Diabetic Ketoacidosis in the time of COVID-19: Role of Subcutaneous insulin

Leena Priyambada[1], Joseph I. Wolfsdorf[2], Stuart Brink[3], Maria Fritsch[4], Ethel Codner[5], Kim C. Donaghue[6,7], Maria E. Craig[6,7,8]

[1]Division of Pediatric Endocrinology, Rainbow Children's Hospital, Hyderabad, India

[2]Division of Endocrinology, Boston Children's Hospital, Boston, Massachusetts, USA

[3]New England Diabetes and Endocrinology Center, Waltham, Massachusetts, USA

[4]Department of Pediatric and Adolescent Medicine, Medical University of Graz, Graz, Austria

[5]Institute of Maternal and Child Research, School of Medicine, University of Chile, Santiago, Chile

[6]Sydney Children's Hospital Network, Westmead

[7]Discipline of Child and Adolescent Health, University of Sydney, Australia

[8]School of Women's and Children's Health, University of New South Wales, Sydney, Australia

Executive summary

The International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines 2018 for management of diabetic ketoacidosis (DKA) and the hyperglycemic hyperosmolar state[1, 2] provide comprehensive guidance for management of DKA in young people (Figure 1). Intravenous (IV) infusion of insulin for treating DKA may necessitate intensive care unit (ICU) admission in hospitals in some parts of the world. During the Coronavirus Disease 2019 (COVID-19) pandemic, ICU services may need to be prioritised for care of affected individuals. Particularly in the setting of COVID-19, or other pandemics, ICU admissions for hyperglycemic emergencies may not be practicable, because ICUs may be at capacity with COVID-19 affected patients, or indeed inappropriate due to risk of transmission of

infection to young people with type 1 or 2 diabetes. Hence, while safe management that minimises risk is essential, uncomplicated mild to moderate DKA can be managed outside the ICU setting. The aim of this document, which should be used in conjunction with the ISPAD 2018 guidelines[1], is to ensure that young people with DKA receive management according to best evidence in the context of limited ICU resources. In the midst of the COVID-19 pandemic, this may be applicable in both high resource as well as limited resource settings. The role of physical distancing, hand and respiratory hygiene as well as appropriate use of personal protective equipment as per local protocol are of utmost importance.

Recommendations

- IV insulin remains the standard of care for DKA.[1, 4] IV insulin acts rapidly within minutes and the rate of insulin delivery should be titrated until ketoacidosis resolves. (Level of evidence B)
- IV insulin infusion may be used for management of moderate DKA outside the ICU setting provided protocols are in place and there is appropriate staffing to ensure frequent clinical and biochemical monitoring. (Level of evidence E)
- Subcutaneous (SC) rapid-acting insulin analogs act relatively rapidly, reaching peak serum insulin concentrations within ~60 minutes and peak pharmacodynamic action within ~90-120 minutes of injection.[5] SC rapid-acting insulin analogs can be used for treatment of mild to moderate DKA, particularly outside the ICU setting. (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 guidelines.[1, 6] However, once ketoacidosis has resolved, i.e. pH ≥7.30, serum

bicarbonate ≥15 mmol/L, BOHB <1 mmol/L, and/or closure of the anion gap [1, 7] and the child is able to drink adequately; then the remaining volume of the calculated fluid deficit and potassium replacement if needed can be given orally. (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. (Level of evidence E)

Subcutaneous rapid-acting insulin analogs

- The suggested starting dose of SC rapid-acting insulin analog (lispro or aspart) is 0.15 U/kg one hour after commencement of IV (saline) fluid replacement. Once blood glucose level (BG) falls to 14-17 mmol/L (250-300 mg/dl), add 5% dextrose to the IV fluids. The dose of SC insulin analog can be reduced to 0.1 U/kg every two hours, if the BG continues to decrease by >5 mmol/L (90 mg/dl) per hour. SC doses should be injected every two hours until resolution of DKA. (Level of evidence C)
- BG should be monitored every one to two hours aiming to maintain the level at ~11 mmol/L (200 mg/dL) until ketoacidosis is resolved.[1] (Level of evidence E)
- SC insulin therapy may not be appropriate in severely dehydrated patients (lethargy or unconsciousness, coma, lack of urine output, potential renal failure, cool moist extremities, low or undetectable blood pressure, or a rapid and feeble pulse).[8] SC administration may also not be appropriate when reduced tissue perfusion (capillary refill time >3 sec) persists after fluid resuscitation or in patients with serious co-morbid/precipitating conditions that warrant ICU admission. (Level of evidence E)
- Once the ketoacidosis has resolved and oral intake is tolerated, which usually occurs within 12 hours of initiating treatment in patients with mild to moderate DKA[7], basal (long- or intermediate-acting) insulin can be administered. (Level of evidence E)

