Published in final edited form as:

Mt Sinai J Med. 2008 August ; 75(4): 352–361. doi:10.1002/msj.20055.

Past, Present, and Future of Insulin Pump Therapy: A Better Shot at Diabetes Control

Jennifer Sherr, MD and William V. Tamborlane, MD

Department of Pediatrics and the Yale Center for Clinical Investigation, Yale University School of Medicine, New Haven, CT

Abstract

With the advent of continuous subcutaneous insulin infusion (CSII) therapy and the findings of the Diabetes Control and Complications Trial (DCCT) the management of type 1 diabetes has changed drastically. Over the past 30 years since its development, the effectiveness of CSII as compared to other modes of intensive treatment has been assessed. Additionally, improvements in pump delivery systems have been made. Herein the findings of the studies on pump therapy will be reviewed. Selection criteria of patients for pump use and how to initiate pump therapy will be presented. Finally, newer findings on continuous glucose sensors will be discussed as the next era of pump therapy continues to focus on the goal of developing an artificial pancreas.

Keywords

Type 1 Diabetes; Continuous Subcutaneous Insulin Infusion (CSII); insulin pumps; multiple daily injections (MDI)

Dawn of Pump Therapy

Continuous subcutaneous insulin infusion (CSII) pump therapy was introduced to treat patients with type 1 diabetes in the late 1970's (1,2). Until then, care of individuals with type 1 diabetes was crude, involving one or two daily injections of NPH and regular insulin of animal origin that was not purified, adjusting insulin doses based on urinary glucose excretion, and dietary counseling focused on limiting simple sugars and maintaining fixed macronutrient intake at each meal. Due to the limitations of this regimen and fear of hypoglycemia, particularly in children, glucose levels often averaged over 300mg/dL. It is also important to remember that at that time, a causal relationship between poor glycemic control and the development of complications was suspected but not yet proven. Thus, it is not surprising that the demonstration that CSII could provide a more physiologic method of insulin replacement in T1DM was enthusiastically received (1-4). Self-monitoring of blood glucose (SMBG), hemoglobin A1c assays (HbA1c), and purified insulin preparations were also introduced in the late 1970's and the basal bolus approach utilized for CSII was adapted for use in multiple daily injection (MDI) regimens. These advances made intensive treatment of T1DM possible and set the stage for the Diabetes Control and Complications Trial (DCCT) that was launched in 1983.

Intensive therapy did not come without a price. An increased risk of severe hypoglycemia, due in part to reductions in counterregulatory hormone responses to hypoglycemia, was demonstrated (5,6). This acquired inability to symptomatically identify low blood glucose

levels due to repeated episodes of mild hypoglycemia was named “hypoglycemia-associated autonomic failure” (7) and made patients even more vulnerable to severe hypoglycemic events. Consequently, the need to solve the puzzle of the relationship between hyperglycemia and vascular complications became even more urgent and compelling.

Setting the Bar: Results of the DCCT

In 1993, the findings of the DCCT were published and showed that the benefits achieved from intensive therapy in regards to the development and progression of complications outweighed the associated two to three fold increase in the risk of severe hypoglycemia (8). This beneficial effect was also shown in subgroup analysis of the relatively small number of adolescents who participated in the study (9) and persisted for many years after completion of the randomized clinical trial (10). With this focus on intensive therapy to prevent complications and improvements in pump technology, use of CSII increased dramatically with the most rapid growth being in the number of children and adolescents with T1DM who started to receive this therapy.

Non-randomized Studies of Pump Therapy

Very few children and adolescents with T1DM used CSII prior to the late 1990's. Even though the percentage of intensively treated subjects who switched from MDI to CSII therapy increased steadily during the DCCT, the majority of these subjects were adults with T1DM. In the paper describing the analyses of DCCT results in the subset of adolescents, the investigators themselves questioned whether the goals of intensive therapy could be effectively translated into pediatric diabetes practice. To examine this question, the Adolescents Benefit from Control (ABC's) of Diabetes Study was undertaken by Grey and colleagues (11). In this prospective study, 75 subjects ranging in age from 12-20 years were started on intensive therapy (11). Subjects chose the mode of intensive therapy delivery, with 25 choosing CSII and 50 choosing MDI (11). Those in the CSII group had a mean drop in HbA1c of 0.9% while those in the MDI group had a mean drop of 0.5% (11). Despite this improvement in control, the CSII group demonstrated a 50% reduction in episodes of severe hypoglycemia, a finding which was opposite of the DCCT data (11). However, weight gain increased with intensive therapy in both MDI and CSII-treated subjects with better metabolic control (11). Interestingly, adolescents on CSII reported less difficulty in coping with diabetes (11).

Since that report, many clinical outcome studies have examined the effects of switching from MDI to CSII in children of various ages (Table 1). A very consistent picture emerged from these studies: mean HbA1c fell by 0.2-0.9% (12-25), the frequency of clinically important hypoglycemia was reduced (12-19,21-25) and BMI z-scores did not increase (12-16,18,20-25). Of note, the mean HbA1c values achieved across these studies (i.e. ~7.5%) is considerably lower than those attained by adolescents in the intensive group in the DCCT (i.e., 8.1%). In a 2003 meta-analysis of 11 studies with a parallel design, the weighted summary mean difference in HbA1c between CSII and MDI/conventional therapy was 0.95% with a 95% CI of 0.8-1.1% (26).

From these non-randomized studies, some additional observations deserve attention. In two studies, patients were switched from conventional therapy to either MDI with glargine (the current “gold standard” of MDI treatment) or CSII (27). Subjects who switched to CSII showed improved glycemic control versus those who switched to glargine (17,20). Concern also existed about the use of CSII in infants, toddlers, and pre-school children but a number of studies have shown that CSII is particularly efficacious in this age group (12,18,21,23). Other studies have highlighted that CSII may be beneficial in subjects with the highest

baseline HbA1c with a mean decrease in HbA1c of 1.7% from the subpopulation of patients who had a baseline HbA1c >10% in Nimri's study (22). It is also important to realize that the beneficial effects of CSII were sustained during long-term use in three of the four non-randomized studies that followed patients for more than 3.5 years (18,24,25,28).

