Treatment of diabetes mellitus using an external insulin pump: 
the state of the art

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Abstract

The aim of diabetes treatment is to achieve tight glucose control to avoid the development of chronic diabetic complications while reducing the frequency of hypoglycaemic episodes. Continuous subcutaneous insulin infusion (CSII) using an external pump is an intensive diabetes therapy recognized to improve metabolic control and glycaemic instability, and to reduce the frequency of severe hypoglycaemia. For years, the theoretical advantages of the insulin pump (constancy of basal delivery, adjustable basal rates, and low insulin depots allowing the reduction of glycaemic variability) have contributed to its reported superiority compared with multiple daily injections (MDI). However, insulin pump therapy is now challenged by new MDI regimens based on long-acting insulin analogues that could replace the use of CSII. As a consequence, health professionals now have to determine which patients are likely to benefit the most from CSII. Recently, several studies reported that children and adolescents, and patients whose blood glucose imbalance was initially the most pronounced with basal-bolus regimens, would particularly benefit from CSII. Other indications were also proposed in marginal clinical situations with highly selected patients in whom a significant improvement of blood glucose was demonstrated. Finally, the use of CSII in type 2 diabetic patients now appears to be a good alternative to the ineffective MDI regimens observed in some of these patients. However, past experience with CSII indicates that candidates for insulin pump therapy must be carefully selected and strongly motivated to improve their glucose control. Use of CSII also requires strict medical supervision by physicians and a regular programme of patient education by paramedical teams, to ensure optimal responsible use of this technique by healthcare professionals.

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Résumé

Traitement du diabète par pompe à insuline externe : l’état de l’art

Le but du traitement du diabète est d’obtenir un équilibre glycémique satisfaisant afin d’éviter le développement des complications chroniques du diabète et, dans le même temps, de réduire la fréquence des épisodes hypoglycémiques. La perfusion continue d’insuline utilisant une pompe externe est un traitement intensif efficace du diabète, reconnu pour améliorer l’équilibre et l’instabilité glycémique, réduire la fréquence des hypoglycémies sévères. Pendant de nombreuses années, les avantages théoriques du traitement par pompe à insuline (débit de base constant, débits de base ajustables, faibles dépôts d’insuline réduisant la variabilité glycémique), ont conduit à rapporter une supériorité de cette thérapeutique comparée aux multi-injections d’insuline. Cependant, la pompe à insuline est aujourd’hui en compétition avec les nouveaux schémas de multi-injections basés sur l’utilisation des analogues lents de l’insuline qui pourraient supplanter cette insulinothérapie intensive continue. Ainsi, les professionnels de santé doivent évaluer les patients qui peuvent bénéficier le plus du traitement par pompe à insuline. Récemment, plusieurs études ont montré que les enfants et adolescents, ainsi que les patients initialement les plus mal équilibrés sous multi-injections, pourraient tirer particulièrement bénéfice de ce traitement. D’autres indications peuvent également être pro-

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1. Efficacy of external insulin pump treatment in glycaemic control

The aim of type 1 diabetes treatment is to achieve tight glucose control to avoid chronic complications while reducing the frequency of hypoglycaemic episodes in everyday life. Over the past few decades, considerable efforts have been made to improve the tools used for insulin therapy. The development of continuous subcutaneous insulin infusion (CSII) and, more recently, of short-acting insulin analogues that exhibit beneficial pharmacokinetic properties represent important advances in the treatment of diabetes.

CSII using external insulin pumps was introduced in the 1970s as a way of achieving and maintaining strict control of blood glucose concentrations in type 1 diabetic patients [1], mimicking physiological insulin release better than did multiple daily injections (MDI). The exclusive use of soluble, short-acting insulin, infused subcutaneously at the same site for two or three days, reduces the variability of insulin absorption compared with long-acting insulin [2,3]. CSII allows greater flexibility in insulin infusion, as different basal rates can be programmed and meal boluses adjusted when required.

1.1. CSII vs MDI using regular insulin

Several studies have shown the superiority of CSII over MDI in terms of HbA1c [4-7]. In the Diabetes Control and Complications Trial (DCCT), HbA1c levels in the intensive-treatment group were significantly lower with CSII than with MDI (-0.2 to -0.4%) [8]. However, as the patients who were randomly assigned to receive the intensive treatment were allowed to choose between CSII and MDI instead of being randomly allocated to the type of therapy, the DCCT results are biased.

Nevertheless, two meta-analyses of trials comparing CSII and MDI regimens have been carried out, involving 600 and 1,547 patients, respectively [9,10]. Their conclusions showed an overall advantage of CSII over MDI, with a decrease in HbA1c of 0.4-0.5% together with a reduction in insulin requirements. But, as the definition and reporting of hyperglycaemia were different in the two studies, the findings of these meta-analyses are less than fully informative. However, the available data do indicate that CSII use was associated with a decrease in the frequency of mild hypoglycaemic episodes [10], and this was probably related to the reduced variability of blood glucose concentrations, as measured by standard deviation [9]. In patients prone to severe hypoglycaemia, the use of CSII resulted in a large and sustained reduction of such episodes [11]. Quality of life has been assessed in a limited number of studies, using different measures and different concepts [12], making it difficult to draw any definite conclusions. However, these few studies showed CSII therapy to have either a favourable or neutral effect on quality of life, depression and anxiety [13].

1.2. CSII using regular insulin vs analogues

Several randomized controlled trials have shown that CSII with rapid-acting insulin analogues was more efficient in controlling postprandial glycaemia and HbA1c concentrations than CSII with regular human insulin [14-16] (Table 1). One meta-analysis concluded that the use of insulin analogues with a pump results in a modest (0.26%), but significant, reduction in HbA1c compared with soluble insulin [17]. The pharmacokinetic properties of the rapid-acting insulin analogues were certainly responsible for this slight superiority due to an improvement in postprandial glucose levels and glucose stability.

1.3. CSII vs MDI using rapid-acting analogues

It was, therefore, necessary to investigate whether the introduction of the short-acting insulin analogues would modify the relative performances of CSII and MDI. In fact, with either CSII or MDI, the optimal meal insulin is a rapid-acting insulin analogue, which has pharmacodynamic advantages over regular human insulin, including faster absorption, earlier onset and shorter duration of action.

However, the efficacy of CSII compared with MDI therapy has only been evaluated in a limited number of randomized controlled trials in which rapid-acting analogues were used...
for both regimens, with three out of four studies pointing to the superiority of CSII [18-21] (Table 2). It should be noted that the basal insulin used in these four studies was NPH insulin. The pooled analysis of these studies suggests that CSII is associated with better glycaemic control, particularly in those patients with initially suboptimal control [22]. The magnitude of the effect of CSII on glycaemic control compared with MDI is similar to previous findings in trials using regular human insulin, with a difference in HbA1c concentrations between CSII and MDI of -0.35%. The relative benefit of CSII over MDI was found to increase with higher baseline HbA1c levels (Fig. 1) [23]. Nevertheless, the results obtained with CSII were superior to those achieved with MDI, whatever the levels of baseline HbA1c. The fourth study found that

Table 1
Superiority of rapid-acting insulin analogues over regular human insulin in CSII

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Difference in HbA1c (%)</th>
<th>Hypoglycaemic episodes</th>
<th>Standard deviation</th>
<th>Insulin doses (U/day)</th>
<th>Side-effects (incidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinman et al., 1997 [14]</td>
<td>Double-blind crossover, 3 months</td>
<td>30 CSII lispro/humulin</td>
<td>-0.34</td>
<td>&lt; 3 mm/l</td>
<td>NA</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Melki et al., 1998 [15]</td>
<td>Open crossover, 3 months</td>
<td>39 CSII lispro/actrapid</td>
<td>-0.53</td>
<td>&lt; 2.2 mm/l</td>
<td>-0.36 mm/l</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Renner et al., 1999 [16]</td>
<td>Open crossover, 4 months</td>
<td>113 CSII lispro/humulin</td>
<td>-0.13</td>
<td>NA</td>
<td>=</td>
<td>=</td>
<td></td>
</tr>
</tbody>
</table>

NA, not available; =, similar

Table 2
Rapid-acting insulin analogues: CSII vs MDII

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Difference in HbA1c (%)</th>
<th>Hypoglycaemic episodes</th>
<th>Standard deviation</th>
<th>Insulin doses (U/day)</th>
<th>Side-effects (incidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanaire-Broutin et al., 2000 [18]</td>
<td>Crossover, 4 months</td>
<td>41 MDII/CSII</td>
<td>-0.35%</td>
<td>NS</td>
<td>-11 mg/dl</td>
<td>-8.8 U/day</td>
<td>=</td>
</tr>
<tr>
<td>Tsui et al., 2001 [19]</td>
<td>Parallel, 9 months</td>
<td>13 CSII</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DeVries et al., 2002 [20]</td>
<td>Parallel, 4 months</td>
<td>39 CSII</td>
<td>-0.84%</td>
<td>+0.96/ patient/week</td>
<td>-21.1%</td>
<td>-19 U/day</td>
<td>=</td>
</tr>
<tr>
<td>Retnakaran et al., 2004 [22]</td>
<td>Pooled analysis</td>
<td>139 MDII/CSII</td>
<td>-0.35%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoogma et al., 2005 [21]</td>
<td>Crossover, 6 months</td>
<td>272 MDII/CSII</td>
<td>-0.23%</td>
<td>mild: -6.1/ P-Y severe: -0.3/P-Y</td>
<td>-14 mg/dl</td>
<td>-26%</td>
<td>cutaneous complications: +0.18/P-Y</td>
</tr>
</tbody>
</table>

NS, not significant; NA, data not available; P-Y, patient-years; =, similar
CSII significantly reduced the risk of both mild and severe hypoglycaemia [21].