Subcutaneous short-acting regular insulin

- SC administration of short-acting regular insulin every four hours is also a safe and effective alternative to IV insulin infusion in children with DKA and pH ≥7.0.[9] A suggested starting dose is 0.13 to 0.17 U/kg/dose every four hours (0.8 to 1 U/ kg/day given in divided doses), increased or decreased stepwise by 10–20% based on the BG prior to insulin injection. Dosing frequency may be increased to every 2 hours if acidosis is not improving.[10] (Level of evidence C)

Intramuscular (IM) regular 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)

COVID-19 and personal protective measures

COVID-19 is a highly infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). According to current evidence, COVID-19 virus is primarily transmitted between people through respiratory droplets and contact routes. Airborne transmission in certain circumstances and feco-oral transmission have also been postulated.[11] The World Health Organization (WHO) has emphasized that the most effective preventive measures in the community include performing meticulous hand hygiene, including washing hands with soap and water for 20 seconds and use of alcohol-based disinfectant hand sanitizers, avoiding touching eyes, nose, and mouth; practicing respiratory hygiene by coughing or sneezing into a bent elbow or tissue and then immediately disposing of the tissue; use of elbow/fist bumps to avoid hand shaking; and maintaining social distance (a minimum of 1 meter) from persons with respiratory symptoms.[11] Wearing of masks or scarves may assist in promoting healthy

distancing. During this time of SARS-CoV2 pandemic, COVID-19 should be considered in the patient with DKA, and a diagnostic procedure that follows local guidelines should be carried out to exclude this diagnosis.

COVID-19, children and diabetes

Children, adolescents, and young adults with COVID-19 have generally experienced less severe clinical manifestations than older adults or were asymptomatic.[12, 13] In an analysis of more than 2100 children, 5% developed hypoxemia and 0.6% progressed to acute respiratory distress syndrome (ARDS).[12] Underlying pulmonary pathology and conditions that impair immunity (such as primary immunodeficiency disorder, chemotherapy for malignancy, chronic immunosuppressive therapy, solid organ transplant, or hematopoietic cell transplant) have been associated with more severe outcomes.[14] Anecdotal evidence suggests that children with diabetes have not shown a different disease pattern or susceptibility when compared to children without diabetes.[15]

In many places, however, hospital services remain closed for non-COVID-19 ailments. There have also been concerns 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, anecdotal reports have suggested that as a result of delay in seeking medical attention, affected individuals have presented with more severe DKA.[16]

The importance of sick day management and maintenance of standard diabetes care at home in order to prevent DKA and avoid visits to the ED cannot be overemphasized.[17-19] Families should

be educated regarding non-omission of insulin, healthy eating, continuing physical activity at home, remaining hydrated and treating the underlying symptoms. Frequent BG monitoring and checking for ketonuria/blood ketones when indicated should be encouraged. In individuals using a continuous glucose monitoring system (CGMS), confirmatory BG monitoring should be performed with fingerpricks, especially if ketosis is present. Rapidly changing BG levels in DKA may limit the value of CGMS. When hospital admission becomes necessary, during this time of the pandemic, the earliest possible discharge should be considered.

Telehealth and/or telephone consultations for sick day management and routine diabetes care should be encouraged. In particular, telephone advice regarding specific sick day questions and the need to seek formal face-to-face evaluation may assist in identification and prevention of children at risk of DKA. Advances in technology such as downloading records from insulin pumps and CGMS, and remote monitoring should be used wherever possible to optimize glucose control.