The use of insulin pump therapy from the time of diagnosis has also been investigated. In the early days of pump therapy, a 2-year randomized clinical trial evaluated the efficacy of CSII in comparison to conventional therapy in 30 children with new-onset T1DM and demonstrated that the CSII arm had significantly lower HbA1c levels (29). It was interesting that CSII was well accepted in newly diagnosed patients at a time when such therapy was still in its infancy. In a more recent non-randomized study, 28 patients were offered pump therapy within the first month of diagnosis, and all accepted participation in the study (30). As expected, improved glycemic control was seen with CSII. Equally important, patients reported no adverse impacts of diabetes on flexibility of lifestyle compared with before diagnosis showing the beneficial effects from a psychosocial standpoint in regards to pump therapy (30).

Recent database review of clinical factors, including gender, ethnicity, socio-economic status, duration of diabetes, and insulin regimen on HbA1c levels was reported by our clinic (31). One of the strongest predictors of low HbA1c was found to be use of CSII with 286 patients on this therapy having a mean HbA1c of 7.2% compared to 8.1% in the 167 patients on MDI therapy (31). In the same study, it was demonstrated that lower socioeconomic status was associated with poor metabolic control (31). Clearly, non-randomized studies have paved the path for pump therapy that has been supported further by randomized trials.

Randomized Studies of Pump Therapy

A number of randomized studies have assessed the efficacy of CSII versus multiple daily injections using NPH as the basal insulin (Table 2). DeVries and colleagues reported on 79 patients recruited from 11 Dutch centers in a randomized crossover design (32). Given a high dropout rate the trial was transitioned to a parallel clinical trial, which showed improved HbA1c in those on CSII therapy (32). A randomized, crossover trial was completed by Weintrob and colleagues in which 23 children were studied on both MDI and CSII for a duration of 3.5 months on each therapy (33). This study demonstrated no difference between treatment groups in regards to HbA1c or hypoglycemia; however, patients reported higher treatment satisfaction on CSII (33). The large "5 Nations Trial" demonstrated lower HbA1c, less blood glucose variability, and higher quality of life scores in those receiving CSII therapy (34). Other studies have demonstrated no difference in HbA1c in MDI vs. CSII (35-38) but the majority of these studies were in very young children where target glucose levels were set considerably higher than in older children and adolescents. Moreover, it is very clear that a major advantage of CSII in the youngest pediatric patients from the perspective of parents is that it makes living with diabetes much more bearable (39).

A meta-analysis assessing CSII versus intensive insulin injection therapy via randomized controlled trials was published in 2002. This meta-analysis examined 12 randomized controlled trials and showed a reduction of 0.44 in the HbA1c (confidence interval 0.20-0.69) in patients using CSII (40). There was also a ~14% drop in total daily insulin dose in patients using CSII (40). Many of the studies in this meta-analysis used NPH rather than long-acting insulin analogues in their MDI groups, even though the peaking of NPH and its variable absorption make it less ideal for basal insulin replacement than glargine or detemir (27).

A randomized, parallel group clinical trial was completed by our group in 32 conventionally treated subjects who were randomized to either CSII or glargine and bolus doses of aspart (41). The CSII group was found to have lower HbA1c levels in comparison to the glargine group and also in comparison to their baseline HbA1c levels. Fasting plasma glucose concentrations did not differ between the two groups, indicating similar adequacy of basal insulin replacement. However, SMBG performed at lunch, dinner, and bedtime demonstrated significantly lower blood glucose levels in the CSII group (41). These findings suggest that lack of compliance with bolus dosing likely contributed to the higher blood glucose and HbA1c levels in the MDI group. Schiaffini and colleagues demonstrated similar findings in their randomized trial of 36 children between 9-18 years old who were followed for 2 years after being randomized to either MDI with glargine or CSII (42). While both treatment arms showed improvement in glycemic control based on HbA1c levels at 1 year, only the CSII group continued to demonstrate improved HbA1c after 2 years of therapy (42).

The very flat time-action profiles of new long-acting insulin analogs places a premium on strict compliance with and need for insulin injections for every meal and snack, which may be difficult for older children and adolescents. This is a reason why several pediatric diabetes centers utilize a compromise approach that employs NPH mixed with aspart or lispro in the morning and long-acting analogues with aspart or lispro at dinner (43). Some even mix the rapid and long-acting analogs together to save an extra injection without adverse effects on metabolic control (44).

Bolus and Beyond: The New and Improved Insulin Pumps

While many of the studies demonstrating the effectiveness of pump therapy were being completed, insulin analogues and technological advances changed the way CSII therapy evolved. The desire for smaller, more portable pumps (45,46) was realized as pumps shrunk to the size of a pager. In the DCCT, regular insulin was used; however, the advantages of rapid-acting insulin analogues (lispro and aspart) are now well recognized (47,48). With regular insulin the delayed peak led to postprandial hyperglycemia, while rapid-acting analogues allow for a more physiologic peak in insulin action. As the duration of action of regular insulin is longer, the risk of hypoglycemia in the late post-prandial period is also increased. It should be noted, however, that the goal of mimicking the natural peak and duration of endogenous insulin remains elusive even with rapid-acting analogues (49).

