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ISPAD GUIDELINES

ISPAD Clinical Practice Consensus Guideline: Diabetic ketoacidosis in the time of COVID-19 and resource-limited settings-role of subcutaneous insulin

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Abstract

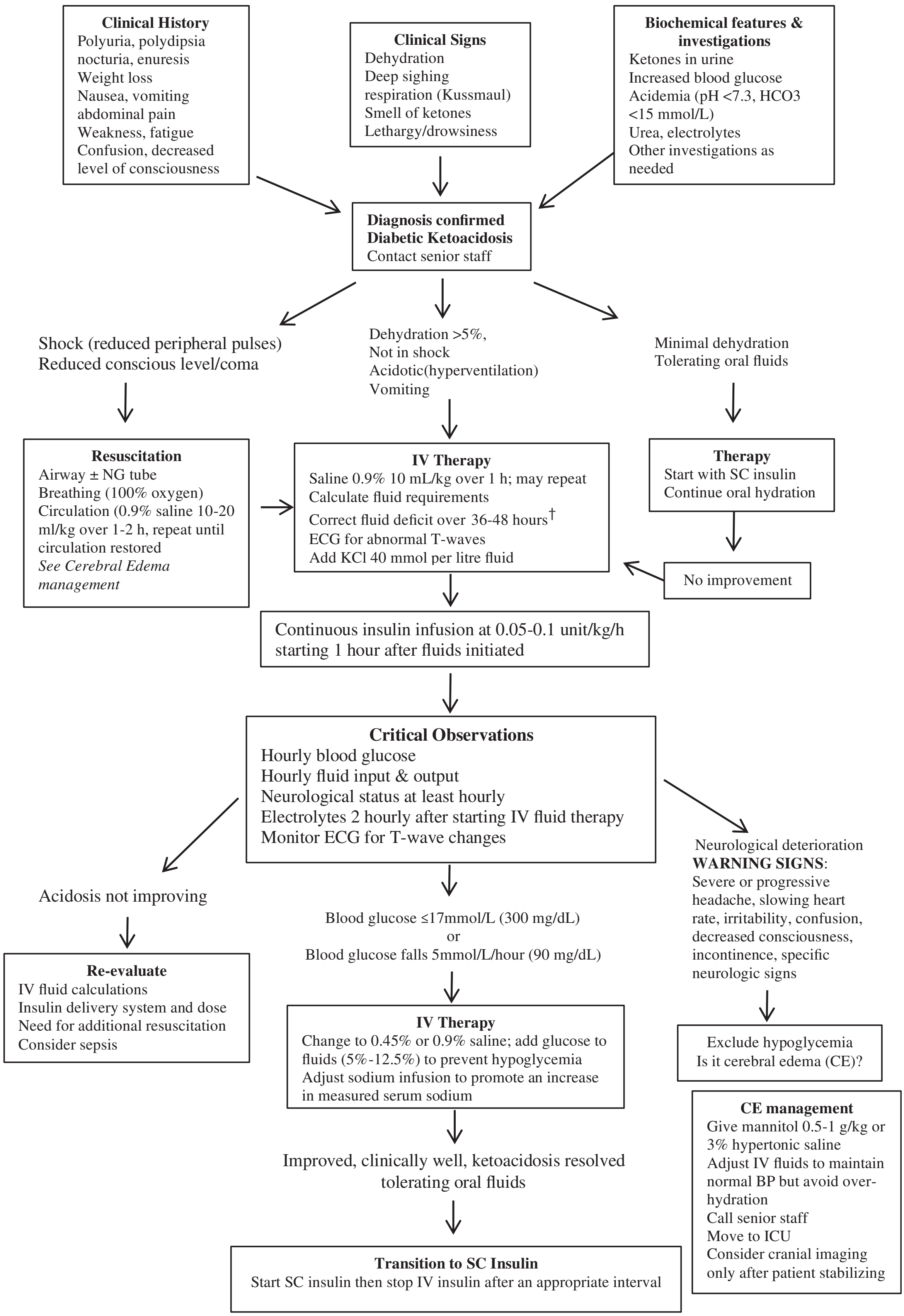
The International Society for Pediatric and Adolescent Diabetes Clinical Practice Consensus Guideline 2018 for management of diabetic ketoacidosis (DKA) and the hyperglycemic hyperosmolar state provide comprehensive guidance for management of DKA in young people. Intravenous (IV) infusion of insulin remains the treatment of choice for treating DKA; however, the policy of many hospitals around the world requires admission to an intensive care unit (ICU) for IV insulin infusion. During the coronavirus 2019 (COVID-19) pandemic or other settings where intensive care resources are limited, ICU services may need to be prioritized or may not be appropriate due to risk of transmission of infection to young people with type 1 or type 2 diabetes. The aim of this guideline, which should be used in conjunction with the ISPAD 2018 guidelines, is to ensure that young individuals with DKA receive management according to best evidence in the context of limited ICU resources. Specifically, this guideline summarizes evidence for the role of subcutaneous insulin in treatment of uncomplicated mild to moderate DKA in young people and may be implemented if administration of IV insulin is not an option.

