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ISPAD Clinical Practice Consensus Guidelines 2024: Diabetes Technologies: Insulin Delivery

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Abstract

The ISPAD guidelines represent a rich repository that serves as the only comprehensive set of clinical recommendations for children, adolescents, and young adults living with diabetes worldwide. This chapter builds on the 2022 ISPAD guidelines, and summarizes recent advances in the technology behind insulin administration,

with special emphasis on insulin pump therapy, especially on glucose-responsive integrated technology that is feasible with the use of automated insulin delivery (AID) systems in children and adolescents.

A SUMMARY OF WHAT IS NEW OR DIFFERENT?

This chapter focuses on insulin pump therapy, with a greater emphasis on glucose-responsive integrated technology that is feasible with the use of automated insulin delivery (AID) systems. The chapter also includes connected insulin pens and insulin pump therapy without AID functionality. As behavioral, psychosocial, and educational considerations of insulin delivery devices are a central part of diabetes self-management and use of insulin delivery devices, these topics are also addressed.

Updates and Changes to previous recommendations include:

1. Additional details on AID incorporating data from clinical trials complemented by real-world evidence.
2. Additional focus and details that delineate potential benefits of these systems with new data for youth of all ages, from preschoolers to young adults
3. New data regarding insulin pump therapy that does not involve AID (non-AID)
4. An emphasis on approaches to optimize outcomes for all forms of insulin delivery devices, including insulin pump therapy as well as behavioral, psychosocial, and educational considerations for optimizing the daily use of these devices.
5. A summary of the growing evidence of the technology benefits beyond glycemic outcomes including person-reported outcomes and experience measures and impacts on the quality of life of youth and their caregivers.

1. Introduction

- It is recommended that youth be offered the most advanced insulin delivery technology that is available, accessible and acceptable for them. **[A]**
- System choice should be based on individual needs and preferences. **[A]**

In 2018, ISPAD created the first consensus guidelines on Diabetes Technology.[1] In 2022, this guideline was divided into two intertwined chapters that continue for this update. Information on Insulin Delivery is covered in the current chapter, and Glucose Monitoring with a discussion of both blood glucose monitoring (BGM) and continuous glucose monitoring (CGM) presented in ISPAD 2024 Consensus Guidelines Chapter on Diabetes technologies: glucose monitoring[2]. This chapter reviews insulin delivery technologies in children, adolescents, and young adults with a focus on practical advice and clinical implementation.

Insulin pump use continues to increase in many diabetes practices. Despite this, disparities persist between the historically most advantaged and disadvantaged groups, even in locales where the technology is widely available.[3] Inconsistencies in the availability, cost reimbursement and/or insurance coverage for diabetes technologies contribute to disparities regionally, nationally, and across health systems that are challenging for individuals with low economic status, lower educational attainment, and in lower resource settings[4]. Recognition of these disparities becomes even more important as the systems become more autonomous. Eligibility criteria for treatment based on glycated hemoglobin (HbA1c) value, ability to count carbohydrates, and or other self-management factors might exclude users that would benefit most, as people with higher baseline HbA1c experience greater glycemic improvements [5].

While diabetes care has traditionally centered on achieving consensus guideline targets for HbA1c, there has been greater adoption of time in range (TIR) and other glucose metrics as CGM-derived or "technology-derived" metrics to guide clinical decision-making and define treatment goals[6] [7]. This greater emphasis on diabetes technologies has driven important research evaluating how the potential burdens of diabetes technologies can be mitigated by the benefits they may provide, how to set realistic expectations for new device-based therapies to

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ensure transitions to advanced technologies are associated with shared decision making alongside appropriate device training.
Aligning with WHO's availability, accessibility, acceptability, and quality (AAAQ) "right to health" framework, this guideline mirrors that belief in recommendations regarding insulin delivery technologies.". As all technology, of course, should be tested properly before being used in children, a "Q" for quality is a necessity [8]

2. Insulin pumps

Recommendations

- Insulin pump therapy is recommended and appropriate for youth with diabetes, regardless of age. [A], baseline glycemia **[A]** and T1D duration. **[B]**
- Infusion set failures may occur with any insulin pump therapy and must be recognized promptly to avoid diabetic ketoacidosis (DKA). **[B]**

Insulin pump therapy as a platform for insulin delivery provides the basis for more advanced glucose-responsive insulin delivery technologies. While there is a clear benefit to using more advanced technologies, it is also recognized that these systems are currently not available or affordable for all people living with diabetes or do not fit their personal preferences.

The Evidence for Insulin Pump Therapy

Diabetes registry data have demonstrated increased uptake of pump therapy over time in youth with type 1 diabetes (T1D) in the US[9] and Germany[10]. During the periods evaluated, HbA1c trended down in all age groups, except preschoolers (0.5-<7 years old), while TIR increased by ~5 percentage points in all age groups.[11] Additional comparisons of large diabetes registries with nearly 55,000 pediatric people with diabetes (PWD) reported pump use was associated with lower mean HbA1c (pump 8.0±1.2% (64±14 mmol/mol) vs injection: 8.5 ± 1.7% (69±17 mmol/mol), p <0.001).[12] Similar data from an international network of reference centers reported that pump use was associated with lower HbA1c and daily insulin dose compared to MDI.[13] One prospective examination of nearly 1000 youth on either pump or MDI therapy found lower retinopathy and peripheral nerve abnormality rates in the insulin pump-treated group despite similar HbA1c values.[14] Meta-analyses have shown reductions in mean HbA1c [15-17], decreased severe hypoglycemia (SH) rates[17], and a reduction of total daily insulin doses with insulin pump therapy.[15, 16] The long-term benefits of pump therapy have been demonstrated with sustained improvement in glycemia. [18-20] Further data have also shown pump therapy is associated with lower rates of SH and DKA than MDI. [20-23]

Baseline glycemia should not preclude insulin pump therapy as those with the highest HbA1c levels (>9.0%) experience the largest decline in HbA1c once pump therapy is initiated.[24] Furthermore, no minimum T1D duration is required before transitioning to this mode of insulin delivery, as insulin pump therapy, even from the time of diagnosis, is successful in achieving glycemic targets [25-28]. While availability, costs, and reimbursement or insurance coverage for insulin pumps impact the use of this technology [12, 29], a recent cost-effectiveness analysis performed using IQVIA CORE Diabetes model in China found that pump therapy use equated to lower total lifetime costs when compared to MDI, related to expected delays in the development of diabetes complications[30].

Insulin Pump Therapy: Barriers to Adoption of and Reasons for discontinuation

Wide variations in the mode of insulin delivery prescribed exist amongst clinical centers, even those with similar populations. [29] Indeed, US data highlight variability in the frequency of pump adoption related to race and ethnicity (e.g. non-Hispanic White individuals) and socioeconomic status (private or public health insurance). [31] The DPV registry also observed an association with sex and migration background in Germany. [32]Variability in pump use between centers may be in part explained by healthcare professional (HCP) preferences, which impact the proportion of people using pumps in a given center.[33-39] In some countries, non-coverage, or incomplete coverage of pump therapy by the health care/insurance system also drives low insulin pump adoption .[12, 29]

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Besides HCP preferences, barriers to technology among PWDs also impact individual use of technology. Potential barriers to pump use identified include concerns regarding the device's physical footprint of the device on the body, interference of the device in everyday activities, therapeutic effectiveness, and, to a lesser extent, the financial burdens it may cause.[40]

Pump therapy discontinuation is uncommon, with the DPV registry noting a low attrition of just 4% of pump users.[41] Adolescents aged 10-15 years had the highest rate of pump discontinuation, and those who discontinued were more likely to be female.[41] Similar results were noted in a US-based registry analysis, with reasons for discontinuation including problems with wearability (57%), personal dislike or feelings of anxiety towards the pump (44%), and difficulties with glycemic outcomes (30%).[42] Additionally, higher levels of depressive symptoms have also been reported to precede cessation of pump use. [43]

Early studies have documented a 2 to 5-fold higher risk of DKA among individuals using pump therapy. However, recent studies have shown an attenuation in this risk.[44, 45] Therefore, education on the risk of DKA and strategies to manage persistent hyperglycemia are crucial in preventing these complications. The future feasibility of using subcutaneous continuous ketone monitors offers a potential solution to enhance the management of ketone levels. [46]

Complications of Insulin Pump Therapy: Infusion sets, lipodystrophy, and skin irritation

Insulin pump-related adverse events are relatively common, affecting 40 to 68% of pump users. They include infusion set failures, pump malfunctions and problems with alarms.[47-51] There is no conclusive evidence regarding optimal choice between steel cannuals and flexible teflon catheters, as well as the suitability of specific infusion sets based on the user´s age or individual characteristics. As steel cannulas are less likely to kink or dislodge, they may be ideal for the youngest children. However, the major concern regardless of infusion set type is the potential for full or partial occlusion or dislodgement, thereby interrupting insulin delivery and increasing the risk of diabetic ketoacidosis (DKA). Strategies for identifying failed infusion sets include fault detection algorithms that utilize sensor glucose levels and insulin delivery data to predict potential failures have been described.[52, 53]

Lipohypertrophy, or local fat accumulation at the site of insulin administration, is another frequently encountered issue with pump therapy.[54] Lipoatrophy, fat loss at the site of prior insulin infusion sites, is less common and more observed in those with multiple autoimmune conditions.[55] Both conditions are categorized as lipodystrophy. A cross-sectional study of children and adolescents with T1D demonstrated a greater risk of lipodystrophy in those with higher concomitant circulating insulin autoantibody titers.[56] Lipodystrophy can impact how insulin is absorbed and thus lead to deterioration in glycemia. To avoid lipohypertrophy, it is recommended that infusion set placement be rotated with every new insertion. Once detected, the affected area should be avoided to allow the tissue to heal, which often takes several months. There are reports on the use of special insulin products being beneficial to lipoatrophy[57].