The technologic capabilities of pumps have also advanced. Programmable pumps have allowed for titration of basal rates and varying bolus doses in a wide array of delivery options. Programmable pumps have been shown to lead to improved pre-prandial glycemic control and fewer episodes of overnight hypoglycemia versus nonprogrammable pumps (50). One of the features of pumps that is particularly important in treating adolescents with T1DM is the bolus history function that allows clinicians and parents to assess whether patients are missing bolus doses of insulin (51,52). In 48 patients on pump treatment a cross-sectional study demonstrated that those who missed <1 bolus per week versus those who missed ≥ 1 mealtime bolus had better HbA1c, 8.0% vs. 8.8 % respectively ($p = .0001$) (52). Mealtime alarms can be set with CSII, which may provide at least temporary improvement in metabolic control (53).

The fear of hypoglycemia remains a major obstacle that prevents patients and parents from achieving HbA1c goals. Although patients with T1DM are encouraged to exercise regularly, the risk of hypoglycemia during and on the night after exercise is substantially increased. Recent studies completed by the Diabetes Research in Children Network (DirecNet) showed that the risk of hypoglycemia increased both during exercise and on the night following a 75

minute period of moderate intensity aerobic exercise in patients on fixed insulin dosing (54,55). A randomized crossover study was subsequently done to assess the efficacy of suspending the basal rate on CSII during exercise. Suspending basal rates decreased the risk of hypoglycemia, defined as a blood glucose <70mg/dL, from 43% to 16% (56). The ability to individually titrate the correct basal rate not only during exercise but also on the night following exercise provides a clear benefit for those on CSII as compared to those on fixed MDI regimens (57).

With all of the advances in pump therapy the question as to when youth with type 1 diabetes can begin to have autonomy with their care has been debated. One study showed that parents' reports of CSII skill mastery and the age at which clinicians' expectation of skill mastery are similar (58). Yet, the key to successful transition remains adult supervision during the transition period and tailoring the timing of autonomy based on an individual's maturity and understanding of pump therapy.

Going Beyond the Numbers- Psychosocial Benefits of CSII

Non-randomized and randomized studies have shown benefits of CSII that go beyond improvements in glycemic control. Quality of life scores measured via different scales have shown improvement in patients treated with CSII and CSII-treated patients have reported higher treatment satisfaction versus MDI therapy (32-34). A large non-randomized case control study recently showed greater lifestyle flexibility, decreased fear of hypoglycemia, and improved treatment satisfaction when CSII subjects were compared to those on MDI therapy whether it be a glargine or NPH-based regimen (59). In a study of 16 children between 3-5 years old, parents reported decreased diabetes related worry in patients on CSII (41). In three randomized studies, >95% of subjects decided to continue on CSII therapy after study completion (35-37).

In a recent study, parents of young children with T1DM were found to have a moderate level of fear in regards to hypoglycemia and there was a positive correlation between fear and mean daily blood glucose levels (60). Fear of hypoglycemia may be a particular problem in young children in day care. However, in a study of children under age 7 being treated with CSII, HbA1c levels and risk of severe hypoglycemia were lower when children were cared for by paid providers as compared to when the mother was the primary daytime caregiver (18). In a qualitative study, parents of young children with T1DM reported that "everyone in the family experienced more freedom, flexibility, and spontaneity in their daily lives" with CSII therapy (39). A therapy that provides better disease management while allowing for greater normalcy in life is ideal for any chronic disease in pediatrics and CSII therapy clearly represents the best current approximation of this ideal to many families.

Price of Improved Care

In the DCCT, the cost of intensive care was assessed and it was determined that MDI therapy cost approximately \$4,000/year while CSII therapy cost \$5,800/year (61). This was in comparison to conventional therapy, which was estimated to cost \$1,700/year (61). Most of the cost in the intensive treatment group was associated with greater frequency of outpatient visits and resources used. The additional cost of CSII therapy was associated with cost of the pump and supplies required for the pump. However, in light of the decreased risk of complications associated with improved glycemic control the benefits of intensive therapy would be expected to have an effect on later health care costs associated with treatment for complications. In a retrospective analysis of annual retinopathy screening in our practice, none of the patients who met ADA screening guidelines for retinopathy screening was found to have retinopathy (62). Therefore, with more stringent control provided by intensive therapy the guidelines for routine screening of complications may

need to be revised and costs for both treatment of complications and screening of complications may be reduced.

Reimbursement for the preventative services provided to youth with T1DM only covers a fraction of costs associated with multidisciplinary team management of this disease (63). At our center, advanced nurse practitioners are key members of the team who interact most frequently with the patients and parents (64). However, lack of reimbursement for non-physician members of the treatment team has led to financial problems (63). Therefore, while pump therapy may remain more expensive and intensive therapy requires more involvement of the multidisciplinary team the risk of complication development would pose a much greater burden on health care costs.

Practical Considerations of Pump Therapy

Based on the findings of randomized and non-randomized studies it is safe to conclude that CSII is an effective method for treatment of patients with type 1 diabetes regardless of age. This sentiment has been echoed in a position statement by the Lawson-Wilkins Drug and Therapeutics Committee and the recommendations of a recent Consensus Conference that examined the evidence supporting use of pumps in pediatrics (65,66). CSII was deemed to be the most physiologic method of insulin delivery currently available. It was also noted that CSII offers the possibility of more flexibility and more precise insulin delivery than MDI. (66). Guidance as to when CSII therapy should be considered was also provided in the consensus statement (Table 3). Moreover, the Consensus Conference indications for using pumps in pediatrics cover virtually any child or adolescent with T1DM. However, it is just as important that treatment teams select appropriate candidates for this therapy.

