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REVIEW

Insulin Delivery Technology for Treatment of Infants with Neonatal Diabetes Mellitus: A Systematic Review

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ABSTRACT

Neonatal diabetes mellitus is a rare disorder of glucose metabolism with onset within the first 6 months of life. The initial treatment is based on insulin infusion. The technologies for diabetes treatment can be very helpful, even if guidelines are still lacking. The current study aimed to provide a comprehensive review of the literature about the safety and efficacy of insulin treatment with technology for diabetes to support clinicians in the management of infants with neonatal diabetes mellitus. A total of 22 papers were included, most of them case reports or case series. The first infants with neonatal diabetes mellitus treated with insulin pumps were described nearly two decades ago. Over the years, continuous glucose monitoring systems were added to treat these individuals, allowing for a better customization of insulin administration. Insulin was diluted in some cases to further minimize the doses. Improvement in technology for diabetes prompted clinicians to use new devices and algorithms for insulin delivery in infants with neonatal diabetes as well. These systems are safe and effective, may shorten hospital stay, and help clinicians weaning insulin during the remission phase in the transient forms or switching from insulin to sulfonylurea when suggested by the molecular diagnosis. New technologies for insulin delivery in infants with neonatal diabetes can be used safely and closed-loop algorithms can work properly in these situations, optimizing blood glucose control.

Keywords: Neonatal diabetes mellitus; Insulin infusion systems; Insulin pump; Hybrid closed loop; Advanced hybrid closed loop; Diabetes technology

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Key Summary Points
Technology for insulin delivery in individuals with diabetes is suggested irrespective of age.
Insulin pumps, and more recently automated insulin delivery systems, are safe and effective even in infants with neonatal diabetes mellitus.
Technologies for insulin delivery may shorten hospital stay and support clinicians in insulin dosing and in switching from insulin to oral hypoglycemic agents when suggested.
Automated insulin delivery systems with closed-loop algorithms can be the gold standard for treating infants with neonatal diabetes mellitus.

INTRODUCTION

Neonatal diabetes mellitus (NDM) is a rare disease defined by the presence of severe hyperglycemia requiring treatment mainly before 6 months of age and less frequently between 6 months and 1 year [1]. NDM incidence is between 1:21,000 and 1:350,000 live births, with the highest incidence in those countries with high rates of consanguinity [2–5]. It can be classified into transient NDM (TNDM) and permanent NDM (PNDM) [6, 7] and insulin therapy must be started if necessary. Genetic testing is suggested in all patients and a switch from insulin to sulfonylureas is recommended for carriers of KCNJ11 and ABCC8 abnormalities [1, 8, 9].

Continuous subcutaneous insulin infusion (CSII) should be taken into consideration in these patients, as it permits the administration of very small insulin doses and avoids severe hypoglycemic episodes due to the unpredictable feeding patterns of neonates [10, 11]. Technology for insulin delivery is recommended and appropriate for youth with diabetes, regardless of age. Indeed, standard insulin pump therapy is recommended for all youth with diabetes if access to more advanced diabetes technologies, including sensor-augmented pump therapy (SAP), low glucose suspend (LGS) or predicted low glucose suspend (PLGS) system, and automated insulin delivery (AID), is limited [12].

This paper presents a systematic review of the significant literature on the use of technology for insulin treatment in patients with NDM.

MATERIALS AND METHODS

The literature search was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13] and provides a review of the current literature about technologies for insulin delivery in the management of NDM. The search for eligible studies was performed from inception to 20 July 2024 in the PubMed database. The keywords used for the query strings were “Neonatal diabetes mellitus” AND “insulin pump” and “Neonatal diabetes mellitus” AND “Closed loop”. Only “insulin pump” is indexed in the Medical Subject Headings (MeSH) thesaurus, while “Neonatal diabetes mellitus” is indexed as supplementary concept in association with other terms (permanent, hypothyroidism, and so on).