KEYWORDS

COVID-19, diabetic ketoacidosis, resource-limited settings, subcutaneous insulin

1 | EXECUTIVE SUMMARY

The International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guideline 2018 for management of diabetic ketoacidosis (DKA) and the hyperglycemic hyperosmolar state[1,2] provides comprehensive guidance for management of DKA in young people (Figure 1). Intravenous (IV) infusion of insulin remains the treatment of choice for treating DKA; however, the policy of many hospitals around the world requires admission to an intensive care unit (ICU) for IV insulin infusion. During the coronavirus 2019 (COVID-19) pandemic or other settings where intensive care resources are limited, ICU services may need to be prioritized or may not be appropriate due to risk of transmission of infection to young people with type 1 or type 2 diabetes. The aim of this guideline, which should be used in conjunction with the ISPAD 2018 guideline,[1] is to ensure that young individuals with DKA receive management according to best evidence in the context of limited ICU resources. Specifically, this guideline summarizes evidence for the role of subcutaneous (SC) insulin in treatment of uncomplicated mild to moderate DKA in young people and may be implemented if administration of IV insulin is not an option. The levels of evidence follow the American Diabetes Association (ADA) evidence-grading system for "Standards of Medical Care in Diabetes" and are presented in Table 2.[3]



†Fluid deficit to be corrected over 36-48 hours
IV: intravenous; SC: subcutaneous; IM: intramuscular; BG: blood glucose; HCO3: serum bicarbonate

FIGURE 1 Algorithm for management of DKA as per ISPAD 2018 guidelines[1]

2 | RECOMMENDATIONS

- IV insulin acts rapidly within minutes, the rate of insulin delivery can be closely titrated and remains the standard of care for DKA. (Level of evidence B)
- IV insulin infusion may be used outside the ICU setting for management of uncomplicated mild and moderate DKA provided protocols are in place and there is appropriate staffing to ensure frequent clinical and biochemical monitoring. (Level of evidence E)
- SC rapid-acting insulin analogs are effective and can be used for treatment of uncomplicated mild to moderate DKA. (Level of evidence C)
- SC regular insulin is an alternative for treatment of uncomplicated mild to moderate DKA, if rapid-acting insulin analogs and IV regular insulin infusion are not available. (Level of evidence C)
- The management of fluid and electrolytes should be in accordance with the ISPAD 2018 DKA guideline. However, once DKA has resolved and the child is able to drink adequately; then the remaining volume of the calculated fluid deficit and potassium replacement, if needed, may be given orally if resources do not allow continuation of IV fluids. (Level of evidence E)
- Meticulous monitoring of the clinical and biochemical response to treatment is necessary so that timely adjustments in treatment can be made when indicated by the patient's clinical or laboratory data. It is important to recognize individuals who will need ICU care, even during a pandemic. (Level of evidence E)

