studies, including: • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies Supportive evidence from a well-conducted case-control study
C	Supportive evidence from poorly controlled or uncontrolled studies, including: • Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results • Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls) • Evidence from case series or case reports Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

*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.

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 type 1 diabetes (**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 A1C

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 type 1 diabetes, have reported decreases in A1C with CSII (**C**: 4–27, **B**: 28). The mean A1C reported in these studies is comparable with 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 four 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 4 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 type 1 diabetes. 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 1–6 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 of 16 patients) and the MDI/glargine group (2 of 16). Because all of the RCT studies were of short duration (up to 1 year), it is difficult to determine whether 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 has demonstrated improvement in A1C in pediatric patients treated with CSII versus MDI, further well-controlled trials are needed.

Severe hypoglycemia

Achieving optimal blood glucose control is especially challenging in younger patients with type 1 diabetes. 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 families of children with type 1 diabetes 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 blood glucose 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 (**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 RCT trials are needed to confirm whether CSII reduces blood glucose variability in children.

Physical activity and exercise

Although children and adolescents with type 1 diabetes 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 toward an increased rate of late hypoglycemia was observed in the temporary basal group (**B**: 55).

Conclusions. 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 SD score or results in no excess weight gain over a study period of 3.5–12 months (**B**: 32; **C**: 7,56) and over 3–4 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 (~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. RCT trials are needed to evaluate whether young patients treated with CSII are more vulnerable to metabolic deterioration. However, DKA 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).

Conclusion. Efforts to minimize the risk of irritation, scarring, and infection should include 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 that examined the metabolic and psychosocial impact of CSII and 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 the Diabetes Quality of Life for Youth (DQOL) and the Children's Depression Inventory (**C**: 1) and a second RCT of young children with diabetes using the Parenting Stress Index and the 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 of age using CSII had greater A1C reduction and less severe hypoglycemia when daytime care was provided by paid providers rather than the mother (**C**: 10).

Conclusion. Despite the intensive nature of CSII, QOL 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 type 1 diabetes 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-h 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 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 using 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 counseling 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/h incremental changes, which is important when there is a low total daily insulin dose.

2. Sufficient reservoir volume
   - 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
   - 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
   - Alarm features remind a child that a meal bolus has been missed.

5. Waterproof casing
   - Waterproof casing should be considered for youth active in water sports where inadvertent submersion is likely.

Determining which concentration and type of insulin to use

Rapid-acting insulin analogs 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 analogs are only available in a concentration of 100 IU/ml (U100).

Recommendations

1. Although there are no data from controlled studies in children, the use of rapid-acting insulin analogs 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 7 days at 37°C (**C**: 76).
   - Although similar studies with diluted insulin lispro (using Sterile Diluent ND-800) are not yet published, diluted insulin lispro has been successfully used in single cases (**B**: 35; **C**: 77).

3. 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/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 used to minimize the discomfort of inserting infusion catheters, including topical anesthetics, application of ice, autoinsertion devices, distraction, and insertion while the child is asleep.

Catheter features requiring consideration include:

1. Needle length
   - Children usually have significantly less subcutaneous fat than adults. Therefore, the preferred needle length is 6–8 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 $<$90°, especially in adolescents.

2. 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).

3. Tubing length
   - The infusion set tubing length should be tailored for the individual child and his/her activities.

Recommendations

1. Trials with different catheter tubing lengths may be necessary, and when in doubt, the shorter catheter length should be tried first (**E**).
2. For infants and toddlers, the tubing should not be so long that it could pose a risk of strangulation (**E**).
3. 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 prepump 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 insulin units per kilogram), the more pronounced the insulin reduction should be when switching to CSII.

Recommendations

1. In children with good glycemic control and a low frequency of hypoglycemia, the total dose may need to be reduced by 10–20% (**C**: 12,42,78).
2. 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 30–50% 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 ~5:00–9:00 A.M. and, to a lesser extent, in the late afternoon [dawn-dusk phenomenon]).
   - Young children often need more basal insulin between 9:00 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 is usually 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 seven 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 ~30–40 mg/dl (1.67–2.2 mmol/l) higher 2 h after a meal and returning to the preprandial level by 4 h 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 on 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 analogs have a total duration of activity of 4–6 h, with the main activity occurring during the first 3 h 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 and 6 h. 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 h of the first.
3. If a correction bolus fails to reduce the blood glucose within 2 h, 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 or the patient feels unwell or has nausea/vomiting (**E**). Blood ketone testing (measures β-hydroxybutyrate) 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 with body weight
4. Average total daily basal dose (should be ~0.2–0.4 IU/h for toddlers, 0.4–0.6 IU/h for prepubertal children, and 0.8–1.2 IU/h for adolescents)
5. Insulin-to-carbohydrate ratio
6. Correction dose and target blood glucose
7. Average number of boluses per day (to assess for missed boluses)
8. Basal-to-bolus ratio
9. Postprandial 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 type 1 diabetes; 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 £11,461 ± 3,656 (~22,800 ± 7,200$ U.S.) per QALY. Using the Center for Outcomes Research, Basel, Switzerland, 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 of 0.76 ± 0.19 years compared with MDI and an incremental cost-effectiveness ratio of £25,648 (~51,000$ U.S.) 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

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 use a multidisciplinary trained team that usually is not available to the general pediatrician or nonacademic 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 type 1 diabetes, 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.

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