Non-English language papers were excluded. To be as comprehensive as possible, only guidelines and review papers were not included in the Literature Review section. Commentaries and editorials were taken into consideration only if they reported original data. Additional studies were searched from the reference lists of the selected papers. The literature search was carried out by two authors (R.P. and V.C.) and identified 162 manuscripts with the first query string and 23 with the second. Once the criteria had been applied, most of them were excluded for not meeting the predefined criteria and 25 papers were selected from the first search. Only 1 paper was added from the second search, and thus 26 papers were retrieved to assess for eligibility, five articles were excluded either for not meeting the prespecified study treatment or due to the inconsistency of the study population (i.e., other than neonates). Thus, 21

articles were elected for this review and underwent a review of the full text (PRISMA flowchart; Fig. 1). One additional paper was added because it reported the insulin treatment of an infant with NDM with advanced hybrid closed loop (AHCL) even if not retrieved by the literature search [14]. A final number of 22 papers were included in this review paper. The papers were considered irrespective of study setting (hospital or home), subtype of NDM, duration of insulin requirement, and genetic defect. The Population, Intervention, Professions, Outcomes and Healthcare system (PIPOH) summary of this review is presented in Table 1.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Data regarding the treatment of NDM with technologies for diabetes are available from observational studies, case reports, and case series. The main features of selected studies are summarized in Table 2.

The first description of treatment with CSII in an individual with NDM was done by Olinder et al. [15]. They reported on two infants with NDM who were treated with CSII (Minimed 507C and 508 and a Disetronic H-tron V100). No episodes of diabetic ketoacidosis, severe hypoglycemia, and technical issues were reported. Diluted Lispro insulin (10 IU/mL) was used in the infusion sets. The authors concluded that CSII was effective and safe, suggesting that it could be an alternative treatment for these individuals. The same conclusion was drawn by Park

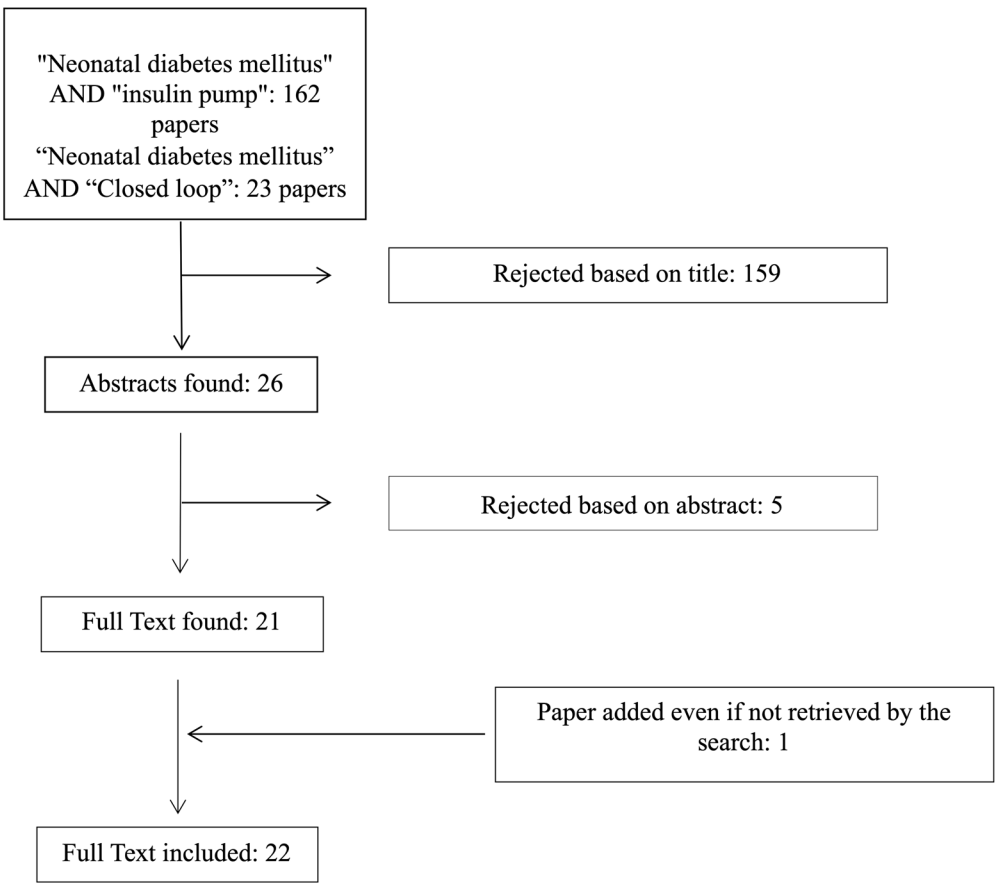

Fig. 1 PRISMA flowchart

Table 1 Population, Intervention, Professions, Outcomes and Healthcare system (PIPOH) summary of this review