> **BOX 1 Definitions**
>
> **Severity of DKA**: ISPAD defines mild to moderate DKA as a venous pH ≥7.1 to <7.3 or serum bicarbonate ≥5-15 mmol/L and severe DKA is defined as pH < 7.1.[1]
>
> **Resolution of DKA** is defined as pH ≥7.30, serum bicarbonate ≥15 mmol/L, BOHB <1 mmol/L, and/or closure of the anion gap as per the ISPAD guideline.[1]

Refer to Box 1 for definition of severity of DKA used here. Please note that the criteria used to define severity of DKA in adults as outlined by ADA[4] (and hence used in the adult studies mentioned here) are different from those used in children.

2.1 | SUBCUTANEOUS RAPID-ACTING INSULIN ANALOGS

- The suggested starting dose of SC rapid-acting insulin analog (lispro or aspart) is 0.15 U/kg, 1 hour after commencement of IV fluid replacement. SC doses should be subsequently administered every 2 hours until resolution of DKA. The dose of SC insulin analog can be reduced to 0.1 U/kg every 2 hours, if the BG continues to decrease by >5 mmol/L (90 mg/dL) per hour even after adding 5% dextrose to the IV fluids. (Level of evidence C)
- BG should be monitored every 1 to 2 hours aiming to maintain the level at ~11 mmol/L (200 mg/dL) until DKA has resolved. (Level of evidence E)
- SC insulin therapy may not be appropriate in severely dehydrated patients (as evidenced by lack of urine output, cool moist extremities, low or undetectable blood pressure, rapid feeble pulse, potential renal failure, lethargy, unconsciousness, or coma). SC administration may also not be appropriate when reduced tissue perfusion (capillary refill time >3 seconds) persists after fluid resuscitation or in patients with serious comorbid/precipitating conditions that warrant ICU admission. Evidence is limited for SC insulin as treatment of DKA in infants and very young children (age <2 years) and hence cannot be recommended in this age-group. (Level of evidence E)

2.2 | SUBCUTANEOUS SHORT-ACTING REGULAR INSULIN

- SC administration of short-acting regular insulin every 4 hours is a safe and effective alternative to IV insulin infusion in children with DKA and pH ≥7.1.
- A suggested starting dose is 0.13 to 0.17 U/kg/dose every 4 hours (0.8 to 1 U/kg/day given in divided doses), increased or decreased stepwise by 10% to 20% based on the BG prior to insulin injection. Dosing frequency may be increased to every 2 or 3 hours if acidosis is not improving. (Level of evidence C)

2.3 | INTRAMUSCULAR INSULIN

- IM insulin may be preferred over SC insulin if there is poor tissue perfusion and IV insulin is not an option. (Level of evidence E)

3 | COVID-19, CHILDREN, AND DIABETES

Children, adolescents, and young adults with COVID-19 generally have experienced less severe clinical manifestations than older adults or have been asymptomatic.[5,6] Underlying pulmonary pathology and conditions that impair immunity (such as primary immunodeficiency disorders, chemotherapy for malignancy, chronic immunosuppressive therapy, solid organ transplant, or hematopoietic cell transplant) have been associated with more severe outcomes.[7] Diabetes may also be an important risk factor for increased severity of illness and mortality in COVID-19 infections.[8] Interestingly, an association between COVID-19 and new-onset type 1 diabetes as well as severe metabolic complications of preexisting diabetes including DKA and hyperosmolarity, for which exceptionally high doses of insulin have been needed, has been reported.[9]

In many places globally, however, hospital services remain limited for non-COVID-19 conditions. There have also been concerns

TABLE 1 Summary of randomized controlled studies comparing subcutaneous to intravenous insulin in children and adults with DKA