Finally, skin irritation is frequently observed after repeated exposure to adhesives from medical devices. A study involving comprehensive dermatological examinations, identified localized eczematous reactions at the site of infusion cannula insertion in 14% of young individuals with diabetes[58]. Additionally, a survey of 143 youth documented that nearly half of the cohort reported non-specific eczema.[59] For more information on skin related issues, please refer to ISPAD 2022 Consensus Guidelines Chapter 19 on “Other complications and associated conditions in children and adolescents with type 1 diabetes”[60].

Practical considerations with pump therapy:

As pump therapy is the basis for other advanced insulin delivery technologies, the benefits and issues mentioned above may also apply to the glucose-responsive technologies discussed in the next sections.

<u>Provider training</u>

Clinicians must be trained on devices to be competent and comfortable offering diabetes technology. However, a survey of pediatric endocrinology fellows in the United States and Canada revealed that only 14.7% had formal training on pump and CGM use[61]. In a subsequent study, pediatric endocrine fellows (n=64) in North America employed case-based vignettes with 20 multiple-choice questions on either CGM or pump therapy delivered via email or a mobile app.[62] Both curricula increased participants´ knowledge base from the pre- to post-test assessment and participants found this method of education engaging.[62] This suggests potential for providers

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to be trained on these technologies through user-driven online learning modules. Without keeping abreast of technological advances, clinicians may inadvertently hinder the adoption and optimal use of these devices.

Educational Resources

To help inform families of various insulin delivery modalities, simplified guides can be helpful to supplement in clinic conversations.

When preparing to transition from MDI to insulin pump therapy, one of the first steps is to have the PWD and their family, select the insulin pump model they would like to use, unless insurance coverage or regional availability dictates the decision. To accomplish this, charts and literature describing the differences among models are helpful. Pump selection should be based on features desired by the PWD and their family, with guidance provided by the clinical team members. Practical information and a framework for understanding AID may be found in this chapter's e-supplement.

Initiating pump therapy

In general, initial pump settings should be derived from an individual's total daily insulin dose. The eTable 1 in the online supplement provides some suggestions. Data from the DPV registry highlight differences in basal insulin programs noted by age groups. Youth under the age of 6 had higher basal insulin requirements from 6p.m.-12a.m., while adolescents (12-18years of age) and young adults (18-25 years of age) had higher basal insulin needs in the early morning hours (~3a.m.-8a.m.). [63]

Pumps have integrated bolus calculators allowing users to enter both the number of carbohydrates to be consumed and glucose values, thus allowing the pump to calculate the bolus insulin dose. Current bolus calculators consider not only the glucose reading but also the insulin on board, thereby preventing insulin stacking.

At the time of pump initiation it is critical to advise families about associated risks, particularly that of potential infusion set failure and consequent metabolic decompensation.[64] A useful framework for optimizing the transition is presented by Deiss et al. [65]

In certain circumstances, individual needs may dictate the specific insulin type to be used. For example in very young children or those with minimal insulin requirements, diluted insulin can be used to accurately deliver very small amounts of insulin, although not all systems are approved for use of diluted insulin.[66-69] Specific recommendations regarding the need to tailor insulin therapy are reviewed in the updated "Insulin and adjunctive treatment in children and adolescents with diabetes" chapter.

Various factors have been associated with successful pump therapy. These include having more pre-programmed basal rates[70] and a greater total number of boluses delivered daily (both correlate with lower HbA1c levels), with basal insulin delivery accounting for <50% of the total daily dose. It is critical to encourage people with diabetes and their families to be engaged with care.[71, 72] The importance of meal boluses/announcements should be highlighted at each follow up visit.

Advanced pump features

More advanced features of pump therapy include the ability to set temporary basal rates that adjust the usually-programmed basal rate for unique day-to-day variations in insulin sensitivity. This includes decreasing delivery before, during and after physical activity or increasing doses for situations like intercurrent illness [73]. Temporary basal rates, including complete suspension of basal insulin delivery can help mitigate hypoglycemia associated with exercise.[74] Similarly, different pre-programmed basal patterns can be utilized for predictable times of differing insulin sensitivity, such as during menstruation.

Insulin boluses can also be delivered in different manners to accommodate differences in food composition: 1) immediately, as a standard or normal bolus, 2) slowly over a specific period of time, an extended or square bolus or 3) a combination of the two, i.e., a combo or dual wave bolus.[73] Boluses for high-fat foods might be best handled as extended or combo boluses as the rise in blood glucose levels following the meal will be delayed by fat. For the extended bolus, the user sets the duration of the extension; whereas, for combo boluses the user not only chooses the duration to extend but also the amount to be delivered upfront (e.g., 40% of the bolus immediately and the remaining 60% over 4 hours). Pumps can also reduce bolus insulin delivery based on the proportion of insulin that is still "active" from the last bolus, which may decrease the likelihood of post-bolus hypoglycemia and SH.

Reviewing data to optimize management

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As insulin pump data can be uploaded or are available through cloud-enabled sharing, clinic visits can be more productive. For more information on care delivery, see ISPAD 2022 Consensus Guidelines Chapter 7 on "The delivery of ambulatory diabetes care to children and adolescents with diabetes"[75].

3. AID

- AID systems, also known as closed loop (CL), are strongly recommended for youth with diabetes **[A]** in order to improve time in range (TIR) by minimizing hypoglycemia and hyperglycemia **[A],** person-reported outcomes, and reduce burden of care **[A],** especially in the overnight period. **[A]**

AID systems, also referred to as closed loop or artificial pancreas systems, adjust insulin delivery in response to sensor glucose data. AID use is increasing in all age groups [11, 31]. Two recent meta-analyses compared AID to other treatment modalities and demonstrated benefits for HbA1c and all TIRs evaluated.[76, 77] Furthermore, the number and variety of available AID systems are increasing, giving many PWD options to choose a system aligned with personal preferences.

AID systems adjust insulin delivery in response to sensor glucose data. This differs from low glucose suspend (LGS) and predictive low glucose management (PLGM), which both only suspend insulin administration. AID systems consist of three components: 1) an insulin pump 2) a CGM sensor, and 3) an algorithm that determines insulin delivery (Figure 1). Many algorithms have been widely tested [78-80], and no single "optimal" algorithm has emerged. Comparisons among them [81-83] are difficult due different study and experimental designs.[81]

Besides control mechanisms, AID systems have other differentiating features. Early, fully AID studies (without meal announcements) demonstrated significant postprandial glycemic excursions and led to the use of a "hybrid" approach, meaning the user needs to manually bolus for carbohydrate intake[84]. With hybrid closed loop (HCL) systems insulin delivery is adjusted based on sensor glucose values. Therefore, the differentiation between "manual or user initiated" and "automated insulin delivery" may be more meaningful than the classic categorization of insulin delivery as being either basal or bolus.

System targets are set in one of two ways; a treat-to-target approach with a single target glucose [e.g. 5.8 mmol/L (105 mg/dL)] at a given time or at all times or treat-to-range approach [e.g. 6.2-8.9 mmol/L (112-160 mg/dL)].[80]

Depending on the individual system's label, there are additional requirements to be met by the user (e.g. minimal amount of insulin, age or weight).

Data from large clinical trials

Outpatient trials have been conducted using RCT [85-93] and single-arm trial designs.[94-100] RCTs have demonstrated that people using different AID systems can achieve ~10-15 percentage points increases in TIR (3.9 – 10 mmol/L, 70-180 mg/dL) when compared to conventional pump therapy, SAP, PLGS, and when upgrading to newer AID versions.[85, 86, 88-93, 101] Similar findings in change in TIR from baseline data collection periods have been noted in single-arm trials.[94, 95, 97-100, 102] Longer outpatient AID studies have also demonstrated concomitant reductions in HbA1c by 0.3-0.7%.[85, 88-91, 93-95, 97-102]

These findings hold across all age groups. AID benefits have been demonstrated in very young children aged 2-5 years, children aged 6-13 years, adolescents, and young adults.