In order to be considered for CSII in our clinic, patients must be performing at least four blood glucose measurements per day, consistently attend follow-up visits, be committed to the goals of intensive insulin therapy, have a solid understanding of basic diabetes management (including carbohydrate counting), and be in at least fair control (i.e. HbA1c $\leq 8.5\%$) as an index of compliance with current injection therapy. Once a patient is deemed appropriate for CSII therapy, selection of a pump is necessary. Table 4 reviews various pumps currently available for use and some of the features of these pumps. All of these pumps are considered “smart” and calculate the dose of insulin required for carbohydrate coverage or correction dose of insulin. The selection of a pump is a based on features desired by the patient/family along with guidance from the multidisciplinary team.

Families are encouraged to review educational materials, DVDs, and computer programs that are shipped with the pumps. Following this an outpatient visit lasting ~60-90 minutes is completed to start the pump. Dosages for pump initiation are based on the current total daily dose (TDD) of insulin that the patient is receiving. Approximately 50% of the TDD is given as basal insulin. This basal insulin is divided across the 24-hour period. For a patient receiving 40 units/day prior to pump therapy 20 units would be the total daily basal insulin dosage and this would be given as ~0.8 units/hr. Various methods are employed to determine correction factors and carbohydrate ratios. If someone is already using these as part of their injection therapy then these same factors can be carried forward. Alternatively, carbohydrate ratio can be calculated by dividing 500 by the total daily dose. Similarly, a correction factor can be derived by dividing 1800 by total daily dose. An even simpler approach that we often use is to determine the carbohydrate to insulin ratios and correction factors based on the patients' age (67).

Patients are advised to check their blood glucose before meals, bedtime, 12a.m., and 3a.m. and call the center as needed for dose adjustments. Following pump initiation, patients

return to routine follow-up being seen in clinic every 3 months with a dose adjustment and emergency line available as needed.

Closing Loop- Advances in Continuous Glucose Monitoring

Continuous glucose monitoring technology has the potential to revolutionize the treatment of T1DM. In comparison to SMBG, which gives the patient only brief “snapshots” as to where their blood glucose lies at the time of the test, continuous glucose sensors provide the opportunity to look at streaming “videos” of data on which changes in dosage can be made. Nevertheless, the ability of currently available devices to provide tangible benefits to patients and their families remains to be established.

In a study of metabolic control in 56 children and adolescents with T1DM that used the Minimed CGMS, almost 90% of patients had a peak postprandial glucose level of >180mg/dl after every meal despite HbA1c levels averaging 7.7% and 70% of patients had a period of asymptomatic hypoglycemia (defined as glucose <60mg/dL) (68). While the original CGMS system provided insights into management problems, the clinical utility of this retrospective, Holter-type system in youth with T1DM is limited.

The GlucoWatch Biographer was the first real-time continuous glucose monitor (RT-CGM) that was introduced but initial studies involving this device were very disappointing. In a large randomized clinical trial comparing the GlucoWatch versus standard SMBG, no change in HbA1c was noted in either group and patients use of the device declined rapidly due to skin irritation, excessive alarms, and inaccurate readings (69).

The current generation of RT-CGM devices being manufactured by DexCom, Medtronic and Abbott are more accurate and user friendly than the first generation of CGM systems (70-72) and early studies have suggested that they may be beneficial in the management of youth with T1DM (73-74). A large scale randomized clinical trial of all three of these systems is currently in progress and should provide a much more comprehensive assessment of their benefits and limitations.

With all the advances in pump technology and improvement in glycemic control, the next frontier for pump therapy will involve closing the loop and making the dream of an artificial pancreas a reality. Indeed, automated closed loop insulin delivery systems that combine external insulin pumps with current RT-CGM devices are already being studied. In a study of 10 patients using a completely automated insulin delivery system, the amount of time that BG was between 70-180mg/dL rose from 63% to 75% (75). However, elevation in postprandial blood glucose led to the hypothesis that a priming bolus of insulin prior to meals could aide in preventing these meal related glycemic excursions. This theory has subsequently been tested by comparing 8 patients on fully automated pumps versus 9 patients on a hybrid-closed loop system (pre-meal priming bolus with closed loop system) (76). Peak post-prandial glucose levels were significantly lower in patients on the hybrid system as compared to the fully automated system (76). With continued study and manipulation, it appears the artificial pancreas can become a viable treatment option for patients with T1DM in the foreseeable future.

Conclusion

CSII therapy has revolutionized diabetes care. With the findings of the DCCT, the importance of stringent glycemic control was identified. Since that time randomized and non-randomized studies have shown the efficacy of CSII across all age groups. Continuous glucose sensors are now changing the way that CSII therapy can improve control by decreasing glycemic excursions and manipulate insulin delivery to avoid otherwise

asymptomatic hypoglycemia detected by these sensors. The endeavor of developing an artificial pancreas is transitioning from dream to reality as newer studies have demonstrated its use and effectiveness in small cohorts.

Acknowledgments

Supported by grants from Stephen J. Morse Pediatric Diabetes Research Fund, the Juvenile Diabetes Research Foundation, and the National Institute of Health (T32 DK063703).