1.4. CSII vs MDI using both rapid- and long-acting insulin analogues

A comparison of CSII and MDI using both rapid- and long-acting insulin analogues is clearly of major interest [cf. below]. However, CSII remains the only treatment that can varying basal insulin delivery to meet anticipated changes in insulin needs. This is particularly important in patients who have variable lifestyles or variable insulin requirements, especially at night, because of the dawn phenomenon or the problem of recurrent nocturnal hypoglycaemia.

CSII is now widely used in type 1 diabetic patients. Although it can be used in type 2 diabetics who are poorly controlled with MDI, the available data are scarce on this topic. Four recent studies have compared CSII and MDI regimens in type 2 diabetic patients [24-27]. A rapid-acting insulin analogue was used with CSII in three trials, whereas the MDI regimen was based on either a rapid-acting insulin analogue and NPH or glargine, a rapid- and long-acting insulin analogue [26]. Two of these three studies concluded that CSII and MDI exert similar efficacy on HbA1c, with a drop of 0.6-1.7% compared with baseline [25, 26]. The third study, conducted in obese type 2 diabetic patients with a baseline HbA1c > 8.5%, suggested that CSII is associated with better glycaemic control [27]. Although more work is needed to determine precisely which type 2 diabetic patients would most benefit from insulin pump therapy, it is worth noting that two studies out of four have reported improvement in quality of life [25].

2. Basal-bolus regimens using insulin analogues vs the insulin pump

2.1. Pharmacokinetic studies

Rapid-acting analogues led to improved MDI treatment by allowing better postprandial glucose control compared with regular insulin, although improvement of HbA1c levels required a simultaneous increase in basal insulin doses [28]. More recently, the long-acting analogues glargine and detemir were assessed in comparison to previously available intermediate-acting NPH or long-acting ultralente, while prandial insulin was a fast-acting analogue. Dinnertime and bedtime glargine allowed better glucose control than four-times-daily NPH, as indicated by the lower HbA1c, lower incidence of mild hypoglycaemia and greater percentage of blood glucose values within target levels during a three-month study [29]. A randomized, controlled, four-month comparison between glargine and ultralente, with aspart insulin used as the prandial insulin, also showed the superiority of glargine on HbA1c, nocturnal blood glucose variability and hypoglycaemic episodes, mainly during the day [30]. In addition, when injected twice daily in combination with aspart insulin at mealtimes, detemir improved HbA1c levels, lowered fasting blood glucose and reduced the risk of minor hypoglycaemia, mainly at night, compared with twice-daily NPH in a randomized 16-week trial [31]. The higher predictability of insulin action with detemir, as already shown in a previous one-dose study involving children, adolescents and adults [32], was a probable contributor to the reduced occurrence of hypoglycaemia. Interestingly, the improvement in glucose control with detemir was not associated with any significant weight gain, unlike with NPH. Also, the daily doses of detemir and NPH were similar, suggesting better efficacy with detemir.

Reported improvements in glucose control with MDI using only analogues raise the question of whether or not CSII remains the unchallenged ‘gold-standard’ treatment. A pharmacological study reported by Bolli et al. back in 2000 compared the pharmacokinetics and pharmacodynamics of NPH, ultralente, glargine and CSII using lispro over 24 hours [2]. Whereas both NPH and ultralente showed a peak of insulin concentration and action followed by waning, both glargine and CSII had peakless profiles and a similar effect on glucose control that extended over the 24 hours. Interpatient variability of insulin action was also less with CSII and glargine than with NPH and ultralente. In addition, the onset of action was quicker, the end of action later and duration of action longer—and all significantly so—with CSII vs glargine [2].

2.2. Clinical studies

In recent years, several reported studies have investigated whether or not glargine and a rapid-acting analogue could work as well as CSII using rapid-acting analogues (Table 3). Out of six identified studies on this topic, only three were randomized prospective trials [33-35]. While one randomized study involving adults showed similar glucose control with the two treatment options [33], a study in children showed the superiority of CSII on HbA1c levels after 16 weeks, with significantly lower average insulin use [34]. In addition, in the latter study, preprandial (lunch and dinner) and bedtime blood glucose values were lower whereas prebreakfast values were similar [34], indicating better coverage with CSII. The most recently published short-term, randomized, crossover study in adults comparing CSII and MDI, including glargine, reported lower fructosamine levels and fewer daily glycaemic excursions with CSII, as assessed by continuous glucose monitoring [35]. Of the other three studies [36-38], two involving children showed improvement in glucose control only with CSII compared with previous therapy using NPH.
mean of daily differences (MODD), mean amplitude of glycaemic excursions (MAGE), and the number and mean duration of hypoglycaemic events showed no differences between the groups. In both groups, MAGE was negatively correlated with age and BMI, but positively correlated with the bolus-basal insulin ratio and frequency of hypoglycaemic events.

From these data, the type of insulin therapy does not appear to be a significant determinant of blood glucose variability in children.

As CSII has no clear superiority compared with MDI using only analogues in unselected groups of patients, the identification of patients who might derive greater benefit from CSII appears to be important. In a retrospective analysis of data from 17 diabetes outpatients clinics in Sweden, Fahlen et al. showed that switching from MDI without long-acting analogues to CSII or glargine improved metabolic control, with a more pronounced effect associated with CSII [42], particularly in patients with higher HbA1c levels and BMI at baseline. These predictive factors of better efficacy with CSII were also identified by Pickup et al. in a series of 30 type 1 diabetic

<table>
<thead>
<tr>
<th>Authors and references</th>
<th>N (type of patients)</th>
<th>Insulin for MDI</th>
<th>Insulin analogue for CSII</th>
<th>HbA1c (%) at end of trial</th>
<th>Other results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolli et al., 2004 [33]</td>
<td>57 (A) 6 months Randomized</td>
<td>Glargine + lispro</td>
<td>Lispro</td>
<td>CSII: 7.0 MDI: 7.2 (NS)</td>
<td>No differences in mean blood glucose, MAGE, hypoglycaemia</td>
</tr>
<tr>
<td>Doyle et al., 2004 [34]</td>
<td>32 (C) 16 weeks Randomized</td>
<td>Glargine + aspart</td>
<td>Aspart</td>
<td>CSII: 7.2 MDI: 8.1 (P &lt; 0.05)</td>
<td>CSII: lower blood glucose profile, insulin dose; No differences in hypoglycaemia, quality of life</td>
</tr>
<tr>
<td>Alemzadeh et al., 2004 [36]</td>
<td>40 (C) 1 year Case-control matched by age and gender</td>
<td>Glargine + lispro</td>
<td>Lispro</td>
<td>CSII: 8.4-7.8 (P &lt; 0.002) MDI: 8.5-8.2 (NS)</td>
<td>No difference in hypoglycaemia</td>
</tr>
<tr>
<td>Lepore et al., 2004 [38]</td>
<td>48 (A) 1 year Non-randomized</td>
<td>Glargine + lispro</td>
<td>Lispro</td>
<td>CSII: 8.0 MDI: 7.8 (NS)</td>
<td>No difference in hypoglycaemia; CSII: lower MAGE index</td>
</tr>
<tr>
<td>Hirsch et al., 2005 [35]</td>
<td>100 (A) 10 weeks Randomized (crossover)</td>
<td>Glargine + lispro</td>
<td>Aspart</td>
<td>CSII: 7.1 MDI: 7.3 (NS)</td>
<td>No difference in hypoglycaemia; CSII: lower fructosamine, 24-h blood glucose</td>
</tr>
<tr>
<td>Schiaffi ni et al., 2005 [37]</td>
<td>36 (C) 6-12 months Retrospective</td>
<td>Glargine + regular</td>
<td>Lispro or aspart</td>
<td>CSII: 8.5-7.6 (P &lt; 0.05) MDI: 8.9-8.3 (NS)</td>
<td></td>
</tr>
</tbody>
</table>

*A, adults; C, children/adolescents; NS, not significant

Table 3
Studies comparing continuous subcutaneous insulin infusion (CSII) using rapid-acting insulin analogues vs multiple daily insulin injections (MDI) using rapid- and long-acting analogues in type 1 diabetic patients

or ultralente [36,37], while the third study, in adults, reported significantly lower glucose excursions and glycaemic variability only with CSII [38].