RCT data from different trials of Tandem Control-IQ® (Tandem Diabetes Care, USA) were used to conduct a meta-analysis, which showed similar benefits including rapid improvement in glycemia after implementation of the system that was sustained over time (adjusted treatment group difference = 11.5 percentage points in TIR). [103]

Since the approval of the first AID systems, recognizing the safety these systems several affords and some of the initial barriers to use, including existing from automation, have been removed.

All youth with T1D can benefit from AID

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Real-world data from commercial closed-loop systems demonstrate the performance and acceptance of this technology outside of trial settings and are summarized in Figure 2 and eTable 2 in the online supplement.
A prospective observational multicenter study in the UK, using several different AID systems in youth aged 2-19 years, showed a reduction in HbA1c of 7.7 mmol/mol (0.6 %) after 3 months with a 15.8 percentage points increase in TIR. While benefits in TIR stabilized following AID initiation and remained present after another 3 months of system use, HbA1c decreased another 7 mmol/mol (0.6 %). [104]
Data from one pivotal trial demonstrated that, while all participants (aged 14-71 years) TIR improved, those with baseline HbA1c >8.5% had the greatest reduction in time above range. In contrast, those with HbA1c <6.5% also benefited from reductions in time below range. [105]. Real-world Tandem Control-IQ® system data from those aged >6 years demonstrated that those with a higher initial glucose management index (GMI), which estimates average HbA1c concentration based on mean sensor glucose values, showed substantial improvement over time. [5, 106] Similarly, real-world use analysis of Medtronic 670G® use in 14,899 PWD (no age demographics provided), demonstrated that for those with a GMI <7%, TIR improved slightly from 76.1% to 78.7%. On the other hand, for the group whose GMI was >8%, improvement of TIR was more substantial, from 34.7% to 58.1%.[107]
These data provide compelling evidence that all PWD can benefit from AID, and HCPs should not limit access to this therapy. HCPs should advocate for AID to be safely incorporated into the management plan of youth and young adults with diabetes. Further, they should provide education and support to help children and families use these devices consistently and as intended.

All currently available AID systems provide the ability to access data on insulin delivery and glucose metrics via software available through online portals, in some countries data transfer is feasible through cloud-enabled transfer from the user's mobile phone. Given the robust nature of this data collection, real-world evidence has surpassed what is feasible in clinical trials. Further, this data highlights that the initial findings in controlled trials are mirrored with real world use. [108, 109]. See eTable 2 and Figure 2.

Practical Considerations for AID

Systematic training of individuals with diabetes and their families/caregivers transitioning to AID therapy is essential.[110-112]

General aspects of education can be found below in section 7.

Frameworks have been developed to teach AID technology use to ensure success with its adoption. The "CARES" strategy (definition see eTable1) has been suggested to help HCP conceptualize the differences and similarities between AID systems.[113, 114] CARES can assist clinicians by summarizing each device's most clinically relevant concepts.

People with diabetes should be generally guided on methods to manage exercise. See ISPAD 2022 Consensus Guidelines Chapter 14 on Exercise in children and adolescents with diabetes[115].
However, carbohydrate intake to treat hypoglycemia may need to be reduced in the context of prolonged basal insulin suspension with integrated systems. A sick day and ketone management training is still important, as the way of insulin administration is the same as in former pump therapy.
Tools to assist PWD to compare devices alongside their clinicians are beneficial.
Practical information and a framework for understanding AID may be found in this chapter's e-supplement.

AID SYSTEMS IN NEWLY-DIAGNOSED CHILDREN

- AID systems are recommended for children newly-diagnosed with type 1 diabetes **[A]** to improve time in range and reduce time in hyperglycemia **[A]**

Two recent randomized controlled trials have evaluated the safety and efficacy of AID technology from the onset of T1D in children and adolescents [116, 117]. Over a follow-up period of up to four years, children and adolescents who used an AID system from diagnosis had more targeted glycemic metrics that sustained over time, with higher TIR and less TAR compared to those using standard insulin therapy. Between-group differences in glucose levels between those using AID and those receiving standard care started to appear six to nine months after diagnosis. [116, 118]. This was despite relatively high uptake of other diabetes technologies (insulin pumps and glucose sensors) in the control group, highlighting the important AID role in this population. Of note, neither study showed any beneficial effect of intensive insulin therapy with AID on beta-cell preservation, as measured by stimulated C-peptide secretion in young people recently diagnosed with T1D.

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AID systems were safe when used from diagnosis and throughout the "honeymoon period" in children and adolescents with T1D. These glucose-responsive systems can effectively manage the variability of exogenous insulin requirements during the period when there is declining residual endogenous insulin secretion and can achieve stable glycemic levels.

Recent data suggest that use of AID from the time of diagnosis may help mitigate the adverse glycemic effects of DKA at presentation [119, 120]. Participants in the CLOuD study (Closed Loop from Onset in Type 1 Diabetes*)* presenting with or without DKA who used an AID system from diagnosis had similar glycemic outcomes at 6-, 12- and 24-months.

Modelling data from the Epidemiology of Diabetes Interventions and Complications (EDIC) study cohort suggests beneficial effects of earlier versus later implementation of intensive therapy in T1D[121]. Earlier implementation was associated with a greater reduction in the risks of kidney and cardiovascular complications compared with later implementation, despite both groups having the same average glycemic exposure over the entire period, highlighting the importance of utilizing therapies that allow tight glycemic management from as early as possible after the diagnosis of T1D.

Preschool children

- AID systems are strongly recommended for preschool children with type 1 diabetes for improvement of glycemia. **[A]**

A variety of AID systems have been tested specifically in young children, with outcomes consistently indicating improved TIR and few episodes of SH or DKA. Specifically, the CamAPS FX® (CamDiab, UK) was tested in 74 children between 1-7 years old during a 16-week period and compared to a sensor-augmented pump. The study showed that in aggregate users of AID experienced a significant increase in TIR, reduction in TAR, and lowering of average glucose value without a significant increase in TBR. One case of SH was reported during AID use [122]. Using this algorithm, a 3-week outpatient RCT conducted in children aged 1-7 years did not demonstrate any benefit of diluted insulin when compared to a standard U100 rapid-acting analog.[123] Importantly, this study also highlighted that very young children have higher day-to-day variability in insulin requirements compared to other age cohorts.[124]

Omnipod 5® (Insulet, USA) was evaluated among 80 children between 2 and 6 years of age for 13 weeks. Its use was associated with a significant increase in TIR (10.9 percentage points) and a significant reduction in TBR (0.27 percentage points). No episodes of SH or DKA were reported [100] Longer term follow up of this same cohort demonstrated that glycemic improvements attained with use of the Omnipod 5 persisted for up to 2 years of after device initiation.

In a study of 46 children between 2-6 years old the MiniMed 670G® (Medtronic, USA) system improved TIR and TAR without a significant increase in TBR compared to the run period (Manual Mode). No SH, DKA or serious adverse events were reported [125]. A different randomized cross-over study compared a predictive low glucose system to the MiniMed 670G® system in 18 young children. TIR was increased from 67.5 % to 72.7% (p=0.018) [126]. Finally, an analysis found that off-label use of the MiniMed 780G® was safe in 35 children between 2-6 years old over a 12-week period. Using this AID led to an 8% increase in TIR (p<0.001) with no significant change in hypoglycemia [127].

A 13-week multicenter randomized trial was conducted in 102 children 2-6 years of age using the Tandem Control-IQ® system. TIR significantly increased from 56.7% to 69.3% in the closed loop arm (68 children), which was accompanied by a significant reduction in TAR (>250 mg/dl, >13.9mmol/L) and HbA1c without an increase in TBR. Two cases of SH and one DKA were reported in the closed loop arm. Benefits were observed over a wide range of demographic and baseline characteristics, including age, race/ethnicity, parental education, income, and baseline glycemia. [128]

A qualitative study in preschool children assessed parent's experience with remote monitoring for glycemic values. While remote monitoring of glucose data helped, parents noted that access to the insulin delivery data was even more helpful [129, 130].

Real World Studies

Although there is limited real-world evidence on the use of AID in very young children, data from clinical trials are supported by real-world evidence, eTable 2. A prospective real-world observational study of people who used

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Loop Open Source included 67 children < 7 years of age. This age group benefited from AID and had a significant increase in TIR (67% to 73%) over six months without a significant increase in TBR [131] .
Real-world use of the Omnipod 5® system has been reported in 376 children between 2-6 years of age. When focusing on those with a time-weighted average target of 110 mg/dL, 68.8% of the children met the AID consensus target of less than 4% TBR, and 57% met the target of > 70% TIR[132].
As a part of the National Health Service pilot initiative in England (1) Medtronic MiniMed 780G®, (2) Tandem t:slim X2® insulin pump with Control-IQ® with the Dexcom G6® CGM (Dexcom, USA) sensor; and (3) CamAPS FX® were studied. The participants were between 1 and 19 years of age. Overall, AID use led to an improvement in glycemic outcomes. Data from young children with type 1 diabetes are shown separately [104].