The COVID-19 pandemic has created an unprecedented need for ICU services, which are becoming increasingly limited. 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. In some parts of the world, IV infusion of insulin for treatment of DKA necessitates ICU admission, however uncomplicated mild to moderate DKA is routinely managed outside the ICU setting in many centres where adequate resources are available.

There is evidence that alternative modes of insulin administration (particularly the SC route) may be safe and effective in managing uncomplicated mild to moderate DKA. These guidelines, along with the ISPAD 2018 DKA guidelines[1], aim to help physicians manage uncomplicated

mild to moderate DKA with SC or IM insulin outside the ICU setting; and are intended to be a resource during COVID-19 and other pandemics, as well as in the setting of limited ICU resources for other reasons, in line with the ISPAD limited care appendix 2018[6], CDIC[18] and LFAC[2] guidelines.

Rationale behind alternative modes of insulin delivery

Pharmacokinetics and pharmacodynamics of subcutaneous and intramuscular insulin

For DKA management to be effective and safe, the insulin used should have a rapid onset and a shorter duration of action. SC rapid-acting insulin analogs are rapidly absorbed into the blood and plasma insulin concentrations reach peak values by ~60 min of administration. The glucose lowering effect reaches a maximum by ~90-120 minutes of injection.[5] 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.[20] Insulin aspart has similar pharmacokinetic profiles and pharmacodynamic effects as lispro and can be used interchangeably in clinical practice.[21]

Evidence for subcutaneous insulin in DKA

Eligible studies were identified through PubMed. The date of last search was 15 April 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.

DKA management using SC rapid-acting insulin analogs was analysed in six RCTs; two pediatric[22, 23] and four adult[24-27]. These studies are summarized in Table 1. Four (one pediatric) trials used insulin lispro[23-26] and two (one pediatric) studies used aspart[22, 27]. There have been no

trials evaluating SC glulisine for DKA. Details of these RCTs are shown in Supplementary Table 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 two hours, commencing 1-2 hours after starting IV saline hydration, until the BG decreased to 13.8 mmol/L (250 mg/dL). Thereafter, 0.15 U/kg was injected every four hours for 24 hours. The control group received IV regular insulin infusion at 0.05-0.1 U/kg/hour. In both groups, hyperglycemia resolved in 6 hours; however, when the SC injections were spaced to four hourly intervals, glucose control worsened 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.[23]

In a similar study, children with mild to moderate DKA were given SC aspart 0.15 U/kg every two hours or 0.05 - 0.1 U/kg/h IV regular insulin infusion.[22] 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.

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 IV regular insulin[24-27] (Supplementary Table 1). 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<0.01) than SC analogs in the non-ICU setting in the single study that performed an economic evaluation.[26]

Published reviews on subcutaneous rapid-acting analogs for DKA

One Cochrane and two systematic reviews published in the last ten years[28-30] evaluated SC rapid-acting analogs for treatment of DKA (Supplementary Table 2). The Cochrane review[28] analyzed the evidence from five RCTs[23-27], between 2004 and 2011, of SC rapid-acting insulin analogs (four lispro, one aspart) for the treatment of DKA. Compared to IV insulin group, the SC group had similar time to resolution of DKA and frequency of hypoglycemia. SC lispro groups had a shorter length of hospital stay (mean 0.4 days shorter). 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 versus IV regular insulin for treating mild or moderate (based on ADA criteria, pH>7.0) DKA.

Two systematic reviews that included RCTs analyzed in the Cochrane review had a similar conclusion that SC rapid-acting insulin was safe and efficacious for mild to moderate DKA.[29, 30] The cost difference noted in the single study[27] was secondary to added ICU charges rather than a true difference in the intensity of care required. It was argued that SC insulin regimen actually increases the nursing work as more frequent nursing interventions (hourly or two-hourly SC injections) are needed.[29] However, larger, appropriately powered studies are needed to evaluate further.

Studies using subcutaneous regular insulin

Regular insulin may be more readily available 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 7.17-7.26) admitted to the general pediatric ward (Supplementary Table 1), a regimen using SC regular insulin every four hours based on a dose of 0.8 to 1 U/kg/day was effective, safe and feasible.[9] More frequent dosing has been used for adults.[10] Hence, if the biochemical response is unsatisfactory, children may require SC regular insulin every 2-3 hours.