The discrepancy between results in adults and children may be related to several factors. Previously reported noteworthy comparisons between glargine and NPH with MDI in children showed no clear benefits to average glucose control with glargine [39,40]. Insulin absorption of glargine after subcutaneous injection in this population probably warrants specific investigation as it may be quicker and, hence, may have a shorter duration of action. The question of whether or not more frequent snacks due to defective coverage by fast-acting analogue injections play a role in higher preprandial (lunch and dinner) glucose levels also needs to be considered. In addition, it should be noted that the occurrence of hypoglycaemia was not reduced by CSII in studies with children. One recent study analyzed glycaemic variability with continuous glucose monitoring in two groups of 14 children with similar HbA1c, and body mass index (BMI) values, treated by either CSII or MDI [41]. Mean blood glucose, absolute mean of daily differences (MODD), mean amplitude of glycaemic excursions (MAGE), and the number and mean duration of hypoglycaemic events showed no differences between the groups. In both groups, MAGE was negatively correlated with age and BMI, but positively correlated with the bolus-basal insulin ratio and frequency of hypoglycaemic events. From these data, the type of insulin therapy does not appear to be a significant determinant of blood glucose variability in children.

As CSII has no clear superiority compared with MDI using only analogues in unselected groups of patients, the identification of patients who might derive greater benefit from CSII appears to be important. In a retrospective analysis of data from 17 diabetes outpatients clinics in Sweden, Fahlen et al. showed that switching from MDI without long-acting analogues to CSII or glargine improved metabolic control, with a more pronounced effect associated with CSII [42], particularly in patients with higher HbA1c levels and BMI at baseline. These predictive factors of better efficacy with CSII were also identified by Pickup et al. in a series of 30 type 1 diabetic
3. Acute complications of insulin pump therapy

3.1. The 10-year DCCT: efficacy and side-effects with CSII

During its early years of clinical use, CSII was associated with an increased risk of acute metabolic complications such as diabetic ketoacidosis (DKA) [4]. As implemented in the Diabetes Control and Complications Trial (DCCT), intensive insulin therapy (CSII and MDII) was demonstrated to achieve near-normal glycaemic control, and to reduce the progression and development of long-term microvascular complications in type 1 diabetes. However, intensive insulin therapy was also associated with a threefold increase in the risk of severe hypoglycaemia and, to a lesser extent, with DKA [44]. More specifically, although the incidence of severe hypoglycaemic events was similar between the two types of intensive insulin therapy, the frequency of episodes resulting in coma or seizure was higher in the CSII cohort than in the MDII group. In addition, the rate of DKA during CSII was significantly 2.25 times more frequent than with MDII (Table 4). While CSII therapy is a more physiological insulin pathway, regimens using a high proportion of intermediate-acting insulin result in the largest subcutaneous depots compared with multiple rapid-acting insulin injections or CSII, thus theoretically prolonging their duration of action [45]. If insulin delivery is stopped because of a malfunction (such as catheter blockage or failure of insulin-pump delivery), then metabolic deterioration could occur more rapidly. This risk was confirmed when type 1 diabetic patients treated by CSII using human insulin experienced an inadvertent interruption of insulin delivery during the night [46].

Although the 1980s were the decade in which CSII therapy first began to be more widely used, there was also a degree of disappointment with their performance. A meta-analysis of studies published before 1993 reported a DKA odds ratio of 7.2 with CSII therapy compared with MDII [47]. The incidence of DKA episodes was high, with a mean of around 10 episodes per 100 patient-years. All of the studies were, however, conducted with human insulin. Other authors reported that, after an initial increase in the rate of DKA during the first year of therapy, the incidence decreased slightly, but significantly, and was reduced in parallel with increased physician experience and improved education of diabetic patients [48].

3.2. Clinical reality: the acute complication rate with CSII

In the most recent studies comparing CSII and MDI over a long period of time (more than 500 patient-months of follow-up) [22], the rates of DKA incidence have been lower than those previously reported, or similar to or lower than those observed with intensive MDI insulin therapy and, indeed, not as high as expected.

In contrast to the DCCT, the rate of severe hypoglycaemia reported in recent studies was lower in patients treated by CSII than in those treated by MDI. In a prospective study of 55 hypoglycaemia-prone type 1 diabetic patients who switched from MDI to CSII, the rate of severe hypoglycaemia was 84% and 81% lower after the first and the second year, respectively, of CSII. In addition, and unlike other stud-
ies, the insulin doses were carefully selected and were 15% lower with CSII, demonstrating a good balance between therapy goals and tools [11] (Fig. 2).

Finally, in a French observational study involving a large and representative population, endocrinologists observed that the incidences of severe hypoglycaemia and DKA in real life were similar to those reported in clinical studies with CSII therapy [49].

3.3. Hypoglycaemia and DKA with CSII using insulin analogues

Recent developments and improvements in pump technology have boosted the capacity of CSII insulin therapy to deliver specific boluses and basal rates that better simulate the physiological insulin response. The wide availability and efficacy of new rapid-acting insulin analogues have also increased CSII efficacy. Three studies have been conducted to analyze the risk–benefit ratio with the use of insulin analogues compared with regular human insulin with CSII. They all reported a significant improvement in HbA1c and, in one, there was a reduction in the hypoglycaemic event to < 2.2 mmol/l [15]. Another noteworthy observation was that no episode of severe hypoglycaemia or DKA was seen. The reduced rate of hypoglycaemia with the use of insulin analogues in an external pump can be explained by preservation of the physiological response to hypoglycaemia: the counter regulatory hormone response was assessed by the hypoglycaemic clamp method after three months of treatment with regular human or lispro insulin in 30 type 1 diabetic patients, and no difference in response was found between the two types of insulin treatment [50]. This suggests that the risk of severe hypoglycaemia can be potentially decreased by an enhanced counter regulatory response to hypoglycaemia and hepatic sensitivity to glucagon.

More recently, a pooled analysis of randomized controlled trials compared CSII and optimized MDI therapy using rapid-acting insulin analogues only [22]. For a total of 139 patients, corresponding to 596 patient-months of follow-up of the CSII group, insulin pump therapy was associated with better blood glucose control and no significant increase in hypoglycaemia risk. Insulin doses were significantly reduced when the data were pooled, and only one episode of DKA was reported in each of the two treatment groups. Compared with basal-bolus regimens using rapid- and long-acting insulin analogues, CSII appears to be superior, especially in paediatric populations. An improvement in HbA1c was also reported without an increase in severe hypoglycaemia incidence, which remained low and similar between the two treatment groups.

Insulin monomers appear to be absorbed 3.3 times faster than hexameric insulin [51]. Consequently, accidental interruption of CSII in patients using such analogues would result in more rapid decompensation of metabolic control. Two studies have explored this phenomenon. The first was an unpaired study, which was unable to demonstrate any difference between insulin analogues and human insulin when the pump was stopped [52]. In the second, crossover study, the type 1 diabetic patients experienced a more marked metabolic deterioration compared with regular insulin when the pump was experimentally stopped for 5 hours. Blood glucose levels were higher in the analogue group by the third hour, associated with a marked decrease in plasma insulin levels in the first hour. Deterioration of a similar magnitude was observed for plasma ketone bodies. However, when the pump was restarted at its basal rate and with an identical programme of additional boluses, metabolic restoration was achieved more rapidly in the analogue group than in the regular insulin group, confirming the extremely rapid action of insulin analogues [53].

On the basis of these findings, new recommendations were proposed for patients using insulin analogues with a pump to check especially for ketonuria or ketonaemia while fasting, at bedtime and on every occasion of unexplained hyperglycaemia > 250 mg/dl [54]. In addition, a new capillary method for detecting ketone bodies is now available and could lead to quicker detection of metabolic deterioration after pump stoppage. In one study of experimental insulin pump interruption, the time needed to diagnose ketosis was significantly shorter with capillary ketonaemia than with ketonuria, and the sensitivity for the detection of ketosis was greater with capillary ketonaemia (80.4% vs 63%) [55].

3.4. Balance between therapy objectives, goals and tools

It became necessary to reconsider the strong relationship between the rate of severe hypoglycaemia and the reduction in HbA1c reported in the DCCT, given the newer data from
studies of CSII. It is worthwhile noting that we did not observe
the exponential relationship between HbA1c and severe hypo-
glycaemia incidence described by the DCCT when HbA1c val-
ues and hypoglycaemia event rates reported in recent studies
were plotted as a graph (Fig. 3).

Physician experience has also increased, leading to a reduc-
tion in the risk of acute metabolic complications—a factor that
is crucial for the proper management of CSII therapy. Also,
insulin delivery is now safer with the use of more appropri-
ate insulin analogues, and the new external CSII pumps that
have disconnectable catheters are better tolerated by patients.
Metabolic deterioration can be detected more rapidly using
the new devices, which can also increase the frequency, accu-
racy and sensitivity of blood glucose determinations and
ketone-body tests, while the insulin profile can now be bet-
ter matched to a given patient’s needs.

Finally, with reasonable glycaemic control targets and ade-
quate patient education, there is no increased risk of acute
complications with CSII compared with MDI. Indeed, there
now appears to be an excellent balance between the twin
objectives of reducing the risk of acute metabolic complica-
tions while achieving better diabetes control.