School-aged children

- AID systems are strongly recommended for school-aged children with type 1 diabetes. **[A]**

School age represents a relevant threshold for AID therapy, as Tandem Control-IQ® system is approved for children aged 6 years and older, while the Medtronic Minimed 670G/780G® systems are approved for those aged 7 years and above. In a 16-week RCT involving 78 children aged 6-14 years in the intervention group using the Tandem Control-IQ® system resulted in an 11% higher TIR and a 0.4% (4 mmol/mol) lower HbA1c compared to a control group using sensor-augmented pump (n=23). While no SH was observed, 4 cases of DKA occurred in the intervention group. TBR did not differ. [133] A post-hoc analysis showed a high baseline TIR as predictor for greater success in AID use, while those with lower baseline TIR experienced the most significant improvement.[134]
The iLet® (Beta Bionics, USA) system operates differently from all other AID systems, as it does not require or allow manual entry of meal carbohydrate amounts (discrete grams of carbs to be consumed). Instead, a qualitative approach to meal announcement is employed. Additionally, system initiation is solely based on an individual's weight. In a large multicenter trial, 219 participants 6-73 years old, showed a 0.5% (6 mmol/mol) lower HbA1c compared to the control group (entire study population) and 11 percentage points more TIR with same TBR after 13 weeks.[135] The 165 pediatric participants (6-17 years) showed benefits in all CGM metrics and HbA1c. The group with higher baseline HbA1c demonstrated the highest reduction in glycemia.[136] In a subsequent 13 week extension phase, the pediatric group showed an additional 0.55 % (6.0 mmol/mol) reduction in HbA1c and 12.3 percentage points more TIR compared to baseline.[137] While no DKA occurred and 10 SH events were reported in the overall population during the initial RCT, no SH was found in the pediatric extension phase, with one DKA case reported that was associated with catheter occlusion.
A 4-week RCT with 60 participants aged 7-80 years compared the Minimed 780G® AID system to PLGM. In a cohort aged 7-13 years (n=19), TIR was increased 11.8% when using the AID mode, with no difference in TBR between the study groups. This effect was more pronounced during the night. No severe hypoglycemic events were observed throughout the entire population, with one mild DKA occurring during the PLGM phase. Not surprisingly, more targeted glycemic results were observed when the target was set to the lowest permissible in the system (100 mg/dL; 5.6 mmol/L) lower.[86]
In a single-arm trial involving 112 children using Omnipod 5® pump for 3 months, data were compared to a 2-week baseline phase where participants used their usual insulin regimen. HbA1c decreased by 0.71% (8 mmol/mol), with a TIR increase of 15.6% without differences in TBR. One DKA case and one SH occurred in the pediatric group, with infusion site failure and delayed meal consumption after bolusing identified as the reasons, respectively. Children with higher baseline HbA1c showed a greater reduction, when compared to those with HbA1c levels <8% at baseline [5].
The Diabeloop system has the algorithm installed on a hand-held device, and is not prescriptive in terms of insulin pump utilized in the system. In a small cross-over RCT with 21 participants, a pediatric version of the commercially-available adult system was investigated. After an inpatient period, the system was used for 6-weeks at home. No severe events occurred (SH or DKA). Compared to the control condition, where participants used an insulin pump and a sensor without predictive function, the intervention with the AID system led to higher TIR (66.2%vs. 58.7%) and reduced hypoglycemic events (25.5 vs 48 during the period) and TBR (2.6 % vs. 5.2%) nearly 2-fold. Surprisingly, mean glycemia did not differ significantly with 8.82 mmol/l (158 mg/dL) in the intervention and 9.05 mmol/l (162 mg/dL) in the control group[138].

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In a 12-week multicenter, crossover RCT with 25 children and adolescents, the CamAPS FX® System showed 8.9% more TIR with a 24.7% nocturnal difference in TIR when comparing AID use to SAP therapy. There were 2 hyperglycemic events without acidosis due to catheter occlusion in the AID intervention period compared to SAP.[139]
All systems provide improvements in glycemia in terms of TIR and HbA1c without increasing the risk for severe hyper- or hypoglycemic events in this age group.
These data from clinical trials are supported by real-world evidence, eTable 2.

Adolescents

- AID systems are strongly recommended for adolescents with T1D. **[A]**

Adolescence is typically characterized as the most challenging period for maintaining optimal glucose levels throughout a PWDs' lifespan [140].
An early study in this age group including adolescents with suboptimal glucose management, showed early improvement of glycemia after initiation of AID [141], with 10.8 percentage points more TIR compared to the control group using SAP.
The FLAIR study (Fuzzy Logic Automated Insulin Regulation) compared the first-generation Medtronic 670G with the second-generation Medtronic 780G in a randomized crossover design trial in adolescents and young adults aged 14 to 29 years old and [142]. Compared to 670G, the second-generation Medtronic system incorporates new features including selectable target glucose set-points (100, 110 and 120 mg/dL-5.6/6.1/6.7 mmol/L), autobolus functionality that delivers correction doses automatically if sensor glucose rises above 120mg/dL (6.7 mmol/L) and maximal automated basal insulin delivery has been reached, and an automated meal-detection algorithm, which when triggered, enables the system to deliver more aggressive autocorrection boluses. Twenty percent of the study cohort was using MDI at baseline and almost one-third (27%) of the study participants had suboptimal glycemia [defined as HbA1c >8.5% (70 mmol/mol)] at baseline. Each study period lasted 12-weeks, TIR improved from 57% at baseline on their usual insulin delivery modality to 63% during the 12-week period of 670G® use, and to 67% during the 3-months using the 780G®. Improved TIR was attained because of reduced TAR; hypoglycemia exposure remained similar between treatments and was minimal. There was a significant reduction in HbA1c between closed-loop periods in favor of the 780G® system. Importantly, glycemic benefits were observed irrespective of baseline treatment modality and baseline HbA1c. Some of the improvement in glucose management between the closed-loop systems may be attributable to increased time when the system was in automated mode (75% with 670G and 86% with the 780G), due to fewer exits per week from automation with the advanced system. From a safety perspective in this population, there was one episode of SH while using the 780G® system and none while using the 670G® system. No cases of DKA were reported.
Compared to PLGM, one study showed TIR improvement of 14.4 percentage points with 780G® [86], and another small RCT observed a 10 percentage points increase in TIR compared to a run-in phase with PLGM [143]. This improvement was associated with significantly higher bolus insulin amounts, which were delivered as auto-corrections by the system, which accounted for approximately 69.9% of the total bolus dose in the trial.
Forty adolescents (above age 14) and young adults up to the age of 25 participated in a 6-month RCT of the Tandem Control-IQ® system compared to those on sensor-augmented pump therapy [88]. In this age group, AID use led to TIR that was 13.3 percentage points higher in the intervention group with no difference in TBR. HbA1c was 0.35 percentage points (4 mmol/mol) higher in the control group who used sensor-augmented pump therapy. Compared to other study participants, this age group had less user initiated boluses observed.[103]
Data from adolescents using the Omnipod 5® system were reported collectively with the 124 participants aged 14-70 years. The cohort as a whole demonstrated increased TIR by 9.8 percentage points, accompanied by a 0.38 percentage points (4 mmol/mol) reduction in HbA1c. TBR was also reduced from 2% to 1%, with two events of SH after manual bolus administration. People with higher baseline HbA1c (defined as HbA1 >8%) showed a greater reduction in HbA1c by the end of the 3-month study[5].
Similar to both the school aged and pre-school age groups, all systems studied appear to improve glycemia (TIR, HBA1c) without increasing the risk for severe hyper- or hypoglycemic events in the adolescent age group.
The data derived in clinical trials are echoed in real world evidence, eTable 2.

Young adults

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- AID systems are strongly recommended for young adults with type 1 diabetes. **[A]**

Ease of use of AID technology is an important consideration to realizing the clinical benefits, particularly in the young adult population. Improvements in glycemic outcomes are highly correlated with greater time spent in automation; AID system use greater than 70% is associated with attaining ≥70% TIR [144-146].
Many RCTs have now demonstrated the safety and efficacy of AID systems, both commercially available and open-source systems, compared to non-automated insulin therapies, SAP therapy, and system that interrupt insulin delivery based on either a threshold or in a predictive fashion both in young adults with type 1 diabetes [86, 135, 141, 147-151].
Two studies discussed above, the FLAIR study and one Tandem Control-IQ study included both adolescents and young adults. In another Control-IQ® study, a subgroup of 40 participants aged 14 to 24 years using the Control-IQ® system had a mean TIR from 51% at baseline to 64% after 6 months[152]. Similar glycemic benefits have been observed when other commercially available AID systems have been used in young adults. A subgroup of 11 participants aged 13 to 21 years using the Cambridge closed-loop algorithm showed a 14% increase in TIR over 12 weeks[141].
Real-world data parallels the findings from clinical research trials (eTable 2), where sub-analyses by age group are presented[145, 153] [132] [154].
In young adults, competing priorities and psychosocial challenges are important factors in self-management and glycemic outcomes[155]. AID system user data in this age group shows the lowest engagement in therapy with the fewest user-initiated boluses and the most automated corrections compared to other age groups.[156, 157] Despite this, the beneficial effect of AID on TIR is statistically-similar across all age groups [103]. Further supporting the use of AID in this population, both trial data and real-world data has consistently shown that the greatest clinical benefits occur in those with the highest HbA1c or lowest time in range at the time of initiation of the AID system [5, 103, 134],[157, 158]).