Reference	Comparator/dose	Comparator group characteristics (n, mean age ± SD)	DKA severity (pH)	Inferiority	Superiority
Razavi et al[16]	*SC aspart*: 0.15 U/kg q2h	n = 25, 8.6 ± 0.8 years	> 7.1	Nil	Shorter stay for moderate DKA (3.4 vs 4.4 days)
Della et al[21]	*SC lispro*: 0.15 U/kg q2h, then q4h	n = 30, median 11.3 years, range 3-17 years	7.17 ± 0.10	Glucose control sub-optimal with q4h SC insulin	Nil
Karoli et al[22]	*SC lispro*: SC bolus 0.3 U/kg, then 0.2 U/kg 1 hour later and then 0.2 U/kg q2h. Reduced to 0.1 U/kg q2h if BG <13.8 mmol/L	n = 25, 35 ± 11 years	7.16 ± 0.11	Nil	Nil
Ersoz et al[23]	*SC lispro*: IV regular insulin bolus 0.15 U/kg, then SC lispro 0.075 IU/kg q1h	n = 10, 38.7 ± 19.7 years	7.15 ± 0.11	Nil	Nil
Umpierrez et al[15]	*SC lispro*: SC Bolus 0.3 U/kg followed by 0.1 U/kg q1h until BG < 13.8 mmol/L, then 0.05 to 0.1 U/kg q1h	n = 20, 37 ± 12 years	7.17 ± 0.10	Nil	Lower hospital cost in non-ICU SC group
Umpierrez et al[24]	*SC aspart-1* Bolus SC: 0.3 U/kg Then 0.1 U/kg q1h Then 0.05 U/kg q1h at BG < 13.8 mmol/L *SC aspart-2*: Bolus SC: 0.3 U/kg Then 0.2 U/kg 1 hour later and q2h Then 0.1 U/kg q1h at BG < 13.8 mmol/L	n = 15 in each group SC aspart-1: 36 ± 8 years SC aspart-2: 38 ± 12 years	7.15 ± 0.12	Nil	Nil

regarding delays in seeking hospital care for diabetes-related emergencies in children and adolescents as well as delayed diagnosis of new cases of type 1 diabetes as families are apprehensive about taking their child to an emergency department (ED) because of fear of exposure to COVID-19. Thus, reports have suggested that as a result of delay in seeking medical attention, affected individuals have presented with more severe DKA.[10]

Telehealth is emerging as an extremely useful alternative to in-person consultations in providing health care remotely. In the context of the COVID-19 pandemic, telephone consultations for sick day management and routine diabetes care should be encouraged. This may assist in identification of children at risk of DKA, help in prevention of DKA, and avoid ED visits.[11] Families should be educated to not omit insulin, remain hydrated, and treat the underlying symptoms of an intercurrent illness[12-14], as well general advice regarding healthy eating and continuing physical activity at home. Frequent monitoring for BG (and ketones when indicated) should be encouraged. In individuals using a continuous glucose monitoring system (CGMS), confirmatory finger-prick BG should be performed, especially if ketosis is present. Notably, rapidly changing BG levels in DKA may limit the value of CGMS. Advances in technology such as downloading records from insulin pumps and CGMS, and remote monitoring should be used wherever possible to optimize glucose control.