	Parameter	Specification
P	Population	Infants with neonatal diabetes mellitus with technology for insulin treatment
I	Intervention	Treatment with insulin delivered by insulin pump with or without and continuous glucose monitoring system, managed or not by an algorithm
P	Professions (target users)	Diabetes care providers
O	Outcomes	To summarize current evidence on safety and efficacy of devices for subcutaneous insulin delivery
H	Healthcare setting	Hospital or home

et al. [16], who treated an infant with TNDM and showed wide serum glucose fluctuation. Both groups suggested that CSII may shorten the length of hospital stays in these children. In addition to the evidence about safety and effectiveness, Tubiana-Rufi [17] described her experience over 18 years with 17 children and adolescents (8 with PNDM). She confirmed previous data and showed that CSII allows for easy adaptation of insulin dosing, more flexible based on the current feeding regimen. She suggested that very small insulin doses could be administered after insulin dilution (5–10 IU/ml).

Interestingly, Ortolani et al. [18] described the first infant with NDM treated with CSII integrated with a continuous glucose monitoring system (CGMS). In their paper, they described three patients with PNDM due to INS gene mutation, all of them treated with CSII. Insulin was not diluted, and the authors stated that both treatment strategies are feasible and safe not only in the hospital setting, but also at home. Moreover, they suggest that CSII–CGM integrated system may be superior to CSII only. The same conclusion was achieved with the use of the MiniMed 530G system, the first-generation artificial pancreas system, which allowed for fine insulin dosing with automation algorithms preventing hypoglycemia [19]. In contrast, in addition to the advantage of CSII, the CGM system could be also technically difficult, as reported in a 6q24-related TNMD with severe intrauterine growth retardation [20].

The postnatal growth and HbA1c levels in NDM were evaluated by Alyafie et al. [21] in five patients treated with a pump and in four patients treated with multiple daily injections (MDI). Even if no statistical significance was reached, the authors suggest that insulin pumps could be associated with better glucose control and catch-up growth at 24 months of age.

A Swedish study reported data from six neonates with TNDM treated with an insulin pump (Medtronic MiniMed Paradigm Real-Time and Paradigm VEO) from day of life 5–54 to day of life 17–145 [22]. The authors diluted insulin 1:10 (final concentration 10 IU/ml) as described by the manufacturer. The meal boluses represented 70–80% of the total daily dose of insulin and they were personalized for each patient on the basis of CGM values and amount of milk. The authors concluded that these devices are safe for neonates with NDM and effective in improving blood glucose control. However, they suggested that the staff should have good technical skills to use this technology properly. Support for the staff involved in NDM management comes from the video and the paper by Zanfardino et al. [23, 24], who reported technical information about the management of the insulin pump infusion set in these patients who usually present low birth weight and scarce subcutaneous adipose tissue.

A few different and interesting clinical aspects are pointed out in some case reports. Passanisi et al. concluded that both insulin pumps and long-acting insulin injections alone are effective, but proper expertise is mandatory [25]. The use of an insulin pump was reported also in very rare situations such as homozygous *PTF1A* enhancer mutation (two neonates) [26], *GLIS3* mutation (two twins) [27], and Donohue

Table 2 Summaries of studies on diabetes technology for the treatment of infants with neonatal diabetes mellitus in this systematic review

Authors	Study design	Main findings	Study outcome
Olinder, 2006 [15]	Case series Two infants with DMN treated with CSII Baby A: MiniMed 507 C from 3 weeks of life to 2 months and > 2 months of life with Medtronic Baby B: Disetronic h-tron v100 since 4 days of life	Both had good metabolic control (median HbA1c values) without any episodes of severe hypoglycemia and without significant complications	Mean blood glucose decreased after 12 months of CSII: Baby 1: from 8.53 mmol/l (153 mg/dl) to 4.43 mmol/l (80 mg/dl) Baby 2: from 5.5 mmol/l (99 mg/dl) to 5.5 mmol/l (99 mg/dl) Median HbA1c during the first year of CSII: baby A 5.3% (35 mmol/mol), baby B 5.7% (39 mmol/mol)
Park, 2013 [16]	Case report Female infant with TNDM treated with CSII	Patient's glucose levels were soon stabilized without hypoglycemia and other systemic complications by CSII. Insulin pump is safe and effective treat NDM	Insulin basal rate: 0.021–0.023 U/kg/h. Stable glycemic control achieved within 1 week. No cutaneous or systemic complications associated with CSII. Normal growth (weight 25–50° centile, height 50° centile)
Passanisi, 2014 [25]	Case series Two infants treated with CSII or subcutaneous glargine injections, respectively	The authors claim that CSII is the most physiological modality to deliver insulin, hence it should be regarded as the treatment of choice. However, both CSII and subcutaneous insulin glargine injections were safe and effective for the treatment of TNDM in their experience, allowing for a personalization of care	Infant 1: good metabolic control [glucose value between 5.5 and 8.3 mmol/l (99 and 149 mg/dl)] with basal insulin delivery of 0.01 U/kg/h. Discharged at 36 days of life, insulin discontinued at 56 days of life