4. Non-Automated Insulin Delivery

Practical considerations for non-AID use

Critical to the integration of SAP, LGS, PLGS, and even AID is successful adoption of sensor therapy. For evidence on sensor therapy, please refer to the ISPAD 2024 Consensus Guidelines Chapter on Diabetes technologies: glucose monitoring[2]. Topics that should be considered when initiating these therapies may include expected frequency of sensor use, and how treatment may vary when interruptions from sensor therapy occur.[159]

PREDICTIVE LOW GLUCOSE SUSPEND (PLGS) SYSTEMS

- PLGS is strongly recommended for all people with T1D who do not have access to AID systems as these systems can mitigate hypoglycemia. **[A]**

PLGS systems interrupt basal insulin delivery to prevent hypoglycemia (Figure 1). Different systems are available; however, not all provide published evidence for successful use and therefore only systems with published peer-reviewed data are recommended for use.[160]
Two RCTs of the Medtronic PLGS approach (Minimed 640G®) have shown reductions in hypoglycemia with PLGS use, [161] [162] with one study demonstrating no concomitant increase in mean glucose, as measured by HbA1c, in the PLGS group. [162] These results have also been echoed during real-world use. [163]
A RCT of the Tandem system (Basal-IQ®) found that PLGS use led to a 31% reduction in sensor time <3.9 mmol/L (<70 mg/dL). [164] Real-world registry data from adults using the Tandem systems show a significant reduction in TBR after PLGS start [165], with no change in mean glucose. [166]
A meta-analysis including data on 493 children in 5 RCTs concluded that there is high quality evidence to support PLGS´ superiority to SAP in decreasing TBR and nocturnal hypoglycemia.[160] This was accomplished without increasing percentage of time spent in hyperglycemia or episodes of DKA.[160] Another meta-analysis concluded that the use of PLGS during the overnight period was associated with an 8.8% lower risk of hypoglycemia when compared with non-PLGS use overnight.[167]

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LOW GLUCOSE SUSPEND (LGS) SYSTEMS

- When AID and PLGS systems are not available, LGS systems are recommended to reduce the severity and duration of hypoglycemia as compared to non-integrated pump and SAP, **[A]** by increased confidence and trust in the technology, more flexibility around mealtimes, and reduced diabetes distress for both people with diabetes and caregivers compared to CSII. **[A]**

With CGM data integrated into an algorithm on an insulin pump, altering insulin delivery based on sensor glucose readings is possible. A Low Glucose Suspend (LGS) system can suspend insulin delivery when the sensor glucose reaches a programmed low threshold (Figure 1). An LGS feature is optional, and the pump functions normally if the feature is switched off, if sensor glucose data are not available, or if the sensor glucose value is above the predetermined threshold value.[168, 169] LGS systems reduce risk of hypoglycemia, which may facilitate user engagement with bolusing.

In the **A**utomation to **S**imulate **P**ancreatic **I**nsulin **R**esponse (ASPIRE) study, hypoglycemia was detected by sensor readings. They were significantly reduced with the use of the LGS system without any deterioration in glycemia as measured by HbA1c.[170, 171] Real-world observational studies, have substantiated the RCT findings showing benefits of LGS over SAP. [163]

While more advanced insulin pump therapies are now available and include PLGS and AID systems, advanced pumps are not available in all countries and may not be covered by certain health/insurance plans. In such circumstances, LGS systems are strongly recommended over other types of pumps. Studies have shown that LGS is cost-effective and should be particularly considered where there is a high risk of hypoglycemia, impaired hypoglycemia awareness or fear of hypoglycemia, which may lead to difficulty with achievement of glycemic targets.[172-174]

SENSOR AUGMENTED PUMP (SAP)

- Sensor augmented pump (SAP) therapy is recommended over MDI with sensor wear of >=60% of the time **[A]**

Sensor Augmented pump (SAP) therapy is defined as the combination or augmentation of a conventional insulin pump with CGM (Figure 1), without the presence of an algorithm. For more details on CGM, please see ISPAD 2024 Consensus Guidelines on Diabetes technologies: glucose monitoring[2].

The benefits of SAP have been demonstrated in RCTs [175] [176-178], including the Sensor-Augmented Pump Therapy for A1c Reduction (STAR) 3 study that compared SAP with MDI and SMBG checks over 1-year in device-naïve participants with T1D including children [176-178] The SAP group had a sustained greater reduction in HbA1c, less time in hyperglycemia, and reduced glucose variability.[178] Rates of SH and DKA were relatively low and did not differ between groups. Achievement of glycemic targets was directly linked to sensor wear duration and was more prominent in the children's cohort (aged 7-12 years) who had sensor use that was 1.5 times higher than adolescents (aged 13-18 years).[178] The crucial impact of regular sensor use has been echoed in other

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trials.[179] For every 10% increase in sensor use frequency there is an associated 1.1 percentage point increase in TIR and a 1.0 percentage point decrease in TAR > 10 mmol/l (180 mg/dl).[180]
Although SAP is more expensive than insulin pump therapy with fingerstick glucose monitoring, the additional clinical benefits and quality-adjusted life years SAP affords provides justification for considering this treatment a good value for the money spent, provided sensor use is persistent.[181, 182]

5. Connected Insulin Pens

- Connected pens, if available and affordable, may be offered to interested youth who prefer not to have an on-body device. **[C]**

Connected insulin pens, also known as smart insulin pens, are an emerging option for youth with T1D to access some of the benefits of diabetes technology when AID use is not feasible or desired. Connected pens can be used with or without a CGM and can either be in the form of a non-disposable pen device or a pen cap that is placed on a disposable pen. Connected pens link to an app on a smartphone, which aids users in dose calculation and helps prevent insulin stacking by tracking insulin on board. Connected pens also capture important data on insulin dose and timing, generating reports that clinicians can use for dose optimization.

Literature supporting the efficacy of connected pens in youth with T1D remains limited. Most studies done to date are in adults and only a few are RCTs; however, overall evidence suggests that connected pens may improve outcomes as noted in a recent systematic review [183].

A recent RCT on a smart pen cap that included adolescents with T1D reported a 5.2 percentage point increase in TIR as well as an increase in on-time injections with connected pen use [184]. A real-world observational study in children and adults demonstrated a 13% reduction in sensor-detected prolonged hypoglycemia (≥10 min) with connected pen use [185]. This finding was echoed by another observational study of connected pen use in youth with T1D, where hypoglycemia was reduced, but not hyperglycemia[186].
Currently, the use of connected pens among youth with T1D is not widespread. A recent study identified several barriers to connected pen use from providers at select centers in the T1D Exchange Quality Improvement Collaborative consortium [187]. Barriers included low provider awareness and lack of training on these devices, lack of insurance coverage, high out-of-pocket costs, need for user education and training on the device, and lack of smartphone availability for younger children. Facilitators of connected pen use that were identified included generating reports with improved quality of clinic visits, providing an alternative to an insulin pump, and improved diabetes management and adherence. More research is needed to determine whether connected pen use should be encouraged in youth with T1D who choose not to use AID.

6. Behavioral, Psychosocial, and Educational Considerations of Insulin Delivery Devices

- AID is recommended to reduce burden, improve perceived sleep quality, and improve treatment satisfaction. **[B]**
- Youth and their caregivers should be educated and counseled about realistic expectations for glycemic outcomes and the effort required for successful use of all insulin pump technologies. **[C]**
- A standardized, structured training program with early follow-up within the first few weeks after device start is recommended to optimize device use. This training can take place in person or remotely. **[C]**

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Behavioral and Psychosocial Outcomes

Initiating and sustaining the use of insulin delivery devices are associated with behavioral and psychosocial considerations, including self-management demands, emotional experiences, family diabetes management, and social factors. These issues may promote or be barriers to optimal engagement in self-management using insulin delivery devices. ISPAD 2022 Consensus Guidelines Chapter 15 on Psychological Care of Children and Adolescents with Type 1 diabetes and other Clinical Practice Guidelines [188, 189] highlight the importance of recognizing and addressing the psychosocial and behavioral needs of youth with diabetes and their families, which have implications for supporting their use of insulin delivery devices.