Evidence for intramuscular insulin for DKA

The pharmacokinetic profile of rapid-acting insulin analogs is similar whether injected IM or SC.[20] IM insulin may be preferred over SC insulin if there is poor tissue perfusion and IV insulin is not an option. During the 1970s, IM insulin was documented to be efficacious for treatment of children with DKA[31], but there have been no subsequent studies regarding the use of IM insulin for treatment of DKA in children. IM injection tends to be more painful than SC injection. The studies using IM insulin for DKA are described in Supplementary Table 3.

Limitations and strengths

There are few RCTs comparing SC rapid-acting insulin analogs with conventional IV regular insulin for treatment of DKA. All the trials involved a small number of participants and the level of evidence was mostly sub-optimal.[28] Data on morbidity and socioeconomic effects were limited. None of the trials reported on adverse events other than hypoglycemia. Nevertheless, the findings support use of SC insulin in resource limited settings, particularly when ICU admission may not be feasible or desirable (such as during pandemics).

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 1, Figure 2). Larger, appropriately powered studies in the paediatric age range are needed. Meanwhile, there is sufficient evidence to recommend consideration of SC insulin therapy in circumstances where ICU resources are limited or must be prioritised for other patients and treatment with IV insulin is not feasible.

Box 1: Key points

- IV regular insulin infusion may be used for management of moderate DKA outside the ICU setting provided protocols are in place and there is appropriate staffing to ensure frequent clinical and biochemical monitoring.
- SC rapid-acting insulin analogs can be used for treatment of mild to moderate DKA, particularly outside the ICU setting.
- 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.
- The management of fluid and electrolytes should be in accordance with the ISPAD 2018 DKA guideline. Once ketoacidosis has resolved and the child is able to drink adequately; then the remaining volume of the calculated fluid deficit and potassium replacement if needed can be given orally.
- 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.
- The suggested starting dose of SC rapid-acting insulin analog (lispro or aspart) is 0.15 U/kg one hour after commencement of IV fluid replacement, administered every two hours until resolution of DKA. Once BG falls to 14-17 mmol/L (250-300 mg/dl), add 5% dextrose to the IV fluids. The dose of SC insulin analog can be reduced to 0.1 U/kg every two 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 four hours, increased or decreased stepwise by 10–20% 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 one to two hours aiming to maintain BG ~11 mmol/L (200 mg/dL) until ketoacidosis is resolved.

- SC insulin therapy may not be appropriate in severely dehydrated patients, when reduced tissue perfusion (capillary refill time >3 sec) persists after fluid resuscitation or in patients with serious co-morbid/precipitating conditions that warrant ICU admission.
- IM insulin may be preferred over SC insulin if there is poor tissue perfusion and IV insulin is not an option.
- Once the ketoacidosis has resolved and oral intake is tolerated basal (long- or intermediate-acting) insulin can be administered.

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	Inferiority	Superiority
Razavi[22]	*SC aspart:* 0.15 U/kg q2h	n=25 8.6±0.8 yrs	pH.>7.1	BG higher at end of treatment (p ns)	Shorter stay for moderate DKA (3.4 vs 4.4 days)
Della[23]	*SC lispro*: 0.15 U/kg q2h, then q4h	n=30 median 11.3 yrs, range 3-17 yrs	pH >7.0	Glucose control sub-optimal with q4h SC insulin	nil
Karoli[24]	*SC lispro*: SC bolus 0.3 U/kg, then 0.2 U/kg 1 h 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 yrs	pH >7.0	nil	nil
Ersoz[25]	*SC lispro*: IV regular insulin bolus 0.15 U/kg, then SC lispro 0.075 IU/kg q1h	n=10 38.7±19.7 yrs	pH >7.0	nil	nil
Umpierrez[26]	*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 yrs	pH >7.0	nil	Lower hospital cost in non-ICU SC group
Umpierrez[27]	*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 h 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 yrs SC aspart-2: 38 ± 12 yrs	pH >7.0	nil	nil

Supplementary Table 1: Studies on Subcutaneous Insulin in DKA: Study characteristics and levels of evide