Table 2 continued

Authors	Study design	Main findings	Study outcome
Huggard, 2015 [28]	Case report Use of CSII in a neonate diagnosed with Donohue syndrome	CSII with SAP was started after discontinuation of intravenous insulin. CSII with SAP was chosen to manage frequent wide fluctuations in blood sugars on intravenous insulin. Insertion of catheters was challenging due to the neonate low body weight. Hypoglycemia was only observed when continuous feeds were discontinued and deterioration of abdominal distention	CSII improved the quality of life of the infant and his family, avoiding episodes of hyperglycemia and symptomatic hypoglycemia
Kapellen, 2015 [11]	Observational study Retrospective analysis of patients < 1 year of age ($n = 58$ T1DM, $n = 67$ NDM, and $n = 43$ early diabetes and negative B-cell antibodies) treated with CSII selected from the German/Austrian Diabetes-Patienten-Verlaufsdokumentation database	Preliminary assessment of CSII treatment in neonates and infants. Authors recommend the lower quartile for insulin dosage as the starting value in nonketotic patients	Similar total daily dose with lower pre-meal insulin at onset in infants with NDM than in infants with T1DM. To provide a useful initial guide to start CSII treatment
Ortolani, 2015 [18]	Case series Three infants with a dominant INS/PNDM mutation started on CSII	CSII alone is a feasible and safe therapeutic strategy for neonates or infants with diabetes, not only at the hospital, but also at home. CSII-CGM integrated system may be superior to CSII only	HbA1c at onset and 12 and 24 months of age: Infant 1: NA, 6.1%, (43 mmol/mol) and 5.7% (39 mmol/mol) Infant 2: 7% (53 mmol/mol), 5.7%, (39 mmol/mol) and 7.1% (54 mmol/mol) Infant 3: 13.6% (126 mmol/mol), 8.5% (69 mmol/mol), and NA

Table 2 continued

Authors	Study design	Main findings	Study outcome
Fudvoye, 2016 [20]	Case report Case of severe IUGR and TNDM managed by CSII. CSII and glycemic monitoring carried out by capillary sampling because was technically difficulties to apply CGM	CSII could be an accurate, almost physiologic method to treat newborns, and its major benefit was the ability to flexibly follow the baby's blood glucose fluctuations	Growth: catch-up growth; at 9 months: weight, length, and head circumference around 15th centile. Progressively reduction of blood glucose fluctuation until insulin withdrawing
Marin, 2016 [19]	Case report 3-month-old girl with PNDM treated with MiniMed 530G	The management was optimal, allowing for delivery of the very small doses of insulin necessary to treat this infant	Blood glucose levels constantly < 11 mmol/l (200 mg/dl) HbA1c: at NDM onset 13.3% (123 mmol/mol). Progressive improvement of blood glucose control [last HbA1c 7.7% (61 mmol/mol)]. No severe hypoglycemia Appropriate growth
Rabbone, 2016 [29]	Case series Four infants with NDM successfully treated with CSII and CGM. In two cases with KCNJ11 gene mutation, CSII use in switching therapy from insulin to SU is described	CSII therapy is safe, accurate, and more physiological for insulin administration in NDM. CSII is also helpful for the switch of therapy from insulin to SU for infants with PNDM	Infant 1: no episodes of hypoglycemia and hyperglycemia. HbA1c 8% (64 mmol/mol) before switching to SU Infants 2, 3, and 4: reduction of glycemic variability with improvement of blood glucose control. Appropriate growth
Kurnaz, 2017 [26]	Case series Two patients with NDM harboring the homozygous PTF1A enhancer mutation	CSII + CGM. Not satisfactory blood glucose control	No prevention of hypoglycemia Infant 1: last HbA1c 10.5% (91 mmol/mol) Infant 2: last HbA1c 8% (64 mmol/mol)
Tubiana-Rufi, 2017 [17]	Original research 17 infants with CSII (MiniMed 507, MiniMed 508 and MiniMed 512) requiring insulin therapy for more than 15 days	CSII was safe in the neonatal period, mimicking the physiological insulin secretion, and easier to manage than insulin injections	No severe hypoglycemia or ketoacidosis events occurred. Mean blood glucose level per month was 9.6 mmol/l (173 mg/dl)