Youth with T1D who use insulin pumps tend to experience benefits in health-related quality of life compared to MDI[190],[191, 192] and may have lower depressive symptoms[193]. Parents may also experience improved quality of life.[193, 194] Specific perceived benefits of pump therapy include increased autonomy in diabetes management, a greater sense of control over one's life and diabetes, decreased diabetes burdens, greater flexibility in social activities and eating improved sleep, and higher treatment satisfaction. [191, 195-199] However, these results are not universally reported [197, 200, 201] and psychosocial factors, such as depressive symptoms, may increase the risk of pump use discontinuation.[43]

As AID systems become more accessible, youth and parent trust in the system is of central importance for uptake, but factors may depend on users, device or context.[202] Studies have reported children and adolescents emphasized concerns related to use at school and with peers, while parents' concerns prioritized accuracy and ensuring that systems stabilize glucose levels and reduce risk for long-term complications.[203, 204] Evidence from qualitative research and self-report surveys suggests that caregivers are motivated for their children to use AID systems (including open-source or do-it-yourself systems) primarily to improve glycemic outcomes, lower the risk of complications, reduce diabetes care burdens, interact with diabetes technology less and improve sleep.[205-208]

In recent years, substantial data have been reported regarding the benefits of AID systems for quality of life and well-being for youth and caregivers, in both clinical trial and real-world settings. Advantages include reduced diabetes burden/distress (especially around meals) and mood concerns, reduced fear of hypoglycemia, and worries about glycemic excursions. Additional benefits include greater confidence related to diabetes management, increased autonomy for the child, ability to participate in social activities, and improved treatment satisfaction.[104, 127, 191, 207-221]. At the time of T1D diagnosis, AID has also been shown to assist in adapting to this chronic medical diagnosis as compared to MDI.[217]

There are also indications of perceived improvements in sleep for both youth and parents, though significant differences in objectively measured sleep are not typically observed.[104, 204, 208, 213, 214, 216, 222-224]

Though the psychosocial and behavioral benefits of AID use are not universally reported [223-226], the consistent conclusion is that advanced insulin delivery devices do not increase the burden or lead to psychological or behavioral distress, and in many cases, these devices reduce the burden and improve quality of life [215, 222, 227-229].

Limited data describe specific benefits of particular AID devices when compared to others [104, 230], but some specific features are valued by youth and families. Qualitative data regarding experiences with remote monitoring suggest a number of specific benefits (e.g., greater access to therapy data, increased comfort being away from the child or relying on other caregivers, fewer disruptions to play, sleep, and social activities) [231], especially for parents of young children[129].

While the evidence regarding positive psychosocial impacts of AID is growing, psychosocial barriers to optimal self-management remain. Notable barriers include perceived high workload required to maintain AID function and frustrations with technical glitches (e.g., frequent exits from automated delivery modes), as well as concerns about device size/visibility and stigma. Physical discomforts have also been reported, as well as burdens related to alarms causing sleep disruptions, limitations in remote monitoring access for parents, and difficulties with the required calibration of some devices.[211, 217, 232, 233]. Notably, these concerns were more common with first-generation HCL systems compared to newer systems [234, 235]. Newer AID devices that use factory-calibrated CGM, which eliminate/minimize the need for capillary blood glucose checks with a glucometer have been found to reduce many of the burdens associated with AID devices and improve sustainability of use, especially in youth. [236] Indeed, data suggest improvements in burden and satisfaction for adolescents, young adults, and parents using advanced HCL devices compared to sensor-augmented pumps and earlier HCL systems [223, 234, 237].

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Education and Training for Insulin Delivery Devices

Education and device training are important to ensure effective pump use and to promote sustained device use and ongoing success. [111, 112, 238, 239] Structured training programs with early follow-up within the first few weeks of use can optimize device use. Evidence indicates that virtual training is similar in effectiveness to in-person training and may facilitate more rapid AID uptake and reduce training burdens for both families and HCPs.[240-243] The training program should emphasize education on the basics of CGM use, required diabetes self-management tasks to optimize the device (i.e., pre-meal bolusing), and common troubleshooting for the specific device. This education also helps ensure new users have realistic expectations of their device and understand the self-management behaviors needed for optimal outcomes. It is imperative that users understand the safety principles of managing persistent hyperglycemia and infusion site failure (i.e., when to check ketones, change infusion site, and/or give insulin by injection). These principles are vital for the safe use of any insulin pump therapy to prevent DKA and are equally applicable to use of AID technologies[244]. Users who discontinue insulin delivery devices are most likely to discontinue within the first 1-3 months of use.[144, 245] Therefore, follow-up within the first month of use is helpful to assess system use and glucose trends, to allow the provider or diabetes educator an opportunity to identify early any challenges the user may be experiencing, and to provide an opportunity for targeted re-education to help the user overcome challenges and improve outcomes. Furthermore, youth may benefit from adjustments to any modifiable pump settings (i.e., insulin-to-carbohydrate ratios) to improve glycemic outcomes when transitioning from MDI or a conventional insulin pump to AID. A follow-up call or visit in the first month provides the opportunity for the clinician to make these changes[246].

Practical Considerations for Behavioral, Psychosocial and Educational Considerations of Insulin Delivery Devices

When integrating diabetes technology into the care of youth with diabetes, families of all backgrounds (socioeconomic, racial, etc.) should be informed about the spectrum of insulin delivery devices from conventional pumps to AID systems. Clinicians should portray insulin delivery devices as an option that can be a good fit for all youth and families, provide education, and encourage youth and families to review vetted websites and device informational materials. Further, it is critical for the diabetes team to recommend the most advanced device technology available that the person with diabetes is interested in and to not make assumptions about interest or capability. Clinicians should refrain from having youth and families "earn" the right to use devices (i.e., achieve a certain HbA1c before considering starting a device). If payers/insurance companies require logging or other documentation before device approval, convey that directly to the family and advise this is not a requirement of the diabetes care practice/team. Further, while counting carbohydrates and delivering boluses consistently for all meals and snacks is the optimal way to use most AID devices, carb counting or a history of consistent bolusing should not be a pre-requisite for AID use. Significant benefits using AID can still be obtained for those who struggle to count carbohydrates or deliver meal boluses consistently. Even those who do not bolus consistently can experience significant improvement in glycemic outcomes, and alternative bolus strategies, such as using fixed meal doses instead of carbohydrate counting, can improve TIR[103, 105, 247-249]

Assessing youth or family concerns and other barriers to device uptake and use should be part of routine clinical practice. Providers should seek to work with the youth and their families on ways to break down barriers and increase facilitators of device use. This may require referral to a psychological or behavioral/mental health professional, who can teach problem-solving skills and other strategies to support device uptake and sustained use.[250]

Non-certified Open-Source AID approaches

- If people with diabetes choose to use open-source automated insulin delivery systems, support from care providers is encouraged. **[E]**

Recognizing the inherent delays in conducting clinical trials and obtaining regulatory approval for new technologies, the past decade has seen the creation of open-source automated insulin delivery systems. Through an online community, the DIY approach has been adopted by several thousand people with diabetes and their families. *In silico* studies have demonstrated the relative safety of the system through simulations with both meal bolus over- and underestimation as well as what might occur with delayed bolusing. [251] Additionally, a real-

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world prospective observational study of 558 users, more than half <25 years old, showed improvement in TIR and reductions in the incidence of SH events with system use, suggesting these systems can be used safely and effectively.[131] As these systems do not have regulatory approval, healthcare professionals should be cautious about recommending these devices in preference to commercially available systems. Yet, when people with diabetes choose to use an open-source system, a consensus statement endorsed by some organizations suggests that providers should support them.[252] One RCT in those aged 7-70 years compared the use of an open-source developed algorithm to a control group using SAP. The AID group showed an increase in TIR of 10% leading to an adjusted difference between groups of 14%. However, it is important to note that the setting of this clinical study differed from the typical daily open-source use as it was a preset device with support from a clinical team. [253] While PWD may independently build their DIY AID systems, the diabetes care team remains essential for core diabetes self-management education and support for DIY AID use. Clinicians should consider learning the key system characteristics to facilitate supporting PWD in optimizing settings to help them meet glycemic and personal goals safely and effectively.

7. Conclusion

AID is an established therapy and has become the standard of care in jurisdictions and healthcare settings where it is available and accessible. Just as our everyday lives have vastly changed with the integration of new technologies, with increased connectivity, the technological revolution has had an enormous effect on the management of diabetes and modes of insulin delivery. This reality means that individuals of all ages with diabetes can carry a smartphone with CGM or AID application and that glycemic data can be monitored in a cloud-based manner from everywhere.