4 | DIABETES AND ICU CARE

DKA is usually managed in an ICU in many parts of the world; however, uncomplicated mild to moderate DKA is often managed outside an ICU setting in centers that have adequate resources. In some hospitals, IV insulin may be the reason for prompting ICU admission even in stable mild to moderate DKA. The COVID-19 pandemic has created an unprecedented need for ICU services. Hence, it is essential to reserve ICU beds for those at greatest need and to manage patients out of the ICU setting whenever safely possible. The risk of infection transmission can also be minimized if young individuals with diabetes can be admitted to a medical ward away from people infected with COVID-19 in the ICU. Added ICU charges also escalate the cost of treatment.[15] Hence, if IV insulin is the main reason for ICU admission, alternative modes of insulin administration (particularly via the SC route) may be safe and effective in managing uncomplicated mild to moderate DKA so that ICU admission can be avoided. Non-ICU hospital admission has also been associated with shorter duration of hospital stay.[16]

This guideline, along with the ISPAD 2018 DKA guideline,[1] aim to aid physicians manage uncomplicated mild to moderate DKA with SC or IM insulin. This is intended to be a resource during COVID-19 and other pandemics, as well as in the setting of limited ICU resources for

TABLE 2 ADA evidence-grading system for "Standards of Medical Care in Diabetes"[3]

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

other reasons, in line with the ISPAD limited care appendix 2018,[17] Changing Diabetes in Children (CDiC),[14] and Life For A Child (LFAC)[2] guidelines. It is important to remember that meticulous clinical and biochemical monitoring for tailoring therapy and identifying patients who will need ICU services is essential.

5 | RATIONALE FOR ALTERNATIVE MODES OF INSULIN DELIVERY

There is evidence that alternative modes of insulin administration (particularly via the SC route) may be safe and effective in managing uncomplicated mild to moderate DKA. We searched studies using SC or IM insulin for treatment of DKA, in children and as adults, with or without an IV insulin control group. Eligible studies were identified through PubMed. The date of last search was 30 Jun 2020. Reference lists from included randomized controlled trials (RCTs) and systematic reviews were also examined. Studies and reviews involving SC or IM (short-acting or rapid-acting) insulin in participants of any age or sex with DKA were included.

5.1 | Pharmacokinetics and pharmacodynamics of subcutaneous insulin

For DKA management to be effective and safe, the insulin used should have a rapid onset and a short duration of action. SC rapid-acting insulin analogs are rapidly absorbed into the blood and plasma insulin concentrations reach peak values by ~60 minutes of administration. The glucose lowering effect reaches a maximum by ~90 to 120 minutes after injection.[18] When compared to short-acting regular insulin, rapid-acting insulin lispro showed greater glucose-lowering effect during the initial 2 hours after administration. The pharmacodynamic effects were similar for insulin lispro whether it was given IM or SC.[19] Insulin aspart has similar pharmacokinetic profile and pharmacodynamic effects as lispro and can be used interchangeably in clinical practice.[20]

6 | EVIDENCE FOR SUBCUTANEOUS INSULIN IN DKA

DKA management using SC rapid-acting insulin analogs was analyzed in six RCTs; two pediatric,[16,21] and four adult.[15,22-24] These studies are summarized in Table 1. Four (one pediatric) trials used insulin lispro[15,21-23] and two (one pediatric) studies used aspart.[16,24] There have been no trials evaluating SC glulisine for DKA. Further details of these RCTs are presented in Supporting Information, Table S1.

6.1 | Pediatric studies using subcutaneous rapid-acting insulin analogs for DKA

In children with DKA (pH > 7.0), SC lispro was given at a dose of 0.15 U/kg every 2 hours, commencing 1 to 2 hours after starting IV saline hydration, until the BG decreased to 13.8 mmol/L (250 mg/dL). Thereafter, 0.15 U/kg dosing was spaced to every 4 hours for 24 hours. The control group received IV regular insulin infusion at 0.05 to 0.1 U/kg/hour. In both groups, hyperglycemia resolved in 6 hours; however, spacing the SC injections to four hourly intervals worsened the blood glucose control in the SC arm and resolution of acidosis was significantly prolonged compared to those who received IV insulin. These observations suggest that SC injections of a rapid-acting analog should continue at two hourly intervals until resolution of DKA.[21]

In a similar study, children with mild to moderate DKA were given SC aspart 0.15 U/kg every 2 hours or 0.05-0.1 U/kg/h IV regular