4. Insulin pump in paediatric populations

Although CSII has been used in children for more than
20 years [56], the technique had not been widely used in most
countries until recently. In fact, European paediatricians were
early pioneers in the treatment of type 1 diabetic children,
able to achieve remission [57] and the disappearance of severe
hypoglycaemia in very young children [58], and in a high
proportion of children and adolescents [59]. Over the past
few years, reports of international clinical experience and
studies of CSII in type 1 diabetic children have increased
dramatically [60-63], bringing more knowledge and evi-
dence to support the use of CSII in the paediatric population.
Numerous studies, mostly non-randomized, were carried out
in paediatric patients who were switched from injections to
pump therapy, and showed that CSII is certainly feasible, well
accepted and effective in such a population, and can also be
managed safely across all age groups. HbA1c was improved
(mean reduction of 0.6%) or remained stable, the frequency
of hypoglycaemia was decreased and a better family quality
of life (more flexibility in everyday activities, less hypogly-
caemia, fewer injections) was reported among this population,
demonstrating the advantages of pump therapy in young chil-
dren (Table 5, Fig. 4) [58,64].

![Fig. 3. DCCT findings compared with recent studies of CSII therapy,
which show a lack of correlation between the reduction in HbA1c and the
incidence of severe hypoglycaemic events.](image)

<table>
<thead>
<tr>
<th>More physiological regimen</th>
<th>Adjustment of each premeal and snack insulin dose (boluses), and of nocturnal basal rates (in young children, nocturnal insulin needs are physiologically much lower than during the day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>More accurate</td>
<td>Insulin dose changes in smaller fractions (0.05 U, 0.1 U or 0.2 U)</td>
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<tr>
<td></td>
<td>Greater accuracy of low doses</td>
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<tr>
<td>More comfortable</td>
<td>Children: injection every 2 days vs 2/day</td>
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<tr>
<td></td>
<td>Parents: less anxiety (less hypoglycaemia)</td>
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<tr>
<td></td>
<td>Children and parents: flexibility of treatment in everyday life (at mealtimes, during sleep)</td>
</tr>
<tr>
<td>Easier management of</td>
<td>Common infectious illnesses</td>
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<tr>
<td></td>
<td>Episodes of hyperglycaemia with ketonuria</td>
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<tr>
<td></td>
<td>Food refusals</td>
</tr>
<tr>
<td>Patient preference</td>
<td>Preferred by more parents and children in randomized and non-randomized paediatric studies</td>
</tr>
</tbody>
</table>

The dawn phenomenon, reduction of hypoglycaemia and
improvement of hyperglycaemia are the most common indi-
cations for starting CSII therapy [65]. The superiority of
pump therapy over MDI in children has been inconsistently
seen in randomized controlled trials, with the pump achieving
better glycaemic control in one study [34], but not in others
[61,66]. A recent attempt to determine predictors of insulin
pump success in a cohort of youths just beginning pump
therapy [67] grouped the causes of pump discontinuation into
five main categories: major medical problems (DKA, insulin
omission); diabetes burnout; minor problems (infusion-site
issues); body image associated with wearing a pump; and
weight gain. The baseline HbA1c was not a predictive factor
of success or not and, after a mean follow-up of 3.8 years,
the patients who remained on pump therapy had significantly
lower HbA1c levels compared with those who discontinued
the therapy (8.4% vs 9.4%, \(P=0.01\)). Other factors associated
with pump discontinuation were gender, older age at diabetes diagnosis, advanced pubertal status, less monitoring of blood glucose and a higher rate of severe hypoglycaemic events in the year following the start of pump therapy. This analysis of the success or failure of CSII may explain the results observed in a recent study comparing CSII and MDI in ‘real life’ during a 3-year follow-up. CSII was found to be superior to MDI only in the first year of pump therapy, and not by the end of the follow-up [68]. An international consensus statement has recently been published that summarizes the indications for adolescent patients and offers specific recommendations [69].

Over the past 10 years, major advances in insulin pump therapy have facilitated their use in children: pumps are small and lightweight; they allow tiny increments in dosage of 0.05 or 0.1 U; and the cannula is shorter (6 mm in length) with no needle. Skin tolerance has considerably improved with the use of Teflon cannulae, which are also more convenient, allowing disconnection for baths or swimming. Furthermore, as discussed previously, short-acting analogues are easier to manage in pumps, especially in young children [70].

The limits of pump therapy are well known; the risk of DKA due to obstruction of catheters must be prevented by specific parent education. To further prevent such complications, the cannula should be removed every two [71] or three days [59], and ketone bodies need to be measured in the event of hyperglycaemia [54]. When the insulin pump was discontinued in one study, beta-hydroxybutyrate levels rose linearly by 0.2 mmol/l/h in children [72]. The proper education of parents and children, and supervision by a specialized paediatric diabetes team, are the keys to successful CSII therapy in young people. Under these conditions, CSII can be indicated for diabetic children and adolescents (Table 6). In some cases, its use may need to be discussed or delayed because of possible non-compliance with the diabetes regimen, insufficient daily monitoring of blood glucose, lack of contact with the paediatric team and/or psychiatric patients, parents or other instability in the family.

In the European PedPump Study (Round 2) of paediatric patients undergoing pump therapy under real-life conditions, 1086 children and adolescents from 30 centres in 17 countries were recruited. Their mean HbA1c was 8.0 ± 1.3%, with a mean pump therapy duration of 2 years, which was lower than that of 3805 type 1 diabetic children and adolescents unselected for insulin therapy (mean 8.6%) [73], but slightly higher than that in clinical trials of CSII (around 7.6%). How may these real-life outcomes be improved? Results of the recent Guard Control Study [74] suggest that sensor-augmented pumps (Paradigm RT®, Medtronic) could help in the realization of the full potential of pump therapy. The challenge in future will be to demonstrate the long-term benefits of pump therapy in type 1 diabetic children with the reduction of vascular complications.

<p>| Table 6 |</p>
<table>
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<tr>
<th>Possible medical indications for the use of insulin pumps in children</th>
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<tbody>
<tr>
<td>- High HbA1c</td>
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<tr>
<td>- Frequent and/or severe hypoglycaemia</td>
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<tr>
<td>- Blood glucose instability (especially in young children)</td>
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<tr>
<td>- At the onset of diabetes in neonates and very young children</td>
</tr>
<tr>
<td>- Dawn phenomenon</td>
</tr>
<tr>
<td>- Pain with or phobia to insulin injections</td>
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<tr>
<td>- Failed multiple injection therapy</td>
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5. Insulin pump during pregnancy

Managing preexisting diabetes during pregnancy presents a significant challenge to diabetologists, obstetricians and paediatricians. It has long been recognized that maintaining maternal glucose levels within normal physiological limits provides the best maternal and perinatal outcomes in pregnancy complicated by diabetes [75]. In such patients, medical treatment and counselling must be provided during the preconception period to achieve the normal glycaemic control needed to avoid poor fetal outcomes. Prepregnancy care is associated with improved glycaemic control in early pregnancy and with significant reductions in adverse pregnancy outcomes (malformations, stillbirth and neonatal death) and very premature delivery. However, prepregnancy care has no impact on glycaemic control in later pregnancy, and fails to reduce the risks of macrosomia and preeclampsia [76].

In addition to frequent monitoring of maternal capillary glucose levels and an appropriate diet, an individualized regimen of insulin treatment is an important part of the therapeutic regimen. Insulin requirements vary during pregnancy, and many patients may experience a decline in insulin requirements between weeks 8 and 12 of pregnancy. This may be due to overinsulinization soon after pregnancy confirmation, as well as a decline in progesterone secretion towards the end of the first trimester—which occurs overnight. Insulin requirements subsequently increase as the pregnancy progresses [77].

Since even small variations in glycaemic control can affect fetal health, the use of CSII via an insulin pump is a useful option for many patients. Ideally, insulin pump therapy should be initiated prior to pregnancy to allow glucose control to become normalized, thereby reducing the risk of spontaneous abortion and fetal malformations. Nevertheless, few studies have been published over the past decade describing the use of insulin pumps in pregnancy complicated by diabetes.

5.1. Advantages and disadvantages of CSII during pregnancy

The advantages and disadvantages of insulin pump therapy during pregnancy are, in general, similar to those for non-pregnant patients, but there are some specific features. CSII provides a pattern of insulin release that more closely resembles physiological insulin production. Programmable bolus-dosing using square-wave boluses reduces the risk of glucose excursions and hyperglycaemia. This is particularly interesting as gastric emptying is delayed in normal pregnancy. Such a physiological change combined with gastrointestinal paralysis may produce a mismatch between the onset of action of rapid-acting insulin taken with a meal and the hyperglycaemia peak several hours later. In addition, the patient’s ability to control the overnight basal infusion rate may help to prevent night-time hypoglycaemia and automatically increase the basal rate as morning approaches to reduce the dawn phenomenon.

Insulin pump use requires a high level of patient vigilance and commitment—and even more so during pregnancy. Patients on CSII must check their capillary glucose levels eight to 10 times every day. This, however, is not a disadvantage, as all patients with pregnancy complicated by diabetes must follow a strict SMBG (self-monitoring of blood glucose) schedule. During the third trimester, increased levels of human placental lactogen, prolactin, cortisol and progesterone create a diabetogenic situation. The likelihood of ketoacidosis developing is, therefore, significantly greater than in the non-pregnant patient.

During pregnancy, women have an increased risk of developing infections, sometimes at the pump insertion site. To reduce this risk, patients are advised to change their pump catheter every 24 to 48 hours. The abdominal wall should be avoided as an infusion site during pregnancy because insulin absorption becomes unpredictable as the abdominal tissue thins with the progression of pregnancy. For this reason, it is better to choose alternate sites.