The true test of new technologies, reducing glycemic variability while achieving greater TIR and improving quality of life, is passed. It is reasonable to expect that in the years ahead, there will be significant growth in this aspect of diabetes care and that progressive technological solutions will allow people with diabetes, and their families, an improved ability to attain glycemic targets while reducing the burdens of daily diabetes care and improving quality of life. In the long term, the integration of more physiologic insulin delivery afforded by AID systems will further minimize the risk of diabetes complications. Long-term data to prove its additional benefits for secondary conditions and cardiovascular risk are yet to come.

Clinicians engaged in the care of PWD have an obligation to remain abreast of new technology developments to optimize uptake and use. Broader implementation of technology into clinical care will also require an understanding of the cost-benefit of therapies to justify payer coverage, as many of these technologies are expensive and consideration of total lifetime costs alongside reductions in overall healthcare expenditures require further evaluation [30]. Additionally, interoperable approaches should provide options to interchange separate components, which would allow users to customize treatment through their diabetes management devices along with appropriate data sharing.

Updates are anticipated in this rapidly evolving area of research and practice to further the ISPAD's aim: "a better world for children, adolescents, and young adults with diabetes"

Conflicts of interests

TBI- research support from Dexcom, Vitalaire, Ypsomed. Speakers honoraria from DexCom, Insulet, Lilly, Medtronic, NovoNordisk, Sanofi, Synlab, Ypsomed. He participated in Advisory boards from DexCom, Insulet, Medtronic, Tandem, Ypsomed. He serves as chair in the EXPAMED-Panel Diabetes/Endo of EMA for new medical devices.

CariB- speaking and consulting fees for Medtronic, Tandem, Insulet and Embecta.

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LE has served on the advisory board of Diabetes Center Berne, Sequel, Abbot, and Medtronic. She has received consulting fees from Tandem Diabetes Care, and has received honorarium fees from Medtronic and Insulet. Her institution has received research support from Breakthrough T1D, Medtronic, Mannkind, and Abbot. LE has received travel accommodations for conferences from Medtronic and Insulet. LE has served as a consultant to

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Jaeb. LE has received honorarium fees from Tandem Diabetes Care. She has received an honorarium for a grand round presentation/CME event sponsored by Sanofi.
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JS- works as a consultant for the following entities with all compensation being <10K per year: Abbott Diabetes, Insulet, Medscape, Medtronic Diabetews, Vertex, Ypsomed. Served on advisory boards for the following entitites with all compensation being <10K per year: Cecelia Health, Insulet, Mannkind, Medtronic Diabetes, StartUp Health T1D Moonshot, and Vertex. Research contracts for which payment is rendered to Yale for work completed from Abbott Diabetes, Dexcom, JDRF/Breakthrough T1D, Insulet, Medtronic, NIH, Provention Bio. Participated in Advisory boards by Insulet, Medtronic, Ypsomed.
KD- received honoraria for participation in the speaker's bureau of Abbott, Eli Lilly, Medtronic, NovoNordisk A/S, and Pfizer. Advisory board for Medtronic and Novo Nordisk.

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TB oversaw completion of the first draft of the guidelines and edited the manuscript. KD outlined the guidelines, reviewed the literature, edited the manuscript, and served as the senior author.

Methodology: A literature search was conducted to gather updated evidence, using a combination of relevant medical subject headings (MeSH, Emtree) and free text terms specific to each chapter's focus. Studies published from 2021-2022 onward, related to children and young adults, were retrieved from MEDLINE. The Project Officer, in collaboration with chapter leads and co-authors, performed the literature searches. The resulting articles (with search terms summarized in Appendix 1) were then uploaded to COVIDENCE for screening and review. Two authors/experts involved in drafting this guideline version, independently screened the articles. Any disagreements were resolved by a third reviewer. Where relevant, further literature was included.
The draft chapter was posted on the ISPAD forum to allow feedback from the greater ISPAD membership. Modifications were made with authorship consensus, with the chapter receiving endorsement from the ISPAD editorial team.
Literature search terms are summarized in Supplementary material.

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Abbreviations

AID: Automated Insulin Delivery
ASPIRE study: Automation to Simulate Pancreatic Insulin Response
ISPAD: International Society for Pediatric and Adolescent Diabetes
BGM: Blood Glucose Monitoring
CGM: Continuous Glucose Monitoring
CSII: Continuous Subcutaneous Insulin Infusion
DCCT: Diabetes Control and Complications Trial
DIY: Do It Yourself
DKA: Diabetic Ketoacidosis
DPV: Diabetes Patienten Verlaufsdokumentation (Diabetes Prospective Follow-up) a registry from Germany
EDIC study: Epidemiology of Diabetes Interventions and Complications study (extension of DCCT)

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GMI: Glucose Management Index
HbA1c: Glycated hemoglobin
HCL: Hybrid Closed Loop
LGS: Low Glucose Suspension
MDI: Multiple Daily Injections
PGLM: Predictive Glucose Low Management
PLGS: Predictive Low Glucose Suspension
PWD: People With Diabetes
RCT: Randomized Controlled Trial
SAP: Sensor Augmented Pump
SMBG: Self-Monitoring of Blood Glucose
SH: Severe Hypoglycemia
STAR study: Sensor-augmented pump Therapy for A1c Reduction study
TAR: Time Above Range
TBR: Time Below Range
TIR: Time In Range
T1D: Type 1 Diabetes
T1DX: Type 1 Diabetes eXchange. Large registry based in the US

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Figures legends

Figure 1. Schematic representation of automated and non-automated insulin delivery
Figure 2. Real World Studies evaluating automated insulin delivery: Percent Time in Range at Baseline and Endpoint

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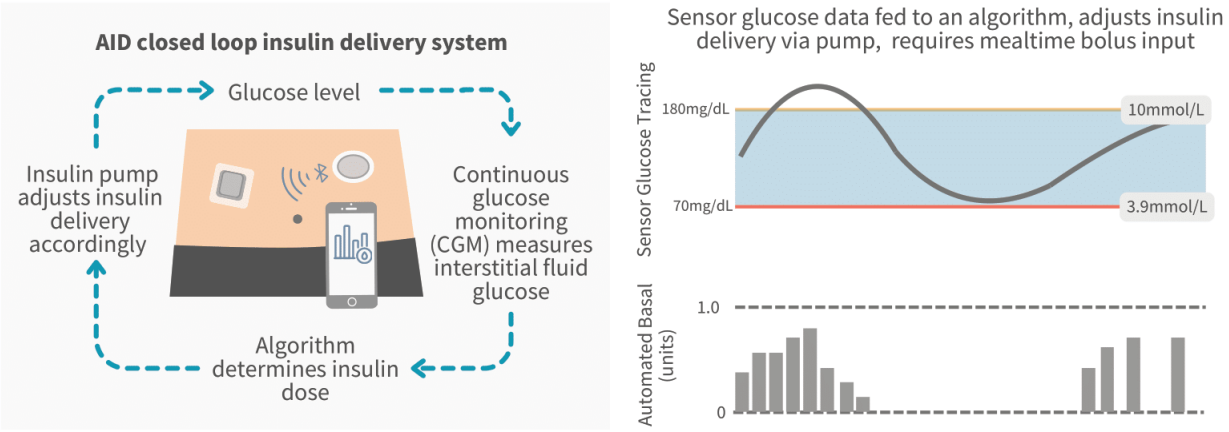
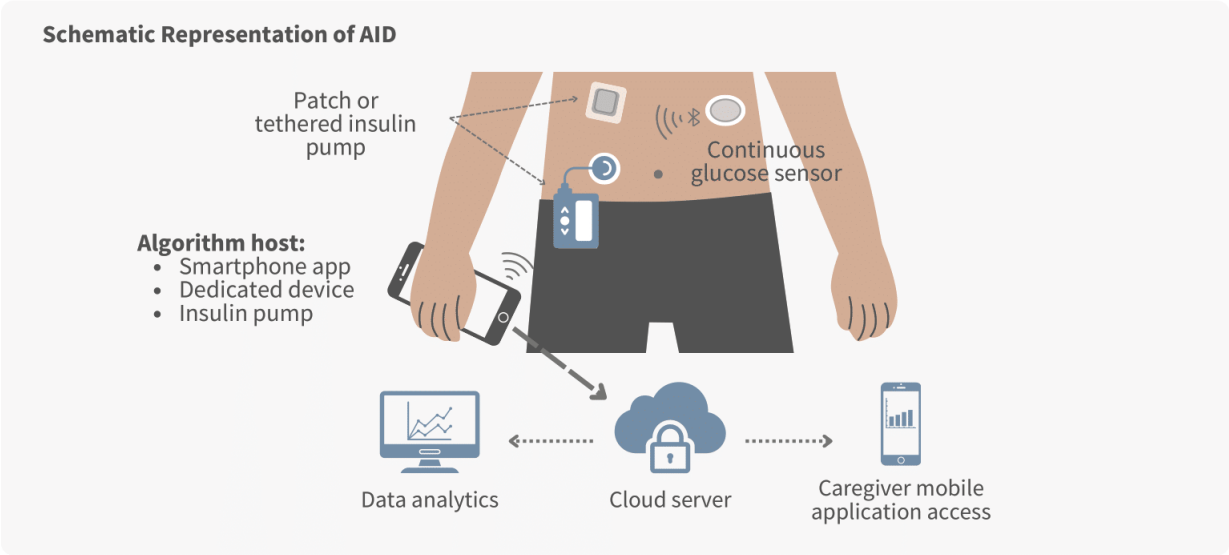
Automated insulin delivery (AID) or Closed Loop, Artificial Pancreas