References

1. Tamborlane WV, Sherwin RS, Genel M, Felig P. Reduction to normal of plasma glucose in juvenile diabetics by subcutaneous administration of insulin with a portable infusion pump. *N Engl J Med.* 1979; 300:573–578. [PubMed: 763270]
2. Pickup JC, Keen H, Parsons JA, Alberti KG. Continuous subcutaneous insulin infusion: an approach to achieving normoglycemia. *Br Med J.* 1978; 1:204–207. [PubMed: 340000]
3. Home PD, Pickup JC, Keen H, Alberti KG, Parsons JA, Binder C. Continuous Subcutaneous Insulin Infusion: Comparison of Plasma Insulin Profiles After Infusion or Bolus Injection of the Mealtime Dose. *Metabolism.* 1981; 30:439–442. [PubMed: 6112654]
4. Lauritzen T, Pramming S, Deckert T, Binder C. Pharmacokinetics of Continuous Subcutaneous Insulin Infusion. *Diabetologia.* 1983; 24:326–329. [PubMed: 6347780]
5. Amiel SA, Tamborlane WV, Sherwin RS. Defective glucose counterregulation after strict glycemic control of insulin dependent diabetes mellitus. *N Engl J Med.* 1987; 316:1376–1383. [PubMed: 3553949]
6. Amiel SA, Sherwin RS, Simonson DC, Tamborlane WV. Effect of intensive insulin therapy on glycemic thresholds for counterregulatory hormone release. *Diabetes.* 1988; 37:901–907. [PubMed: 3290007]
7. Cryer PE. Iatrogenic hypoglycemia as a cause of hypoglycemia-associated autonomic failure in IDDM: a vicious cycle. *Diabetes.* 1992; 41:255–260. [PubMed: 1551485]
8. The DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. The Diabetes Control and Complications Trial. *N Engl J Med.* 1993; 329:977–986. [PubMed: 8366922]
9. The DCCT Research Group. The effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: the Diabetes Control and Complications Trial. *J Pediatr.* 1994; 125:177–188. [PubMed: 8040759]
10. DCCT/EDIC Research Group. Beneficial effects of intensive therapy of diabetes during adolescence outcomes after the conclusion of the Diabetes Control and Complications Trial. *J Pediatr.* 2001; 139:804–812. [PubMed: 11743505]
11. Boland EA, Grey M, Oesterle A, Fredrickson L, Tamborlane WV. Continuous subcutaneous insulin infusion: a new way to achieve strict metabolic control, decrease severe hypoglycemia and enhance coping in adolescents with type 1 diabetes. *Diabetes Care.* 1999; 22:1779–1784. [PubMed: 10546007]
12. Ahern JA, Boland EA, Doane R, Ahern JJ, Rose P, Vincent M, et al. Insulin pump therapy in pediatrics: a therapeutic alternative to safely lower HbA1c levels across all age groups. *Pediatric Diabetes.* 2002; 3:10–15. [PubMed: 15016169]
13. 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. [PubMed: 11158469]
14. 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.* 2003; 16:393–399.
15. 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. [PubMed: 12663587]