Table 2 continued

Authors	Study design	Main findings	Study outcome
Alyafie, 2019 [21]	Observational study Assessment of growth parameters in nine infants with PNDM, during the first 2 years of their postnatal life (five on CSII versus four on MDI)	Most infants with PNDM showed significant catch-up growth within the first 2 years of life. Glyaemic control was better in infants with PNDM on CSII therapy than in those on MDI therapy	HbA1c: 9.6% (81 mmol/mol) in infants on CSII, 10.2% (87 mmol/mol) in infants on MDI after 20 ± 4 months Standardized weight and length were higher in infants on CSII than in those on MDI
Torbjornsdotter, 2020 [22]	Observational study Six infants with NDM successfully treated with CSII (MiniMed Paradigm Real-Time and MiniMed Veo). 1:10 insulin dilution as described by the manufacturer was carried out in three of six	Insulin pumps were safe and decreased the problems of intravenous access and frequent blood sampling, while allowing for shorter length of stay and greater involvement of parents in the care of their infants	No severe side effects such as severe hypoglycemia or local infection
London, 2021 [27]	Case series Non-identical twins born to consanguineous parents with NDM due to GLIS3 homozygous nonsense mutation treated with MiniMed 640G SmartGuard system. 1:10 insulin dilution	Fluctuating blood glucose and intermittent hypoglycemia occurred on follow-up	HbA1c at diagnosis and at 3 years of age: Infant 1: 8.2% (66 mmol/mol) and 6.5% (48 mmol/mol) Infant 2: 7.4% (57 mmol/mol) and 7.0% (53 mmol/mol)
Fukuda, 2022 [30]	Case series Three patients received SAP therapy with smart guard technology using the MiniMed 640G system	SAP therapy was effective to obtain adequate metabolic control. SAP therapy and Smartguard technology may prevent hypoglycemia	Adequate metabolic control with normal growth
Zanfardino, 2022 [23]	Case report Management of a neonate with PNDM due to pancreas agenesis with SAP therapy. SAP therapy (MiniMed 640G with Smartguard)	The use of pump, even with undiluted insulin, should be warranted in all patients with PNDM not suitable for SU treatment	HbA1c drop from 10.3% (89 mmol/mol) to 8.5% (69 mmol/mol) after 20 days of SAP therapy TIR: 59% at 1 month of age; 86% at 16 months of age

Table 2 continued

Authors	Study design	Main findings	Study outcome
Zanfardino, 2022 [24]	Video case report Use of sensor augmented pump therapy in a VLBW late preterm neonate with NDM due to PDX1 gene mutation	Successful treatment with a SAP Therapy and PLGS function in a 34-week neonate with birth weight of 1180 g and limited subcutaneous tissue	At 4 months of age: TIR 62%, TBR 4%. Peculiar site of infusion: arm skin. It was safe and successful
Lee, 2023 [32]	Case report The use of CSII, CGM, AID system, and remote patient monitoring in a case of NDM with focal seizures and diabetic ketoacidosis with a mutation of KCNJ11. 1:10 insulin dilution	The management of NDM with the AID system and RPM under close guidance can lead to safe glycemic control and at-home switch to SU therapy	No hypoglycemia. TIR improved from 4% on MDI to 23% after 1 week of AID
Mancioppi, 2023 [33]	Case report A case of infant with IUGR and NDM due to KCNJ11 gene mutation treated with AHCL system (MiniMed 780G) with only PLGS function on before switch to SU	AHCL is the best treatment option for NDM. SU allows for maintaining good metabolic control and preventing hypoglycemia and neurological damage	TIR > 40% after 1 week of treatment with AHCL
Sakai, 2023 [31]	Case report A small gestational age baby with TNDM treated with SAP therapy with PLGS function on	SAP was successful and the concomitant use of a PLGM system enabled to perform insulin infusion safely and to avoid hypoglycemia	Improvement of blood glucose levels
Wanaguru, 2024 [34]	Case report A preterm infant with 6q24 TNDM treated with AHCL system (MiniMed 780G) with SmartGuard technology. 1:10 insulin dilution with 0.9% normal saline	He was treated for 18 days blood glucose target 6.7 mmol/l (120 mg/dl), active insulin time 4.5 h, and auto-corrections turned on	TIR improved from 25–30% to 40–48%