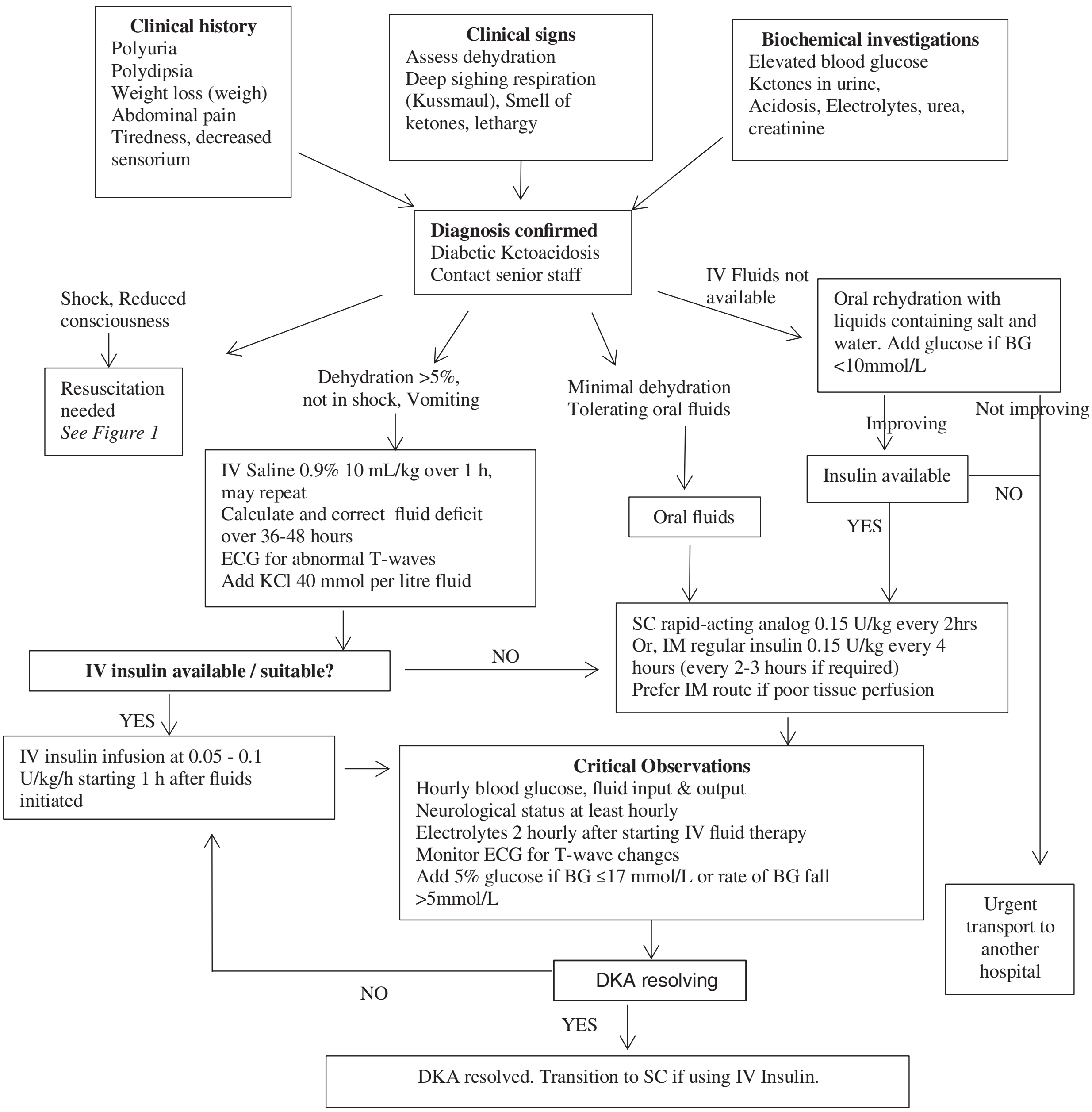


FIGURE 2 Algorithm for management of DKA outside the ICU or in the setting of limited care.[1,2,17] IV, intravenous; SC, subcutaneous; IM, intramuscular; BG, blood glucose; HCO3, serum bicarbonate

insulin infusion.[16] Time to resolution of DKA and rate of decline of BG were similar in both groups and there were no significant adverse effects. Duration of hospitalization was shorter in the children with moderate DKA treated with SC aspart.