16. Willi SM, Planton J, Egede L, Schwarz S. Benefits of continuous subcutaneous insulin infusion in children with type 1 diabetes mellitus. *J Pediatr.* 2003; 143:796–801. [PubMed: 14657831]
17. Alemzadeh R, Ellis JN, Holzum MK, Parton EA, Wyatt DT. Beneficial Effects of Continuous Subcutaneous Insulin Infusion and Flexible Multiple Daily Insulin Regimen Using Insulin Glargine in Type 1 Diabetes. *J Pediatr.* 2004; 114:e91–e95.
18. Weinzimer SA, Ahern JA, 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. *J Pediatr.* 2004; 114:1601–1604.
19. Mack-Fogg JE, Orlowski CC, Jospe N. Continuous subcutaneous insulin infusion in toddlers and children with type 1 diabetes mellitus is safe and effective. *Pediatric Diabetes.* 2005; 6:17–21. [PubMed: 15787897]
20. 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; 21:347–352. [PubMed: 15619291]
21. Jaha 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 Decrease Glucose Excursions and the Risk of Hypoglycemia. *Diabetes Technology & Therapeutics.* 2005; 7:876–884. [PubMed: 16386093]
22. 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. *J Pediatr.* 2006; 117:2126–2131.
23. Berhe T, Postellon D, Wilson B, Stone R. Feasibility and Safety of Insulin Pump Therapy in Children Aged 2 to 7 years with Type 1 Diabetes: A Retrospective Study. *J Pediatr.* 2006; 117:2132–2137.
24. Sulli N, Shashaj B. Long-term benefits of continuous subcutaneous insulin infusion in children with type 1 diabetes: a 4-year follow-up. *Diabet Med.* 2006; 23:900–906. [PubMed: 16911629]
25. Scrimgeour L, Cobry E, McFann K, Burdick P, Weimer C, Slover R, Chase HP. Improved Glycemic Control After Long-Term Insulin Pump Use in Pediatric Patients with Type 1 Diabetes. *Diabetes Technology & Therapeutics.* 2007; 9:421–428. [PubMed: 17931050]
26. Weissberg-Benchell J, Antisdel-Lomaglio J, Seshadri R. Insulin Pump Therapy: A meta-analysis. *Diabetes Care.* 2003; 26:1079–1087. [PubMed: 12663577]
27. Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Di Vincenzo A, Cordoni C, Costa E, Brunetti P, Bolli G. Pharmacokinetics and Pharmacodynamics of Subcutaneous Injection of Long-Acting Human Insulin Analog Glargine, NPH Insulin, and Ultralente Human Insulin, and Continuous Subcutaneous Infusion of Insulin Lispro. *Diabetes.* 2000; 49:2142–2148. [PubMed: 11118018]
28. Hanas R, Adolfsson P. Insulin pumps in pediatric routine care improve long-term metabolic control without increasing the risk of hypoglycemia. *Pediatric Diabetes.* 2006; 7:25–31. [PubMed: 16489971]
29. De Beufort CE, Houtzagers CM, Bruinino GJ, Aarsen R, den Boer NC, Grose WF, van Strik R, de Visser JJ. 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. [PubMed: 2533034]
30. Ramachandani N, Ten S, Anhalt H, Sinha S, Ching J, Finkelstein A, Maclaren N. Insulin Pump Therapy from the Time of Diagnosis of Type 1 Diabetes. *Diabetes Technology & Therapeutics.* 2006; 8:663–670. [PubMed: 17109598]
31. Springer D, Dziura J, Tamborlane WV, Steffen AT, Ahern JH, Vincent M, Weinzimer SA. Optimal Control of Type 1 Diabetes Mellitus in Youth Receiving Intensive Treatment. *J Pediatr.* 2006; 149:227–232. [PubMed: 16887440]
32. DeVries J, Snoek F, Kostense P, Masurel N. A Randomized Trial of Continuous Subcutaneous Insulin Infusion and Intensive Injection Therapy in Type 1 Diabetes for Patients with Long-Standing Poor Glycemic Control. *Diabetes Care.* 2002; 25:2074–2080. [PubMed: 12401759]
33. 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. [PubMed: 12949284]
34. Hoogma R, Hammon P, Gomist R, Kerr D, Bruttomessos D, Bouter K, Wiefels K, de la Calle H, Schweitzer D, Pfohl M, Torlone E, Krinkel L, Bolli G, 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; 23:141–147. [PubMed: 16433711]
 35. DiMeglio L, Pottorff T, Boyd S, France L, Fineberg N, Eugster E. A Randomized, Controlled Study of Insulin Pump Therapy in Diabetic Preschoolers. *J Pediatr*. 2004; 145:380–384. [PubMed: 15343195]
 36. Wilson D, Buckingham B, Kunzelman E, Sullivan M, Paguntalan H, Gitelman S. A Two-Center Randomized Controlled Feasibility Trial of Insulin Pump Therapy in Young Children with Diabetes. *Diabetes Care*. 2005; 28:15–19. [PubMed: 15616227]
 37. Fox L, Buckloh L, Smith S, Wysocki T, Mauras N. A Randomized Controlled Trial of Insulin Pump Therapy in Young Children With Type 1 Diabetes. *Diabetes Care*. 2005; 28:1277–1281. [PubMed: 15920039]
 38. Opipari-Arrigan L, Fredericks EM, Burkhart N, Dale L, Hodge M, Foster C. Continuous subcutaneous insulin infusion benefits quality of life in preschool-age children with type 1 diabetes mellitus. *Pediatric Diabetes*. 2007; 8:377–383. [PubMed: 18036064]
 39. Sullivan-Bolyai S, Knafl K, Tamborlane W, Grey M. Parents' Reflections on Managing Their Children's Diabetes With Insulin Pumps. *Journal of Nursing Scholarship*. 2004; 36:316–323. [PubMed: 15636411]
 40. Pickup J, Matock M, Kerry S. Glycemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomized controlled trials. *BMJ*. 2002; 324:1–6. [PubMed: 11777781]
 41. Doyle E, Weinzimer S, Steffen A, Ahern J, Vincent M, Tamborlane W. 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. [PubMed: 15220227]
 42. Schiaffini R, Patera P, Bizzarri C, Ciampalini P, Cappa M. Basal Insulin supplementation in Type 1 diabetic children: a long term comparative observational study between continuous subcutaneous insulin infusion and glargine insulin. *J Endocrinol Invest*. 2007; 30:572–577. [PubMed: 17848840]
 43. Chase HP, Dixon B, Pearson J, Fiallo-Scharer R, Walravens P, Klingensmith G, Rewers M, Garg S. Reduced Hypoglycemic Episodes and Improved Glycemic Control in Children with Type 1 Diabetes Using Insulin Glargine and Neutral Protamine Hagedorn Insulin. *J Pediatr*. 2003; 143:737–740. [PubMed: 14657818]
 44. Kaplan W, Rodriguez L, Smith O, Haymond M, Heptulla R. Effects of Mixing Glargine and Short-Acting Insulin Analogs on Glucose Control. *Diabetes Care*. 2004; 27:2739–2740. [PubMed: 15505016]
 45. Tamborlane W, Sherwin R, Genel M, Felig P. Outpatient Treatment of Juvenile-Onset Diabetes with a Preprogrammed Portable Subcutaneous Insulin Infusion System. *The American Journal of Medicine*. 1980; 68:190–196. [PubMed: 6986766]
 46. Pickup J, Keen H, Viberti G, Bious R. Patient reactions to long-term outpatient treatment with continuous subcutaneous insulin infusion. *Br Med J*. 1981; 282:766–768. [PubMed: 6783163]
 47. Renner R, Pflutzner A, Trautmann M, Harzer O, Sauter K, Landgraf R, on behalf of the German Humalog CSII Study Group. Use of Insulin Lispro in Continuous Subcutaneous Insulin Infusion Treatment. *Diabetes Care*. 1999; 22:784–788. [PubMed: 10332682]
 48. Weinzimer S, Ternand C, Howard C, Chang C, Becker D, Laffel L, for the Insulin Aspart Pediatric Pump Study Group. A Randomized Trial Comparing Continuous Subcutaneous Insulin Infusion of Insulin Aspart versus Insulin Lispro in Children and Adolescents with Type 1 Diabetes. *Diabetes Care*. 2008; 31:210–215. [PubMed: 17989308]
 49. Swan K, Weinzimer S, Dziura J, Steil G, Voskanyan G, Steffen A, Martin M, Tamborlane W. Effect of Puberty on the Pharmacodynamic and Pharmacokinetic Properties of Insulin Pump Therapy in Youth with Type 1 Diabetes. *Diabetes Care*. 2008; 31:44–46. [PubMed: 17909083]