Table 2 continued

Authors	Study design	Main findings	Study outcome
Delvecchio, 2024 [14]	Case report A full-term infant with 6q24 TNDM treated with AHCL with PLGS function on	A small for gestation age infant was treated with AHCL from 62 to 108 days of life, when complete remission occurred. Insulin was not diluted. He was discharged safely	No episode of hypoglycemia and very good metabolic control

NDM neonatal diabetes mellitus, *TNDM* transient NDM, *PNDM* permanent NDM, *CSII* continuous subcutaneous insulin infusion, *SAP* sensor augmented pump, *T1DM* type 1 diabetes mellitus, *CGM* continuous glucose monitoring, *IUGR* intrauterine growth retardation, *NA* not available, *SU* sulfonylurea, *MDI* multiple daily injections, *TIR* time in range (blood glucose values between 70 and 180 mg/dl), *TBR* time below range (blood glucose values below 70 mg/dl), *AID* automated insulin delivery, *AHCL* advanced hybrid closed loop, *PLGS* with only predictive low glucose suspend

syndrome [28]. Interestingly, Huggard et al. suggested that the decision to start an insulin pump in NDM should be shared with caregivers. Even though their patient died at 4 months, the patient's mother declared her satisfaction with the choice of CSII with a sensor-augmented pump, since it protected her son from hyper- and hypoglycemia and improved his quality of life [28]. An insulin pump was also very helpful for two patients who switched to sulfonylurea after genetic testing, allowing for a safe and progressive decrease in the daily insulin infusion together with the introduction of sulfonylurea [29]. In all these papers, the authors confirmed that insulin pumps, with or without CGM, are safe and effective in blood glucose management.

Consistent support to start insulin pumps in neonates with NDM is provided by Kapellen et al. [11]. In their large cohort of 67 neonates treated with a pump, they report data about the insulin requirement, but no information about gene mutation and transient/permanent form is provided. The median insulin dose at pump start was 0.74 IU/kg (median age 1.8 weeks), with a median basal insulin requirement of 0.56 IU/kg and a median requirement of pre-meal insulin of 0.4 IU/10 g of carbohydrates (I:C ratio 1:25 IU/g of CHO). The dose was adjusted on the basis of blood glucose values, and it was 0.64 IU/kg at discharge (basal insulin requirement 0.43 IU/kg in 63 patients). At the follow-up visit, 35 weeks later, the median insulin requirement was 0.52 IU/kg (median basal insulin requirement was 0.38 IU/kg in 51 patients). The median age at follow-up visit (44 weeks) suggests that most of them had a PNDM. Some data about insulin requirements had been reported previously, but the cohorts were small.

Sensor-augmented pump (SAP) therapy with the MiniMed™ 640G system was described in three patients [30]. The SmartGuard Technology embedded in this system was reported as particularly useful for these infants to prevent hypoglycemia, to manage insulin delivery more accurately, and to reduce the burden of diabetes for the caregivers. Confirmatory data were shown by Sakai et al. in a small for gestational age infant with TNDM [31]. He was treated with continuous intravenous insulin infusion initiated on day of life 4. At 39 days, SAP was started successfully without

any hypoglycemia. After discontinuation of insulin at 58 days of age, the infant was discharged. The authors suggested that CGM may help physicians to decide when discontinue insulin in SAP therapy.