6.2 | Adult studies using rapid-acting insulin analogs for DKA

SC lispro and aspart have been used for adults with uncomplicated DKA (pH > 7.0) at various dose regimens and compared to standard IV regular insulin infusion[15,22-24] (Table S1). Time to resolution of hyperglycemia, time to resolution of DKA, total dose of insulin required, length of hospital stay, and rate of hypoglycemia were similar in both the SC and IV treated groups in all four RCTs. None of the studies reported mortality or cerebral edema. The cost of IV insulin in the ICU setting was 39% higher ($P < .01$) than with SC analogs in the non-ICU setting in the single study that performed an economic evaluation.[15]

6.3 | Published reviews on subcutaneous rapid-acting analogs for DKA

One Cochrane and two systematic reviews, published in the last decade,[25-27] evaluated SC rapid-acting analogs for treatment of DKA

(Table S2). The Cochrane review[25] analyzed the evidence from five RCTs[15,22-24] between 2004 and 2011, which used SC rapid-acting insulin analogs (four lispro, one aspart) for treatment of DKA. Compared to the IV insulin group, the SC group had similar time to resolution of DKA and similar frequency of hypoglycemia. The SC lispro groups had a shorter length of hospital stay (mean 0.4 days). Data on morbidity and socioeconomic effects were limited. No deaths were reported. The authors concluded, on the basis of mostly low- to very low-quality evidence, that there are neither advantages nor disadvantages when comparing the effects of SC rapid-acting insulin analogs vs IV regular insulin for treating mild or moderate DKA.

Two systematic reviews (which included the same RCTs that were analyzed in the Cochrane review) concluded similarly that SC rapid-acting insulin was safe and efficacious for mild to moderate DKA.[26,27] The cost difference noted in the single study[15] was secondary to added ICU charges rather than a true difference in the intensity of care required. It was argued that the SC insulin regimen actually increases the nursing work as more frequent nursing interventions (hourly or two-hourly SC injections) are needed.[26] However, the authors concluded that larger, appropriately powered studies are needed to further evaluate the role of SC vs IV insulin in mild to moderate DKA.

6.4 | Studies using subcutaneous regular insulin

Regular insulin may be more readily available and may be more economical than rapid-acting analogs in resource-limited settings. Evidence for use of SC regular insulin for DKA in children is limited. In a retrospective chart review of clinically stable children with DKA (pH 7.22 ± 0.05) admitted to a general pediatric ward, a regimen using SC regular insulin every 4 hours based on a dose of 0.8 to 1 U/kg/day was effective, safe, and feasible.[28] More frequent dosing has been used in adults.[29] Hence, if the biochemical response in children and adolescents is less than satisfactory with four-hourly dosing, SC regular insulin may be injected every 2 to 3 hours. Further details of this study are described in Table S1.

7 | EVIDENCE FOR INTRAMUSCULAR INSULIN FOR DKA

The pharmacokinetic profile of rapid-acting insulin analogs is similar whether injected IM or SC.[19,30] The efficacy of IM insulin for treatment of DKA in children was reported during the 1970s.[31] However, since then, there is no published literature regarding the use of IM insulin in children. The IM route also tends to be more painful than SC injections, and may be a negative feature for use in children especially as frequent injections are needed for DKA management. Studies using IM insulin for DKA are described in Table S3.