50. Catargi B, Breilh D, Gin H, Rigalleau V, Saux M, Roger P, Tabarin A. A Randomized Study Comparing Blood Glucose Control and Risk of Severe Hypoglycemia achieved by non-programmable versus programmable external insulin pumps. *Diabetes Metab.* 2001; 27:323–327. [PubMed: 11431597]
51. Pankoska 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 Technology & Therapeutics.* 2005; 7:308–314. [PubMed: 15857233]
52. Burdick J, Chase H, Slover R, Knievel K, Scrimgeour L, Maniatis A, Klingensmith G. Missed Insulin Meal Boluses and Elevated Hemoglobin A1c Levels in Children Receiving Insulin Pump Therapy. *Pediatrics.* 2004; 113:e221–e224. [PubMed: 14993580]
53. Chase H, Horner B, McFann K, Yetzer H, Gaston J, Banion C, Fiallo-Scharer R, Slover R, Klingensmith G. The Use of Insulin Pumps with Meal Bolus Alarms in Children with Type 1 Diabetes to Improve Glycemic Control. *Diabetes Care.* 2006; 29:1012–1015. [PubMed: 16644630]
54. The Diabetes Research in Children Network Study Group. Impact of exercise on overnight glycemic control in children with type 1 diabetes. *J Pediatr.* 2005; 147:528–534. [PubMed: 16227041]
55. The Diabetes Research in Children Network Study Group. The Effects of Aerobic Exercise on Glucose and Counterregulatory Hormone Concentrations in Children with Type 1 Diabetes. *Diabetes Care.* 2006; 29:20–25. [PubMed: 16373890]
56. The Diabetes Research in Children Network Study Group. Prevention of Hypoglycemia During Exercise in Children with Type 1 Diabetes by Suspending Basal Insulin. *Diabetes Care.* 2006; 29:2200–2204. [PubMed: 17003293]
57. Tamborlane W. Triple Jeopardy: Nocturnal Hypoglycemia after Exercise in the Young with Diabetes. *JCEM.* 2007; 92:815–816. [PubMed: 17341578]
58. Weissberg-Benchell J, Goodman S, Antisdel Lomaglio J, Zebracki K. The Use of Continuous Subcutaneous Insulin Infusion (CSII): Parental and Professional Perceptions of Self-Care Mastery and Autonomy in Children and Adolescents. *Journal of Pediatric Psychology.* 2007; 32:1196–1202. [PubMed: 17599966]
59. Nicoucci A, Maione A, Franciosis M, Amoretti R, Busetto E, Capani F, Bruttomesso D, Di Bartolo P, Girelli A, Leonetti F, Morviducci L, Ponzi P, Vitacolonna E. Quality of life and treatment satisfaction in adults with Type 1 diabetes: a comparison between continuous subcutaneous insulin infusion and multiple daily injections. *Diabet Med.* 2008; 25:213–220. [PubMed: 18201210]
60. Patton S, Dolan L, Henry R, Powers S. Parental fear of hypoglycemia: young children treated with continuous subcutaneous insulin infusion. *Pediatric Diabetes.* 2007; 8:362–368. [PubMed: 18036061]
61. DCCT Research Group. Resource Utilization and Costs of Care in the Diabetes Control and Complications Trial. *Diabetes Care.* 1995; 18:1468–1478. [PubMed: 8722072]
62. Huo B, Steffen A, Swan K, Sikes K, Weinzimer S, Tamborlane W. Clinical Outcomes and Cost-Effectiveness of Retinopathy Screening in Youth With Type 1 Diabetes. *Diabetes Care.* 2007; 30:362–363. [PubMed: 17259509]
63. Melzer S, Richards G, Covington M. Reimbursement and costs of Pediatric ambulatory diabetes care by using the resource-based relative value scale: is multidisciplinary care financially viable? *Pediatric Diabetes.* 2004; 5:133–142. [PubMed: 15450008]
64. Ahern J, Ramchandani N, Cooper J, Himmel A, Silver D, Tamborlane W. Using a Primary Nurse Manager to Implement DCCT Recommendations in a Large Pediatric Program. *The Diabetes Educator.* 2000; 26:990–994. [PubMed: 11912811]
65. Eugster E, Francis G, the Lawson-Wilkins Drug and Therapeutics Committee. Position Statement: Continuous Subcutaneous Insulin Infusion in Very Young Children with Type 1 Diabetes. *Pediatrics.* 2006; 118:e1244–e1249. [PubMed: 17015512]
66. Phillip M, Battelino T, Rodriguez H, Danne T, Kaufman F. Use of Insulin Pump Therapy in the Pediatric Age-Group: Consensus statement from the European Society for Paediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes, endorsed by the American Diabetes Association and the

- European Association for the Study of Diabetes. Diabetes Care. 2007; 30:1653–1662. [PubMed: 17372151]
67. Tamborlane W, Fredrickson L, Ahern J. Insulin Pump Therapy in Childhood Diabetes Mellitus. Guidelines for Use. Treat Endocrinol. 2003; 2:11–21. [PubMed: 15871551]
68. Boland E, Monsod T, Delucia M, Brandt C, Fernando S, Tamborlane W. Limitations of Conventional Methods of Self-Monitoring of Blood Glucose: Lessons learned from 3 days of continuous glucose sensing in pediatric patients with type 1 diabetes. Diabetes Care. 2001; 24:1858–1862. [PubMed: 11679447]
69. The Diabetes Research in Children Network Study Group. A Randomized Multicenter Trial Comparing the GlucoWatch Biographer with Standard Glucose Monitoring in Children with Type 1 Diabetes. Diabetes Care. 2005; 28:1101–1106. [PubMed: 15855573]
70. Sachedina N, Pickup J. Performance assessment of the Medtronic-Minimed Continuous Glucose Monitoring System and its use for measurement of glycaemic control in Type 1 diabetic subjects. Diabet Med. 2003; 20:1012–1015. [PubMed: 14632702]
71. The Diabetes Research in Children Network Study Group. Accuracy of the Modified Continuous Glucose Monitoring System Sensor in an Outpatient Setting: Results from a Diabetes Research in Children Network (DirecNet) Study. Diabetes Technol Ther. 2005; 7:109–114. [PubMed: 15738708]
72. Wilson D, Beck R, Tamborlane W, Dontchev M, Kollman C, Chase P, Fox L, Ruedy K, Tsalikian E, Weinzimer S, the DirecNet Study Group. The Accuracy of the Freestyle Navigator Continuous Glucose Monitoring System in Children with Type 1 Diabetes. Diabetes Care. 2007; 30:59–64. [PubMed: 17192334]
73. Ludvigsson J, Hanas R. Continuous Subcutaneous Glucose Monitoring Improved Metabolic Control in Pediatric Patients with Type 1 Diabetes: A Controlled Crossover Study. Pediatrics. 2003; 111:933–938. [PubMed: 12728068]
74. The Diabetes Research in Children Network Study Group. Continuous Glucose Monitoring in Children with Type 1 Diabetes. J Pediatr. 2007; 151:388–393. [PubMed: 17889075]
75. Panteleon A, Loutseiko M, Steil G, Rebrin K. Evaluation of the Effect of Gain on Meal Response of an Automated Closed-Loop Insulin Delivery System. Diabetes. 2006; 55:1995–2000. [PubMed: 16804068]
76. Weinzimer S, Steil G, Swan K, Dziura J, Kurtz N, Tamborlane W. Fully Automated Closed Loop Insulin Delivery vs Semi-Automated Hybrid Control in Pediatric Patients with Type 1 Diabetes using an Artificial Pancreas. Diabetes Care. 2008 in press.