Study	Participant characteristics†	Insulin regimens	Time until resolution of DKA (hours)	Time to resolution of hyperglycemia hours)	Total dose of insulin to correct acidosis	Duration of hospital stay (days)	Hypoglycemia	Remarks/Mortality/ Other adverse effects
Pediatric studies								
Razavi et al 2018[22]	RCT *SC aspart* (ward) n=25, 8.6 ± 0.8 Mild/mod DKA: 12/13 *IV* (ICU) n=25, 8.8 ± 0.7 Mild/mod DKA: 6/19, p=0.07	*SC aspart*: 0.15 U/kg q2h *IV regular*: 0.05 - 0.1 U/kg/h infusion	Mild DKA: SC: 10.4 ± 4.2, IV: 10.5 ± 5.9, p = 0.9 Moderate DKA: SC: 13.2. ± 5.4, IV: 16.7 ± 5.7 p=0.09	BG at end of DKA: higher in SC vs IV p-ns Rate of BG fall similar in both groups	*SC*: 1.02 ± 0.4 U/kg *IV*: 3.01 ± 0.23 U/kg, p < 0.001	Mild DKA *SC*: 3.33±1.1 *IV*: 3.17±0.4 P=0.7 Moderate DKA: *SC*: 3.38 ± 0.65 *IV*: 4.42 ± 1.1 p = 0.005	NA No metabolic complications	No deaths Recurrence of DKA within 48 h: SC: 3/25 patients IV: 1/25 patients
Della Manna et al 2005[23]	RCT, n=60 (57 in ED, 3 in ICU) *SC lispro* n=30, median 11.3 yrs (3-17) pH:7.17 ± 0.10 *IV* n=30, 5.5–18 (mean 12.1)yrs pH: 7.18 ± 0.10	*SC lispro*: 0.15 U/kg q2h until BG < 13.8 mmol/L, then q4h for next 24 h *IV regular*: 0.1 U/kg/h infusion	SC: 12 h after BG ≤ 13.8 mmol/L IV:: 6 h after BG ≤ 13.8 mmol/L P<0.05 Bicarbonate given in n=10 (SC-6, IV-4)	Rate of fall of BG similar SC:2.9 mmol/L/h IV: 2.6 mmol/L/h p-ns	Insulin dose in first 6h *SC*: 0.28± 0.19 U/kg *IV*: 0.37± 0.24 U/kg	NA	Mild hypoglycemia (<3.3 mmol/l) IV regular, n = 6; SC lispro, n = 4, p NA).	No deaths or "near death No cerebral edema At 4 hr injection intervals, glycemic control worsened
Cohen et al 2016[9]	Chart review n=76, 11.6±4.0 pH: 7.22 ± 0.05	SC regular insulin 0.13 to 0.17 U/kg q4h Increased or decreased stepwise by 10–20% based on BGL	10.3 (5.5, 14.2)	NA	0.05 (0.04 - 0.06) U/kg/h	na	n=1	None transitioned to IV insulin or to ICU hypokalemia,mostly mild n=14, No cardiac arrhythmias, cerebral edema, or mortality