SC absorption of insulin may be poor when there is reduced tissue perfusion, particularly in the setting of shock or severe dehydration (as evidenced by lack of urine output, cool moist extremities, low or undetectable blood pressure, rapid feeble pulse, potential renal failure, lethargy or unconsciousness, or coma).[32] Hence, in such conditions, insulin should be administered IV, but if giving IV is not an option; the IM route may be preferred over SC.

Figure 2 presents an algorithm for management of DKA in resource-limited settings (adapted from the CDiC/LFAC guidelines).[2,14] Initial assessment should include severity of dehydration, level of consciousness, and evidence of infection. Careful monitoring of vital signs and biochemical parameters as per the ISPAD 2018 guideline[1] is important to assess therapeutic efficacy and complications. The fluid deficit should be corrected over 36 to 48 hours.[33] If there is minimal dehydration, hemodynamic parameters are stable and the child is tolerating oral fluids, then oral hydration may be initiated.

BOX 2 Key points

- IV insulin infusion is the standard of care for management of DKA.
- SC rapid-acting insulin analogs are effective for treatment of uncomplicated mild to moderate DKA and can be used if IV insulin is not feasible, particularly outside the ICU setting.
- SC regular insulin is also an alternative for treatment of uncomplicated mild to moderate DKA, if rapid-acting insulin analogs and IV regular insulin infusion are not available.
- The management of fluid and electrolytes, and monitoring of clinical response, should be in accordance with the ISPAD 2018 DKA guidelines.
- The suggested starting dose of SC rapid-acting insulin analog (lispro or aspart) is 0.15 U/kg 1 hour after commencement of IV fluid replacement, and then administered every 2 hours until resolution of DKA. Once BG falls to 14-17 mmol/L (250-300 mg/dL), 5% dextrose should be added to the fluids. The dose of SC insulin analog can be reduced to 0.1 U/kg every 2 hours, if the BG continues to decrease by >5 mmol/L (90 mg/dL) per hour.
- For SC regular insulin, the suggested starting dose is 0.13 to 0.17 U/kg/dose every 4 hours, increased or decreased stepwise by 10% to 20% based on the BG prior to insulin injection. Dosing frequency may be increased to every 2 hours if acidosis is not improving.
- BG should be monitored every 1 to 2 hours aiming to maintain BG ~11 mmol/L (200 mg/dL) until DKA has resolved.
- SC insulin therapy may not be appropriate in youth with severe dehydration, when reduced tissue perfusion (capillary refill time >3 seconds) persists after fluid resuscitation, in young children (age <2 years) or in those with serious comorbid/precipitating conditions; that warrant ICU admission.

If IV insulin is not available or feasible, then give SC rapid-acting analogs as per the protocol recommended above until DKA resolution occurs. IV fluids and potassium supplementation may be converted to oral route if resources are limited, provided the child has a good oral intake.

8 | LIMITATIONS AND STRENGTHS

There are very few RCTs comparing SC rapid-acting insulin analogs with conventional IV regular insulin for treatment of DKA. All trials involved a small number of participants and the level of evidence was mostly suboptimal.[25] Data on morbidity and socioeconomic effects were limited. None of the trials reported adverse events other than hypoglycemia. Nevertheless, the findings support the use of SC insulin in resource-limited settings, particularly when ICU admission may not be feasible or desirable (such as during pandemics).

9 | CONCLUSIONS

SC rapid-acting insulin analogs or regular insulin are an acceptable alternative to continuous IV infusion of regular insulin for the treatment of uncomplicated mild and moderate DKA (see Box 2, Figure 2). However, larger, appropriately powered studies in the pediatric age range are needed to adequately address the safety and efficacy of SC vs IV insulin in mild-moderate DKA. Meanwhile, there is sufficient evidence to recommend consideration of SC insulin therapy in circumstances where ICU resources are limited or must be prioritized for other patients, or if treatment with IV insulin is not feasible.

PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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