Table 1
Results of switching from injection to CSII therapy in non-randomized pediatric studies

Author (reference)	N	Age (years)	Δ in Hemoglobin A1c from baseline %(p)	Hypoglycemia	BMI
Ahern (12)	161	1-18	0.6-0.7 (<0.02)	Reduced	No change
Maniatis (13)	56	7-23	0.2 (.045)	Reduced	No change
Sulli (14)	40	4-25	0.7 (<0.05)	Reduced	No change
Plotnick (15)	95	4-18	0.4 (<0.001)	Reduced	No change
Willi (16)	51	1-16	0.45 (<0.01)	Reduced	No change
Alemzadeh (17)	40	10-18	0.6 (<0.002)	Reduced	Increased
Weinzimer (18)	65	1-6	0.6 (0.003)	Reduced	Slight decrease
Mack-Fogg (19)	70	2-12	0.5 (<0.0001)	Reduced	Slight increase
Schiaffini (20)	20	6-18	0.9 (<0.05)	No change	No change
Jeha (21)	10	1-6	0.9 (0.01)	Reduced	No change
Nimri (22)	279	1-40	0.51 (<0.01)	Reduced	No change
Behre (23)	33	2-7	0.7 (<0.001)	Reduced	No change
Sulli (24)	42	4-17	0.7 (0.00)	Reduced	Reduced
Scrimgeour (25)	291	Mean age 13.3	0.4 (<0.0001)	Reduced	No change

Table 2
Results of Randomized clinical trials comparing CSII and MDI in patients with type 1 DM

Author (reference)	N	Age (years)	A1c% (CSII vs. MDI)
De Vries (32)	79	18-70	8.4 vs. 9.2*
Weintrob (33)	23	9-14	8.0 vs. 7.9
Hoogma (34)	279	18-65	7.4 vs. 7.7*
DiMeglio (35)	42	<5	8.5 vs. 8.7
Wilson (36)	19	1-7	7.8 vs. 8.1
Fox (37)	26	1-6	7.2 vs. 7.5
Opipari-Arrigan (38)	16	3-6	8.4 vs. 8.2
Doyle (41)	32	8-21	7.2 vs. 8.1*
Schiaffini (42)	36	9-18	7.6 vs. 8.2*

*
p <0.05

Table 3
Indications for use of CSII in Pediatrics (adapted from Reference 66)

Conditions under which CSII should be considered	
1	Recurrent severe hypoglycemia
2	Wide fluctuations in blood glucose levels regardless of A1c
3	Suboptimal diabetes control (i.e., A1c exceeds target range for age)
4	Microvascular complications and/or risk factors for macrovascular complications.
5	Good metabolic control but insulin regimen that compromises lifestyle.
Circumstances in which CSII may be beneficial	
1	Young children and especially infants and neonates
2	Adolescents with eating disorders
3	Children and adolescents with a pronounced dawn phenomenon
4	Children with needle phobia
5	Pregnant adolescents, ideally preconception
6	Ketosis-prone individuals
7	Competitive athletes

Table 4
Pump Options and Features

Pump	Insulin Reservoir Capacity, (Units)	Minimal Basal Rate Increments, (U/hr)	Minimal Bolus Dose Increments, (Units)	Other features
Animas IR-2020	200	0.025	0.05	<ul style="list-style-type: none"> • Smallest pump • Largest Display Screen • 500 food individualized database
Deltec Cozmo	300	0.05	0.05	<ul style="list-style-type: none"> • Integrated Freestyle meter • Enhanced meal maker[®] • Basal rates by day of week • Replacement of basal rate after disconnecting pump
Disetronic Spirit	315	0.1	0.1	<ul style="list-style-type: none"> • Reversible Display • Menu Display Customization Option
Medtronic Paradigm 522/722	180 or 300	0.05	0.1	<ul style="list-style-type: none"> • Only available pump with real-time CGMS on market • Optional remote control for bolus dosing • CareLink Personal Therapy Management Tool
Insulet Omnipod	200	0.05	0.05	<ul style="list-style-type: none"> • No tubing • 1000 common foods in PDA • Freestyle Meter in PDA component

Table 5
Correction Factors and Carbohydrate Ratio Based on Age for Initial Pump Settings

Age (years)	Correction Factor (mg/dL)	Carbohydrate Ratio (grams)*
<3	225	45
4-5	200	40
5-7	150	30
8-11	125	20
Prepubertal and/or <13	75	15
Pubertal and/or >13	50	10

* Often a lower carbohydrate ratio is needed for breakfast (-2 grams for breakfast carb ratio). For example for children <3, start breakfast carbohydrate ratio at 43 grams.