The usefulness of patient monitoring technologies was described in a proband with NDM due to the beta cell potassium ATP channel gene KCNJ11 mutation. CGM and insulin pumps with automated insulin delivery (AID) and remote monitoring technologies allowed for an easy switch from insulin to oral sulfonylurea [32]. This report further supports the safety and effectiveness of technologies for infants with diabetes. Similar data and conclusions about switching from insulin to sulfonylurea under CGM were reported in two cases by Mancioppi et al. [33]. They described a 51-day-old infant started on CSII therapy (MiniMedTM 780G) and CGM (Guardian Sensor 4) with only PLGS function on. Insulin dilution was not necessary. After the detection of a de novo heterozygous pathogenic mutation in the KCNJ11 gene, insulin administration was safely and progressively reduced, with a simultaneous switch to glibenclamide. The safety and effectiveness of AID systems in infants with NDM were also confirmed by Wanaguru et al. [34]. In their case series of four patients younger than 2 years of age, one infant was genetically confirmed to have 6q24 TND on day of life 23. Due to a very low insulin dose (0.8 IU/day), he commenced on AHCL with SmartGuard technology (blood glucose target 6.7 mmol/l with 0.9% normal saline and auto-corrections turned on) on day of life 26 with 1:10 diluted Aspart, and after 18 days he went into complete remission. We reported similar findings in an infant with 6q24-related TNDM treated. He started on MiniMed™ 780G and CGM with only PLGS function on and insulin Lispro 100 IU/ml. The patient was discharged home, he did not experience any hypoglycemia, and discontinued insulin treatment safely when he went into remission [14].

DISCUSSION

NDM is a heterogeneous rare disease. Treatment may be very challenging because of the rarity of the disorder, small insulin doses, and unpredictable feeding. The development of technologies for diabetes treatment provided useful tools for clinicians involved in diabetes care management. Gene mutations can be detected in more than 80% of individuals with NDM [1, 35], less frequently in preterm (66%) than in full-term neonates (83%) [36], prompting the physician to try sulfonylurea in most cases, but even in this situation the first-line treatment remains insulin infusion. The lack of genetic testing is a good point to not try sulfonylurea treatment [1]. At hyperglycemia onset, a differential diagnosis with other causes of neonatal hyperglycemia, such as infection, low birth weight, beta-cell immaturity, parental nutrition, and hypoxia, may be very challenging overall in preterm babies, and a short course of insulin treatment may be required. If hyperglycemia disappears after a few days, NDM can be reasonably excluded from the diagnostic workup. While waiting for genetic testing results, insulin treatment is necessary to normalize blood glucose as much as possible and to allow for appropriate development and weight growth. The remission rate in newborns with TNDM is close to 100% and insulin therapy may be unnecessary if hyperglycemia is mild. On the contrary, if the initial presentation is severe, insulin treatment has to be promptly started and optimized. In infants with PNDM, the initial insulin treatment can be switched to sulfonylurea tablets once sulfonylurea-responsive KCNJ11 or ABCC8 mutations are determined, since sulfonylurea therapy may be critical to improving long-term neurocognitive and neuromuscular outcomes [37]. Management of intravenous infusion can be complicated by infections and displacement, and thus CSII may also be a plausible alternative way to manage newborns with the lowest birth weight. Data from the literature suggest that these devices allow for safer and earlier discharge of infants to home [15, 16]. There are no clinical research studies aiming to evaluate the best way to deliver insulin to infants with NDM and optimal setting. Reasonably, such trials will never be run in consideration of clinical and genetic heterogeneity, and thus our knowledge about the optimal

treatment of these individuals is based on case reports and observational studies.

Given the rarity of the condition, awareness and clinical practice of such conditions can be limited, and thus a review reflects advances in methods to identify, select, appraise, and synthesize findings from available studies. The difficulties in the management and treatment of NMD were pointed out by a recent survey of pediatricians practicing in the Arab Society for Pediatric Endocrinology and Diabetes (ASPED) countries. This survey highlighted that almost all participants (93%) start insulin treatment, preferably after dilution (80%). Interestingly, basal-bolus and insulin pumps were used similarly (36% each), suggesting that the insulin pump was not the most preferred route of administration. The authors concluded that established guidelines for this condition are needed, in consideration of the inhomogeneous treatment despite the good knowledge of this condition [38]. A similar survey was recently closed by the International Society for Pediatric and Adolescent Diabetes, and we hope that the results will be helpful for future treatment.