CSII is useful during delivery for maintaining normoglycaemia. It has been shown that maternal and neonatal glucose levels have an inverse relationship in pregnancy complicated by diabetes. Maternal hyperglycaemia, especially during labour and delivery, overstimulates the fetal pancreas to secrete excess insulin, leading to neonatal hypoglycaemia [78]. In addition, insulin requirements decrease in the postpartum period, and basal infusion and bolus doses often need to be decreased to prevent hypoglycaemia. Also, breastfeeding women are more prone to hypoglycaemia.

Nevertheless, even if glycaemic control is comparable to that with MDI, pregnant women often prefer CSII as it presents several advantages. These include easier treatment of morning sickness and hyperemesis gravidarum, fewer glycaemic excursions and hypoglycaemic events, easier treatment of the dawn phenomenon and improved management in the post-partum period, when insulin requirements may fluctuate. In general, the greater flexibility of CSII leads to better compliance and an improved quality of life for patients during and after pregnancy.

5.2. Experience with CSII

Given the advantages of CSII in decreasing hypoglycaemia and postprandial hyperglycaemia, it is logical to assume that CSII would also be beneficial for pregnant women with diabetes. Published experience of the insulin pump has demonstrated that this type of therapy can achieve glycaemic control comparable to that obtained with multiple-dose insulin injection therapy [79]. Indeed, one study has noted that insulin pump therapy initiated during pregnancy did not lead to deteriora-
tion of glycaemic control, but was associated with maternal and perinatal outcomes and healthcare costs comparable to those for women who were already using the pump before pregnancy or who received MDI. In this study, women who initiated pump therapy during pregnancy were highly likely to continue with the pump after delivery and to maintain better glucose control than patients remaining on MDI [80].

More recently, another study has confirmed that maternal and perinatal outcomes are comparable in patients treated with the insulin pump and CSII compared with conventional insulin therapy on the basis of metabolic control. In patients belonging to a higher White’s class and with more unstable glycaemia, the group using the insulin pump nevertheless achieved metabolic control and outcomes comparable to those of women of a lower White’s class and more stable glycaemic values. This study suggests that insulin pump therapy is useful in problematic and complicated cases [81], and the results are consistent with those reported by French researchers [82].

For women with diabetes who plan to become pregnant, excellent glucose control is necessary to reduce the risks of spontaneous abortion and fetal malformations. Insulin administration through the use of insulin pump therapy could, therefore, prove to be highly useful. In addition, CSII may be used both before and during pregnancy in more complicated patients, such as in those whom conventional intensive insulin treatment fails to achieve good metabolic control, especially as analogues are now being used during pregnancy [83].

Considerable clinical experience supported by a limited number of prospective, randomized trials has demonstrated that insulin pump therapy can be safely used during pregnancy. It can improve maternal glucose control and achieve better perinatal outcomes. However, insulin pump therapy requires that the patient be highly motivated and compliant with the regimen.

6. CSII in hospitalized patients

Hyperglycaemia or deterioration of glucose control in diabetes due to acute illness is frequently observed in hospitalized patients. Considered a physiological response to inflammation, it has now been shown to be an independent factor of morbidity-mortality in critically ill patients [84].

Glycaemia near-normalization essentially using intravenous intensive insulin (IVII) therapy significantly improves mortality and morbidity in intensive care unit (ICU) patients with several critical illnesses such as cardiac or infectious diseases. This improvement appears to be due to neutralization of deleterious hyperglycaemia effects rather than to the specific action of insulin on the inflammatory response (Fig. 5) [85].

No data are available from clinical trials of aggressive inpatient glucose control outside the ICU. The American College of Endocrinology recommends a glucose target of 5.5 mmol/l before meals and a postprandial glycaemia < 9.9 mmol/l for patients not in critical care.

In the ICU, insulin is usually administered by intravenous continuous insulin infusion (IVCI). Outside of critical care, sliding scales and regular insulin are often used. This strategy may be inappropriate by itself as basal insulin is often necessary in such patients, and anticipatory strategies for dosing with insulin result in superior control. Several regimens, involving basal (intermediate- or long-acting) insulin with rapid-acting analogues (lispro, aspart or glulisine) before meals, have been proposed.

In hospitalized patients, however, insulin requirements are affected by a number of factors on a day-to-day basis, such as variations in illness severity and medications (glucocorticoids, pressor drugs). Patients’ diets are often unpredictable as a result of tests, procedures, meal interruptions, medication schedules or simply anorexia. The use of long-lasting analogues is, therefore, difficult. However, CSII allows rates to be adjusted at any time, although intravenous infusion may be difficult to manage outside of critical-care settings. CSII external pumps are now more user-friendly and offer different features such as preprogrammable basal rates, bolus size or alarms to facilitate their handling and management. We have nonetheless to bear in mind that medical care, whatever treatment is used, remains the responsibility of the unit where the patient is hospitalized. This is especially true for diabetic patients treated by CSII and hospitalized in a non-diabetology unit.

Some studies have shown comparable efficacy between CSII and IVCI during uncomplicated ketoacidosis [86] and
glycaemic deterioration due to acute illness in type 2 diabetes [87]. Intravenous and subcutaneous infusions were similar in their rapid control of hyperglycaemia in such patients, and in the speed with which they brought about improvement in mean glycaemia levels (Figs. 6 and 7) [87]. If confirmed, the results of these studies would allow CSII and rapid-acting analogues to be used as an alternative to IVCI for rapidly improving blood glucose levels in hospitalized diabetic patients.

as new modes of insulin therapy such as basal-bolus MDI regimens using insulin analogues, intraperitoneal insulin infusion using implantable pumps, and islet or pancreas grafts have been developed. Also, there is now a growing body of experience as a result of the increased use of CSII in France (due to an official decree [89, 90] and to increased safety conditions of use [91]) and in other countries.

7.1. Long-term indications

As CSII remains more expensive than basal-bolus regimens using analogues and pens, its indications need to be limited to those showing clear proven benefit over MDI [see Efficacy of external insulin pump treatment in glycaemic control]. CSII may also be considered when other intensified insulin regimens fail to achieve adequate glycaemic control.

7.1.1. Elevated HbA1c with MDI

The precise target HbA1c threshold value for initiating pump therapy is as yet not fully confirmed, but it can be set at > 7.0%. In fact, recent studies of pooled results of randomized controlled trials have shown that the fall in HbA1c is proportional to initial HbA1c levels with MDI, which means that patients with high HbA1c values will benefit more from CSII. HbA1c will improve by about 2% in patients with initial levels at 10% compared with only around 0.5% in those with initial HbA1c levels at 7.0%.

7.1.2. Recurrent hypoglycaemia (severe or non-severe)

In general, two randomized trials in non-selected patients using regular insulin have shown a lower frequency of mild and moderate hypoglycaemia in CSII-treated patients compared with MDI [9,10]. However, these results were not confirmed when CSII treatment with analogues was compared with basal-bolus regimens using long- and rapid-acting analogues (Table 3). However, in hypoglycaemia-prone patients, one study demonstrated that CSII can significantly reduce the frequency of severe hypoglycaemic events [11]. Distribution of severe hypoglycaemia in the type 1 diabetic population is highly skewed, with about 5% of patients having 70% of all episodes, making these 5% the minimum target group. Indications may be summarized as follows:

- failure of other insulin therapies to maintain HbA1c targets (<7.0%) without the occurrence of disabling or frequent symptomatic or asymptomatic hypoglycaemic events (>4 per week);
- incidence of ≥1 episode(s) per year of unexplained severe hypoglycaemia.

7.1.3. Marked same-day or between-day variability in glucose

The improvement in glucose control achieved by CSII appears to be related to HbA1c and blood glucose variability
with MDI. Pump therapy is most effective in those who are least controlled by MDI [43]. CSII with analogues allows better insulin absorption predictability and reproducibility (with a decreased standard deviation of mean blood glucose of 11 mg/dl, 21.1% or 14 mg/dl as reported by Hanaire-Broutin et al., DeVries et al. and Hoogma et al., respectively [18,20,21].

7.1.4. Variability of insulin requirements

Compared with injections, the main advantages of CSII include the ability to programme several basal rates, to change the basal rate at any time and to administer boluses when necessary. Variability of insulin requirements may arise from endogenous and/or exogenous causes.

Endogenous causes: The dawn phenomenon—wind glucose levels >8.0-9.0 mmol/l (140-160 mg/dl) in the morning, but good glycaemia at bedtime and no nocturnal hypoglycaemia—is considered a good indication as the basal infusion rate can be preset to increase during the dawn hours.

Exogenous causes: For shift workers, business travellers or workers in a safety-sensitive job, insulin pumps may provide greater lifestyle flexibility in terms of meal boluses and travel. Transient modifications of the basal rate can eliminate the need for snacks during and following physical activity [92].