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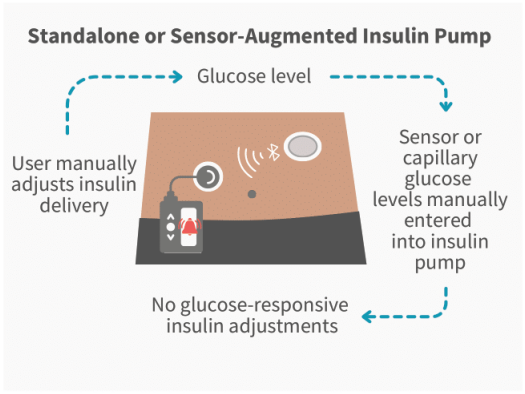
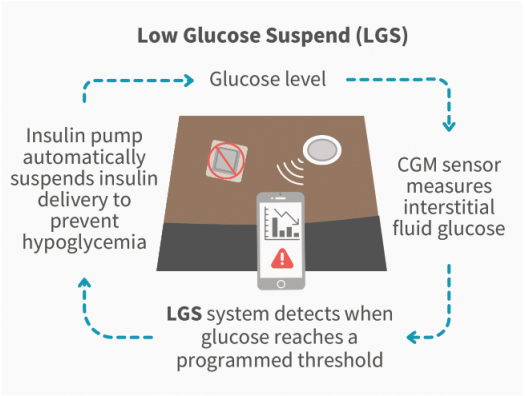
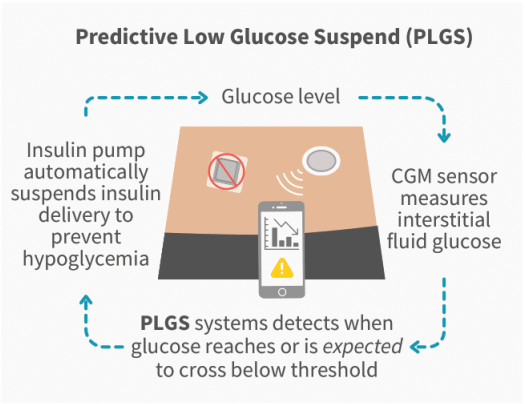
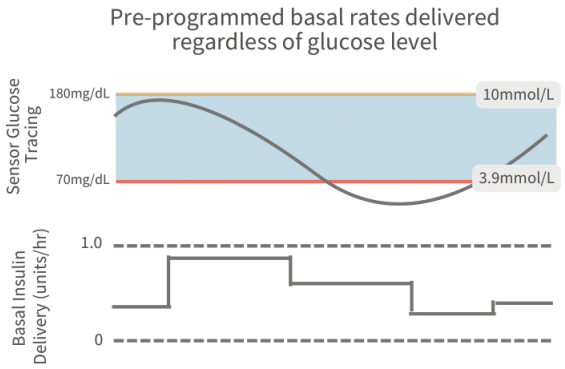
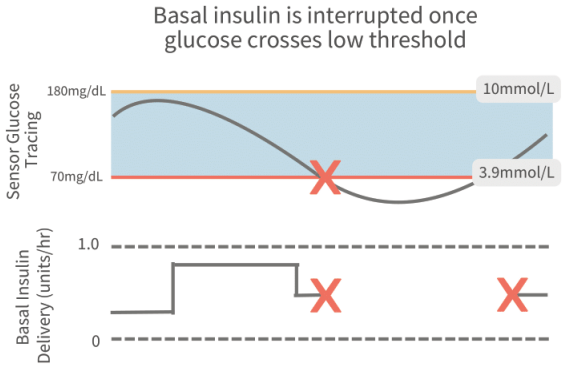
Non-automated insulin delivery

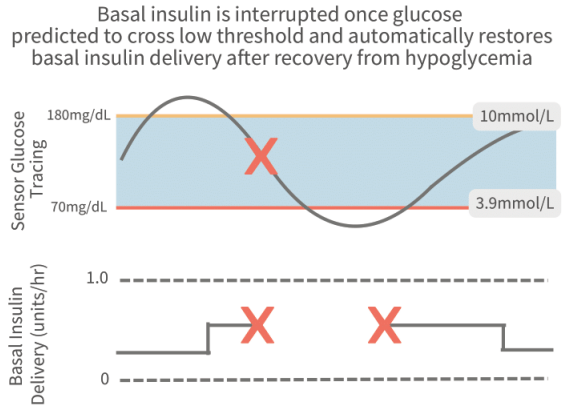












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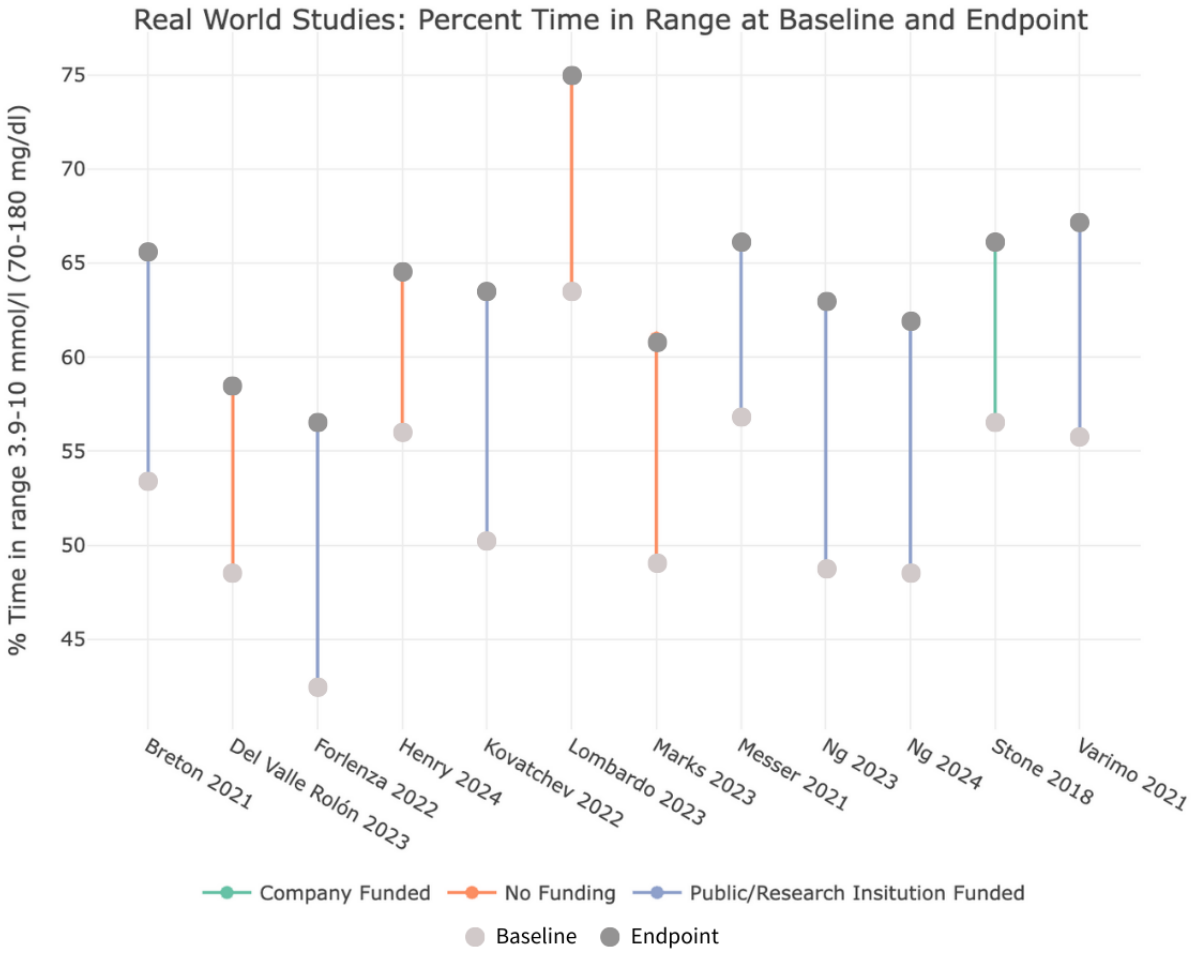

Simplified presentation of real-world evidence of automated insulin delivery, regardless of population, type of data acquirement and length of observation. For detailed information please see eTable 2 (online supplement).

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