The advances in technology for diabetes treatment give physicians a wide range of devices and clinically relevant solutions to treat patients. The first reports about treatment with CSII in infants with NDM showed that this route of administration was safe [15–17]. As these papers are case reports or case series, the only data that aimed to provide clinically useful information to set the insulin pump were reported by Kapellen et al. from 67 infants with NDM [11]. They reported detailed information about insulin dose and treatment management irrespective of genetic diagnosis and clinical course, unfortunately.

A significant step toward the improvement of care was represented by the integration of CSII with CGMS [18–20, 29], which is helpful to avoid hypoglycemia episodes [39]. Despite technical difficulties and lack of randomized trials investigating the real benefits, the CGMS allows for 24-h monitoring with retrospective or real-time evaluation of glucose levels, avoiding blood samplings, and thus fine dosing of insulin and reduction of blood glucose fluctuations [40].

Over the last decade, technology for diabetes treatment has been greatly improved and AID systems have become more widely available [12]. In the case of very low doses, insulin dilution may be helpful in administering minimal insulin doses [18, 20, 25] and allowing the AID systems to work in automode [34]. The use of AID systems with automode function has been reported in some infants more recently [30, 31, 33, 34]. In all these papers, AHCL technology is feasible and safe, allowing for optimization of blood glucose control, early discharge of the patient to home, and supporting the clinicians both in switching from insulin to sulfonylurea and in weaning insulin during the transition to complete remission in infants with TNDM. Despite promising results, delivery of very small doses of insulin in a neonate with NDM and intrauterine growth retardation may be very challenging, and the insertion of needles for insulin infusion and glucose sensing may appear very difficult or nearly impossible. However, it should be noted that the last generation of AID systems cannot be prescribed in infants below 1 year of age and most of them cannot be used under the age of 7. Furthermore, available data suggest that technologies for insulin delivery in infants with NDM can face successfully all the critical points in clinical management, and practical suggestions to manage the infusion sites are provided to support the staff in the management of the devices [23, 24]. Furthermore, the use of an AHCL system has the pros of a lower number of injections to deliver the daily insulin. Technology for diabetes treatment allows normal feeding with normal growth [15, 16, 31], even in newborns with severe intrauterine growth retardation [17]. Finally, unanimously, these devices allow for shortened stay in the hospital, discharging the infants in safe conditions home [14, 15, 17].

This paper has some limitations. First, selected papers are not homogeneous regarding the clinical course, molecular diagnosis, and devices. Second, almost all papers are case reports or case series and there is a limited number of infants. The current study presents data as clearly as possible to provide clinicians useful data for clinical practice. We cannot exclude that some papers could have been missed through our search strategy because of inappropriate keywords. However, the literature on the topic is limited,

and retrieving possible papers by reading the references of each paper reduces this bias as much as possible. Finally, we think that the quality of the evidence is quite poor in most of the papers, as the metabolic outcomes are incomplete in most of them, the AID device is often not specified, and the diluent used with the insulin is often not reported.

In conclusion, the evidence from the current study suggests that AID systems with AHCL technology are helpful for the treatment of infants with NDM. Even in preterm and low birth weight infants, CGMS and insulin catheters can be inserted safely. Treatment goals should be defined with the family members or caregivers for a therapeutic alliance that can be the key to treatment success. The staff of the diabetes team and/or the neonatal intensive care unit should have good technical skills to use this technology properly. AID systems can be used to treat these infants, reducing blood glucose fluctuations and preventing hypoglycemia. In the case of a total daily dose lower than the minimal requirement for the AHCL algorithm, insulin can be diluted to start the automode functionality, otherwise, the algorithm can properly work with the PLGS function on.

Author contributions. All authors (Raffaella Panza, Valentina Cattivera, Jacopo Colella, Maria Elisabetta Baldassare, Manuela Capozza, Luca Zagaroli, Maria Laura Iezzi, Nicola Laforgia, Maurizio Delvecchio) contributed to the study conception and design. All authors read and approved the final manuscript.

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Declarations

Conflict of Interest. All the authors (Raffaella Panza, Valentina Cattivera, Jacopo Colella, Maria Elisabetta Baldassare, Manuela Capozza, Luca Zagaroli, Maria Laura Iezzi, Nicola Laforgia, Maurizio Delvecchio) do not declare any competing interests. Maurizio Delvecchio is an Editorial Board member of *Diabetes Therapy*. Maurizio Delvecchio was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

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