7.1.5. More marginal indications

CSII use has not been compared with other treatments in ‘high levels of proof’ papers because of the small number of cases, but the results based on its theoretical advantages and from the experience of medical teams include patients with:

- Allergy to insulin: CSII represents the ‘gold standard’ for treating insulin allergy. CSII induces desensitization with proven efficacy in patients with type 1 [93] or type 2 diabetes [94] who are allergic to all types of insulin or to only specific types [95];
  - Lipoatrophic diabetes [96];
  - Lipoatrophic areas: CSII efficacy may be increased by adding dexamethasone to the insulin in the pump reservoir [author’s personal experience];
  - Very low insulin requirements (<20 U/d): CSII can achieve basal rates as low as 0.1 U/h and is capable of making tiny basal rate and bolus adjustments [97].

7.1.6. Type 2 diabetes specificities

The use of external pumps in patients with type 2 diabetes is much more recent than in type 1 diabetics [25-27]. In spite of this, it has been proposed by the French Journal Officiel as an alternative therapy in type 2 diabetic patients not controlled by MDI. The use of external pumps in type 2 diabetics has, therefore, become an accepted therapeutic option in countries where it is possible.

Nevertheless, specific points need to be highlighted:

- patients with type 2 diabetes requiring pump treatment may be obese and, therefore, require higher insulin doses. Hypoglycaemia is less frequent in these patients. Patients in whom endogenous insulin secretion is still present are also less ketosis-prone and unstable;
  - oral antidiabetic agents may be concomitantly prescribed, allowing insulin dose-reduction and controlled weight gain, as described in type 1 diabetic patients [98]. Using only simple manipulation of CSII in long-term combinations of metformin plus sulphonylurea appears to be effective and well tolerated in type 2 diabetes [24];
  - patients with type 2 diabetes are generally older and may even be frail. A patient-education programme should then be tailored to their particular needs.

Specific indications for patients with type 2 diabetes include:

- very high insulin requirements: CSII allows a more predictable insulin absorption rate. U500 human insulin instead of U100 insulin analogues may be used, and has proven safety and efficacy in cases of pregnancy [99] and insulin resistance [100-102];
  - diabetes with severe insulin resistance [103]: If this is not linked to SC insulin resistance, CSII may represent a better option than MDI [104]. CSII has the theoretical advantages of allowing a smaller volume of administered insulin and the capacity to deliver higher doses;
    - if CSII fails, then continuous intraperitoneal (IP) insulin infusion with external or implanted pumps [105] may be used, except in cases where insulin resistance is due to circulating antibodies as IP insulin is more immunogenic.

7.1.7. Other types of diabetes

To our knowledge, there is no literature currently available on indications of CSII in any other types of diabetes. However, it is likely that CSII will have the same indications, essentially based on metabolic control, in such patients as those developed for patients with type 1 or type 2 diabetes, provided that specific adjustments are made to account for the nosological origin of these types of diabetes.

7.2. Short-term indications

Although these may be applicable to both type 1 and type 2 diabetic patients, our knowledge and experience have mostly involved type 1 diabetics.

7.2.1. Acute situations

In certain circumstances, glycaemic control needs to be as tight as possible to improve the prognosis of an acute event: in such cases, CSII with analogues (which allow rapid absorption and adjustments) has to be weighed against IV
insulin infusion in terms of its potential benefit of increased autonomy, but with the potential risk of misuse leading to dangerous situations. Nevertheless, it is reasonable to use CSII in patients who are:

- in diabetology units for the treatment of mild ketoacidosis or acute hyperglycaemia as, in such cases, CSII has proved to be as effective as IV insulin, but with fewer side-effects [see Part 6];
- in diabetology units for acute infections or hypertriglyceridaemia >100 mg/dl;
- in hospital for other acute reasons, but only if the patient is conscious and educated on the use of CSII. Remember, however, that medical care remains the responsibility of the unit where the patient is hospitalized;
- undergoing enteral alimentation.

7.2.2. Transient indications of CSII
These include:

- severe painful neuropathy;
- chronic infections, foot ulcers and all wound-healing cicatrization situations;
- pregnancy or the intention to become pregnant;
- in women with type 1 diabetes, the rapid-acting insulin analogues aspart and lispro can now be used during pregnancy. Patients intending to become pregnant or who are already pregnant, but who are unable to achieve tight glucose control with optimized insulin injection therapy should be considered for CSII treatment. This indication of CSII vs MDI is still under debate due to the risk of ketoacidosis. For this reason, the decision has to be carefully weighed and individualized for each given patient in her own usual environment, and by each medical and paramedical team [81,82],

- More specifically, in cases of pregnancy complicated by type 2 diabetes or gestational diabetes (a condition that is growing in frequency), patient education is again a key issue, especially for those from a poor socioeconomic environment; in such patients, the old medical maxim ‘Primum non nocere’ needs to be borne in mind. In one study, CSII compared with MDI in pregnancy complicated by type 2 or gestational diabetes was equivalent in terms of safety and efficacy, but associated with higher doses and weight gain [106]. U500 insulin analogues may be used if insulin requirements are very high [99];
- induction of ‘remission’ of insulin dependency:

- Normoglycaemia induced by CSII [107,108] may transiently restore the first phase of insulin secretion induced by glucose in type 2 diabetes, as previously reported with IV insulin infused by an artificial pancreas [109]. Remission rates were 47.1% and 42.3% in the first and second years, respectively [108]. Factors predictive of success included: shorter history of diabetes; lower postprandial blood glucose levels; higher BMI; and fewer chronic diabetic complications,

- However, larger, randomized studies are necessary before any conclusions can be drawn regarding the use of CSII and its true benefits in this indication.

7.3. Contraindications
These are divided into absolute or relative contraindications, according to the patient, or the patient’s environment or pump.

7.3.1. Absolute contraindications
Due to the patient:
- severe psychiatric disorders;
- rapidly progressive ischaemic or proliferative retinopathy, where any treatment rapidly normalizing glycaemic control before photocoagulation by laser is contraindicated;

Due to the patient’s environment or pump:
- a non-educated medical environment;
- living with extreme circumstances of either heat or cold for professional or personal reasons, as exposure of the pump and reservoir to direct heat such as from the sun, indirect heat such as hot summers or hot professional atmospheres can lead to insulin inactivation. The same applies to very cold circumstances;
- underwater diving (as a sport or profession);
- exposure to high electromagnetic fields (MNR), which may trigger insulin overdelivery.

7.3.2. Relative contraindications
Due to the patient:
- poor compliance with the current management of treatment, including frequent visits to the diabetology centre, monitoring of glycaemia and ketosis testing (see Insulin pumps: medicolegal aspects in France). This contraindication needs to be discussed with each patient, as psychiatric and poorly compliant patients have been shown to benefit from CSII when closely managed by a specialist multidisciplinary service [110];
- patient reluctance, as patient acceptance and motivation are mandatory for effective CSII therapy. Switching to MDI may be proposed in some cases to encourage acceptance;
- poor local hygiene and the presence of Staphylococcus [4];
- end-stage renal failure, because of the risk of acidosis;
- sensory (particularly visual) or gestural impairment (physically handicapped). In these situations, the patient may have difficulty with the technical aspects of pump management, and be more dependent on his/her entourage or medical assistance;

Due to the patient’s environment, insulin or pump:
- living with extreme circumstances of heat or cold for professional or personal reasons, as exposure of the pump and reservoir to direct heat such as from the sun, indirect
heat such as hot summers, or hot professional atmospheres can lead to insulin inactivation. The same applies to very cold circumstances.

In these relative contraindications, the benefit–risk ratio of CSII therapy has to be individualized. In such cases, the indication or contraindication is best discussed in a specialized diabetology unit with experienced medical and paramedical caregivers, and with further multidisciplinary opinions in some cases.

7.4. Ongoing evaluation of indications or contraindications

The patient and the doctor may change, and the technology may move forward. Transient indications may become permanent, while good indications may reveal bad indications, or contraindications may arise. These possibilities emphasize the need for an ongoing evaluation of the indications and contraindications at each patient visit to the diabetologist—with the help of a specialist unit if necessary. Annual evaluation of indications or contraindications by an independent multidisciplinary paramedical and medical team, specializing in diabetology and pump treatment, is mandatory for minimizing the risk of CSII failure through a complete analysis of the benefits, risks and cost-effectiveness of the treatment. It involves a multidisciplinary consultation with the initiating centres, preferably with the participation of the attending diabetologist. This meeting mainly sets out to review the continuation of treatment (or the need to stop it) while also checking that the theoretical knowledge and lessons from the initial intensive training have been retained. For example, it is admitted by the majority of diabetologists that a patient undergoing pump therapy who has had more than two episodes of diabetic ketoacidosis or more than two episodes of severe hypoglycaemia per year (except in cases of pump therapy for a once-a-month occurrence of severe hypoglycaemia) should be taken off the pump. Recurrent skin reactions, such as frequent abscesses or milder infectious reactions at the catheter site, require reinforcement of hygiene education and tests for the presence of Staphylococcus. Local lipohypertrophic reactions at the infusion site again require further education to encourage changing the infusion site more often.

Most conventional indications or contraindications of CSII treatment are now relatively well established. However, difficult situations (marginal indications, relative contraindications) emphasize the importance of an experienced medical and paramedical diabetology team. Along with patient compliance, this is the most important factor for successful treatment with CSII. The evaluation should also include the medical and paramedical teams, and the diabetology consultant, with a requirement for ongoing training. As part of this review procedure, paramedical guidelines have been laid out that emphasize reviewing the patient’s knowledgeability through a generally recognized checklist [111].

8. The future of CSII therapy: closed and hybrid loops

At present, it is still proving difficult to achieve normalization of the glycaemic profile in diabetic patients, despite increasingly advanced treatment options such as pumps and insulin analogues. Ultimately, closing the loop with more physiological insulin regimens will lead to more durable normoglycaemia, better prevention of diabetes complications and an improved quality of life for the patient.

8.1. The ‘loop’ concept

Closing the loop means developing an artificial beta-cell system comprising three elements: a continuous insulin-delivery system; a continuous glucose-monitoring system; and a control system that is capable of interpreting blood glucose levels and/or variations and adjusting the dose of insulin administered with the use of an algorithm [112, 113]. While the objective is a completely autonomous closed loop, the steps leading to it involve an open loop and an open/closed hybrid loop. The open loop needs no autonomous control system, as it is the patient who manages insulin delivery on the basis of blood glucose data provided by the sensor. The closed loop, on the other hand, needs a control algorithm to adjust the dose of insulin administered according to blood glucose levels.

There are several difficulties, one of which is due to the physiological difference between variations in interstitial glucose and plasma glucose levels [114]. The system has to take into account the cumulative time required for various functions: the time needed for the sensor to measure the glucose; the time taken by SC absorption of insulin; and the irreducible time required for insulin action. The total time, which can amount to ½ to ¾ hours, creates a certain inertia depending on the speed of changes in plasma glucose concentrations [115]. Another difficulty arises from controlling the rapid variations in blood glucose, especially after meals, if the system is unable to reproduce the cephalic-phase peak of physiological insulin secretion. This is why a ‘mixed’ open/closed concept is being developed [116, 117] that makes hybrid use of the algorithm: autonomous operation (closed loop) during the fasting and interprandial periods; and manual, non-autonomous operation of the prandial bolus programmed by the patient according to meal time or composition (open loop).

Depending on the body sites used for measuring glucose and delivering insulin [115], an SC–SC, IV–IP, IV–SC or IV–IV approach may be used. The SC approach offers better accessibility and easier use as a result of experience acquired.
over the last few years. This review looks at the SC–SC external system, comprising an external insulin pump to deliver insulin into the SC tissue, with an SC glucose sensor that measures the glucose in the interstitial liquid.

8.2. The external pump as a continuous insulin-administration system

The portable pump is a gold-standard component of a loop. Its efficacy has been demonstrated, and is linked to its continuous administration of insulin and adaptable basal rate. The design of the pump allows considerable flexibility of use, and the SC route is easy to use. The introduction of rapid-acting insulin analogues has provided more immediate action than regular insulin [15,17,118]. There remain, however, limitations related to the administration route, which is not particularly physiological. Insulin action reproducibility is also variable in spite of delivery of the same dose [2].

8.3. The glucose-measuring system

To be a component in the loop, the glucose-measuring system needs to meet several prerequisites: the data need to be continuous or nearly so and in real time; calibration should be easy and efficient; and given the blood glucose variations, the glucose measurement has be sufficiently accurate, and the time of sensor response sufficiently reduced, to produce a suitable therapeutic response. The system also needs to be as small as possible to be acceptable and well tolerated by the patient.

Minimally invasive techniques that involve contact between the sensory mechanism and the tissue or fluid in which glucose concentration is measured are also candidates for the loop, as they can provide continuous glucose readings. Current systems use an electroenzymatic sensor: the Guardian® RT system, for example, displays glucose readings every 5 minutes [119]. This device can be connected to a microdialysis system such as GlucoDay® [120]. Two other systems are expected shortly in the marketplace: the DexCom STS™ [121], which has already received FDA approval; and the Navigator™ [122], which is still undergoing a review of its technical features. Real-time continuous glucose measurement has been validated [74,123] in diabetic patients to facilitate treatment adjustments, improve HbA1c, and reduce the incidence of hyperglycaemia without increasing the severity of hypoglycaemia. The randomized Guard Control study [74] showed that, in type 1 diabetic patients over a three-month period, the continuous or intermittent use of the Guardian® RT system brought about significant improvement in glycaemic control compared with traditional monitoring of capillary blood glucose levels. A recent review summarized how best to use the Guardian system in clinical practice to obtain the available data, and to evaluate and modify the treatment as needed. A base of four records of 3 days for each patient appears to be the optimal use [124].

8.4. Open-loop studies

In an open loop, the patient has to first be given glycaemic targets, the blood glucose correction factor and the amount of insulin needed for ingestion of 10 g of carbohydrates. The patient then has to learn how to adjust insulin rates according to blood sugar trends revealed by the sensor, and how to do a retrospective analysis of the data. Two open-loop studies lasting for six months involved the use of the Paradigm® REAL-Time integrated insulin pump system with continuous glucose-monitoring. The patients were randomized into two parallel groups, one using a traditional pump and SMBG, and the other using the Paradigm® system. The US STAR 1 study is now finished—it involved a population of patients with uncontrolled diabetes despite the use of insulin external pumps. The French multicenter Real Trend Study, the first and only European SC–SC open-loop study, is currently underway in uncontrolled diabetic patients using an analogue-based basal-bolus regimen. The main criterion is the change in HbA1c, while the secondary criteria are the glycaemic mean, blood glucose AUC (area under the curve), total insulin dose, basal-bolus proportion and patient satisfaction.

8.5. The control system for closed or hybrid loops

The most commonly studied algorithms are the model predictive control, or MPC, and the proportional integrative derivative model, or PID. The MPC is a mathematical predictive/adaptive model that sets out to reproduce patient glycoregulation. Eight individual parameters are entered at the start, and the system ‘learns’ for 3 or 4 hours. The system then subsequently predicts glycaemic excursions and suggests a supplemental insulin dose that will bring blood glucose back to a value of around 100 mg/dl. The next step sees the system distinguishing between measured and predicted glucose values, then adapting and recalculating the insulin dose. These steps repeat themselves, and the system is self-learning. The multicenter European ADICOL (Advanced Insulin Infusion using a Control Loop) project used the algorithm in semi-closed or hybrid clinical studies [125]. The study approach was IV–SC (IV pathway for glucose measurement combined with SC pathway for insulin delivery) followed by SC-simulated SC (which meant delaying the IV glucose measurement for 30 minutes to replicate an SC glucose-measuring site) at the end of the study. Results showed that the system was able to achieve normoglycaemia during fasting periods, with no hypoglycaemia and with a gradual reduction in blood glucose standard deviation.

The PID model aims to mimic the dual-phase model of physiological insulin secretion [126]. The algorithm, developed by Medtronic, has been used in closed-loop US studies [127] that showed good blood glucose control at night and during interprandial periods, but poor control of postprandial
excursions. Hybrid-loop tests, on the other hand, showed better postprandial control.

The open-loop stage can be ambulatory, but the use of the continuous glucose measurement system remains intuitive. Its metabolic efficacy should soon be revealed in detail through the results of the STAR 1 and Real Trend studies. The hybrid-loop step, which may be the stepping-stone to a closed loop, is currently under clinical investigation in which the system operates autonomously during interprandial periods, but needs to be notified of meals to provide optimal postprandial control. Clinical research is producing increasingly more efficient systems, sometimes through different approaches. Indeed, the external open loop or hybrid loop may soon comprise a patch pump linked up to a percutaneous sensor.

9. Insulin pumps: medicolegal aspects in France

Insulin pump therapy using fast-acting insulin analogues is now considered the gold-standard intensified insulin therapy. For this reason, pump-related legislation has developed since pump therapy was first registered on the TIPS (Tarification Interministérielle des Produits de Santé, the official French system of tariffs for healthcare products) in 2000. Since then, the conditions that may be reimbursed have been redefined along with a new, redrafted list of refundable products, the LPPR (Liste des Produits et des Prestations Remboursables, replacing the TIPS).

9.1. Background

The management of patients with portable pumps was unclear until 2000. Before then, such patients were managed by organizations that had signed an agreement with the French national healthcare system (Assurance Maladie). From 1987 onwards, it was incorporated into the hospitals’ general budget (although management by organizations remained possible). This situation, however, resulted in major inequalities by not allowing equal patient access to the technology across the nation and did not contribute to the development of continuous insulin infusion therapy. It was finally in 2000 that the ministry decided to register insulin pumps on the same TIPS scale as other pumps and with the same conditions of reimbursement (published in the French Journal Officiel, 10 November 2000) [89].

The new law, with its accompanying recommendations, brought about a radical change in how the treatment was managed. It set out the roles of the initiating centres and service providers authorized to invoice the Assurance Maladie for three types of packages: two of the packages supplied the equipment (pump purchase or rental and the provision of consumables); and one monthly package included technical stand-by support and medical-device vigilance.

9.2. Improvements arising from the new nomenclature

The nomenclature for insulin pumps came into effect on 26 August 2006, with the French government’s decree of 16 July 2006, published in the Journal Officiel. The decree concerned the change in nomenclature for treatment by portable, programmable external insulin pumps, as registered in the first chapter under the first heading of the list of reimbursable products and services provided for under article L. 165-1 of the French social security code [90]. The decree was the result of an opinion handed down by the CEPP (the French Commission for the Evaluation of Products and Services) on 17 November 2004 and 8 March 2006, following two years of work by a multidisciplinary technical commission comprising healthcare professionals, patients’ associations and representatives of supervisory authorities. The decree was supplemented by a specific list of tariffs, rendered by the CEPS (the French Economic Commission for Healthcare Services) on the basis of CEPP technical and medical proposals. The decree includes two clear improvements over the previous law, allowing easier comprehension by users and stricter control by the paying organization.

9.2.1. A genuine set of specifications for all partners

The law lays down a set of specifications for the three main partners involved in the treatment: healthcare professionals; manufacturers; and service providers (Table 7). Service providers are recognized under the new law and their tasks

| Table 7 |

| Redraft of the LPPR (French list of refundable products) for insulin pumps: specific actions and more clearly defined roles for participants |

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<th>Four complementary partners</th>
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<td>Primary-care physician</td>
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<td>Referral centre</td>
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<td>Manufacturer</td>
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<td>Service provider</td>
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<th>Definition of roles</th>
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<td>Clinical initiation</td>
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<td>Technical training</td>
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<td>Medical follow-up</td>
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<td>Home-based technical monitoring</td>
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<td>Pump manufacture and customer service</td>
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<th>Prescription and choice of pump</th>
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<td>Physician</td>
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<th>Initial patient clinical education and annual treatment evaluation</th>
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<td>Centre and service provider</td>
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<th>Provision of material and technical follow-up</th>
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<th>Physician and nursing team training on pump materials</th>
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<td>Manufacturer or service provider</td>
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<th>Service-provider training</th>
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<td>Centre and manufacturer</td>
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clearly defined. For all partners, in addition to a description of specific responsibilities, there is also the notion of ongoing evaluation of the material, the service and patient education.

9.2.2. Technical education recognized and funded

A key point of the law is financial recognition of patient technical education, which includes induction and ongoing training, both of which are clearly defined. A specific budget is allocated for each stage of training, with a lump-sum of 403 euros (including tax) paid out for the induction training; ongoing training is included in a monthly lump-sum payment of 59.50 euros (including tax). Such recognition of “therapeutic technical education” is a fundamental step as previously:

- neither TIPS nor LPPR included reimbursement for patient education;
- and no general patient therapy-related education was reimbursed in France, despite concerted efforts by physician and patient associations to do so.

However, this provision of funds for patients’ technical education involves only service providers, not hospitals, as only these providers are authorized to receive LPPR reimbursements. Nevertheless, it represents a major step forward as it spells out the content and cost of patient education while also stating that the initiating centres may also provide such education.

9.3. Specifications

9.3.1. Medical management

The specifications laid out in the decree define the medical conditions that require patient management. Notably, it provides for treatment initiation to be carried out in a so-called ‘initiating centre’, for which the minimum competencies are spelled out in the decree, and include: at least two physicians specialized in endocrinology and/or qualified in diabetology and nutrition; an organized system for emergency calls; a multidisciplinary team involved in a structured education programme for the pumps; the need for basic clinical experience with the therapy; proximity to a centre for treating metabolic emergencies; and obligatory attendance at least once a year to an ongoing medical training course on pumps.

The initiating centre has three main responsibilities: treatment initiation; evaluation; and caregiver training. The decree stresses that only specialists in endocrinology and/or those qualified in diabetology and nutrition are authorized to renew the centre’s initial prescription and, thus, can follow-up a patient using an insulin pump. Treatment initiation and annual evaluation are the responsibility of the initiating centre.

Special conditions have been proposed for managing the treatment of children, factoring in the specific features accompanying this sort of treatment and the currently available care services.

9.3.2. Pump specifications

The decree also lays out the technical specifications that manufacturers need to follow to obtain a product license for their portable, programmable external insulin pumps. The patient must always be able to access the pump’s programming, and how to do so must be clearly explained in the pump instructions. The device must also be fitted with a system that has an automatic stop function to prevent excess doses, and must be programmable for specific basal rates that range from 0-9.9 IU/h to a maximum increment of 0.1 IU/h, and boluses from 0.1 to 25 U, with a maximum increment of 0.5 U. The system must absolutely not allow automatic bolus triggering.

9.3.3. Content of the provision of services

The role of the service provider is clearly defined here, for the first time, in the ambulatory management of a chronic pathology, notably in terms of patient technical education. The decree states that service providers must be able to educate patients on the technical aspects of all pumps prescribed by the initiating centre. They must also comply with the rules of medical-device vigilance, and have in place a written outline of internal procedures. The initial technical training has to cover the following eight key aspects:

- learning how the pumps work, and the basic (batteries, date, basal rate and bolus) and advanced (including temporary rates, supplemental boluses, use of alarms and reminders, and reprogramming) functions;
- use of consumables (reservoir and catheter) and awareness of the related safety rules;
- reaction to alarms and troubleshooting equipment malfunction;
- basic maintenance;
- precautions for use;
- how to wear the pump;
- awareness of the emergency procedure: telephone numbers, insulin replacement schedule and emergency kit;
- review of knowledgeability after the pump is fitted.

Ongoing technical training is also laid down in a precise description, including:

- review of patient knowledgeability at the beginning and end of training;
- point-by-point revision of the induction training, including patient operation of the material and a review of the safety rules;
- acquisition of knowledge not included in the induction training;
- checking the pump, its maintenance and the patient’s knowledge of reprogramming technique;
- checking an insulin replacement schedule for the patient, the use-by date for the insulin, the pen and the emergency kit.

9.4. Care of patients treated with the insulin pump

Patient management must comply with the recommendations of the decree published in the 2006 Journal Officiel (Table 8).
9.4.1. The decision to initiate treatment by insulin pump

This is the responsibility of the patient’s diabetology/endocrinology consultant (or the diabetologist to whom the patient was referred by the primary-care physician), or a qualified diabetologist or nutritionist. Candidates include all patients who meet the indications validated in 2000—in other words, type 1 or 2 diabetes that cannot be properly controlled through multiple insulin injections. Clinical situations that come under this definition are described in Indications, limitations and contraindications of CSII in diabetes.

9.4.2. Initiation of the treatment

The initiating centre’s multidisciplinary team is responsible for confirming the indication and handling the initial patient management in a healthcare institution (public or private) that fulfils the decreed specifications. Inpatients initiation means that the patient can be given intensive education, particularly regarding the clinical aspects (such as adjusting doses, troubleshooting and defining the replacement protocol), using written protocols, which may differ from one centre to another, but which must all include the conditions for using the medical standby service. The duration of the training period is not specified in the decree.

Technical education can be either carried out by the centre’s multidisciplinary team or delegated to the service provider through a medical prescription (reimbursed on a lump-sum basis). Training through the service provider can be carried out on their premises, at the patient’s home or in the initiating centre.

9.4.3. Ambulatory patient follow-up

Patient follow-up is carried out jointly by the diabetologist and service provider, but the manufacturer may also be involved. The diabetologist performs the usual clinical monitoring and prescribes the material to be delivered by the service provider, along with the monthly healthcare package. The prescription should be for a period not exceeding 6 months. During this time, the service provider: supplies the materials; provides a round-the-clock telephone helpline (the number of which has to be given to the patient), if possible using a technical logbook; provides assistance in the event of a malfunction; and, when necessary, replaces the pump. The provider also checks patient knowledgable after the induction training. The frequency of service-provider contacts is not set out, but at least three contacts during the first year and two in each of the following years appears to be reasonable.

Both physicians and service providers are bound by medical-device vigilance obligations, and are required to report to the AFSSAPS (Agence Française de Sécurité Sanitaire des Produits de Santé) any incident or accident arising from a potential material defect (as opposed to misuse of the material) [91].

The manufacturer may also be called in as they are responsible for customer service with regard to the material. If it proves necessary to change the pump (usually after 4 years of use or as a result of exceptional circumstances), the initiating centre is responsible for validating the change and organizing technical training (either directly or through the service provider), but hospitalization is not recommended.

9.4.4. Annual treatment evaluation

This evaluation mainly sets out to review the continuation of the treatment (or the need to stop it), while also checking that the theoretical knowledge and lessons of the initial intensive training have been retained. It involves a multidisciplinary consultation at the initiating centre, preferably with the participation of the attending diabetologist.

**Conclusion**

Medical practice nowadays is guided by recommendations that set out the conditions that are required for patient management. In the past and unlike the case with type 2 diabetes, such recommendations did not exist for the care of patients with type 1 diabetes. However, the approach adopted with insulin pumps, probably as a result of the special conditions governing their use, is the first step towards greater rationalization of the treatment of type 1 diabetes. In addition, it is also the first time that the therapeutic education and training required for the patient has been clearly laid out.

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Eric Renard carried out clinical trials as main head clinical for Roche, and as co-investigator for Medtronic Inc., Roche, Sanofi-Aventis. He did expert reports for Roche. He gave advisory services to Roche. He attended conferences organized by Roche and Medtronic Inc. as contributor.

Nadia Tubiana-Rufi, Anne Vanberge, Denis Raccah and Michel Pinget have not declared any conflicts of interest.

Bruno Guerci has no conflict of interest.

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