Adult studies								
Karoli et al 2011[24]	*SC lispro* n=25, (ED), 35±11 yrs pH: 7.16 ± 0.11 *IV:* n=25, (ED) 34 ± 13 yrs pH: 7.18 ± 0.04	*SC lispro:* SC bolus 0.3 U/kg, then 0.2 U/kg after 1 h, then 0.2 U/kg q2h. Reduced to 0.1 U/kg q2h if BG <13.8 mmol/L *IV regular*: Initial IV bolus 0.1 U/kg followed by infusion at 0.1 U/kg/h	*SC lispro*: 12 ±2.2 h *IV regular*: 11± 1.6 h p-ns	Hours to BG <13.8mmol/L *SC*: 7.5 ± 6.3 *IV*: 7.2 ± 6.2 p-ns	*SC*: 100 ±14 U *IV*: 104 ± 12 U	*SC*: 6 ± 1.2 *IV*: 6.6 ± 1.5	No. of events *SC*: n=1 *IV*: n=2,	No mortality No recurrence of DKA No venous thrombosis, respiratory distress syndrome, or hyperchloremic acidosis
Ersoz et al 2006[25]	*SC lispro:*n=10, (Adm Unit NA)38.7±19.7 pH: 7.15± 0.11 *IV:* n=10, 48.8±17.9 (Adm Unit n.r.) pH: 7.18 ±0.12	*SC lispro*: IV regular insulin bolus 0.15 U/kg, followed by SC lispro 0.075 IU/kg q1h *IV regular*: IV bolus 0.15 U/kg, followed by continuous infusion	*SC*: 11.2± 4.9 *IV*: 15.3 ± 8.7 p-ns	Hours to BG <11 mmol/L *SC*: 9.4 ± 8.9 *IV*: 12.7 ± 7.5 p-ns	*SC*: 61.7 ±10.9 U *IV*: 65.2± 12.7U p-ns	NA	Nil	No need for IV insulin treatment due to inadequate response No mortality No recurrence of DKA.
Umpierrez et al 2004[26]	*SC lispro:* n=20, (ward/step down) 37±12, pH 7.17 ± 0.10 *IV:*n=20, (ICU) 39±14 pH: 7.19 ± 0.08	*SC lispro:*initial 0.3 U/kg, then 0.1 U/kg q1h until BG<13.8 mmol/L, then 0.05 - 0.1 U/ kg q1h until DKA resolved *IV regular:*IV bolus 0.1 U/kg, then 0.1 U/kg/h infusion until BG< 13.8 mmol/L, followed by 0.05 to 0.1 U/kg/h until DKA resolved	*SC*: 10 ±3 *IV*:11 ± 4 p-ns	Hours to BG <13.8mmol/L similar	*SC*: 84 ± 32 U *IV*: 98 ± 26 U p: ns	*SC lispro*: 4 ±2 *IV regular:* 4± 1 p: ns	n=1 in each group	None transitioned to IV insulin due to inadequate response No recurrence of DKA Treatment in the ICU with IV had 39% higher charges than with SC in ward.
Umpierrez et al 2004[27]	*SC aspart-1:* n=15, (ward) 36 ±8 yrs pH: 7.14 ± 0.09 *SC aspart-2:* n=15, 38 ± 12 pH: 7.15 ± 0.12 *IV regular:* n=15, 40 ± 13, pH: 7.11 ± 0.17	*SC aspart-1:*Initial dose SC: 0.3 U/kg followed by 0.1 U/kg q1h followed by 0.05 U/kg q1h at BG<13.8 mmol/l *SC aspart-2*: Initial SC: 0.3 U/kg followed by 0.2 U/kg 1 h later and q2h, followed by 0.1 U/kg q1h at BG<13.8 mmol/l *IV regular*: IV bolus followed by infusion	*SC aspart-1:* 10 ± 3 *SC aspart-2:* 10.7±3 *IV*: 11 ± 3 p-ns	Hours to BG<13.8 mmol/l *SC aspart-1*: 6.9 ± 4 *SC aspart-2*: 6.1 ± 4 *IV*: 7.1 ± 5 p-ns	*SC aspart-1:* 85 ± 33 U *SC aspart-2:* 94 ± 32 U *IV*: 82 ± 28 U p-ns	*SC aspart-1:*3.4 ± 3 *SC aspart-2:*3.9 ± 5 *IV* : 4.5 ± 3 p-n.s.	n=1 in each group	None transitioned to IV insulin due to inadequate response Similar hypoglycemic events, No mortality No recurrence of DKA

†n, Age (yrs), pH, admitting unit ward/ED/ICU

BG: blood glucose (capillary); DKA: Diabetic Ketoacidosis; SC: subcutaneous; IV: Intravenous; h: hour; ED: emergency department; ICU: intensive care unit; n.r.: not reported; ns: not significant;

Mean (SD) unless otherwise stated.

BG conversions: 33 mmol/L = 600 mg/dl, 13.8 mmol/L = 250 mg/dl, 11 mmol/L = 200 mg/dl, 3.3 mmol/L= 60 mg/dl

Two RCTs were funded by insulin companies[26, 27]

Supplementary Table 2: Published reviews on subcutaneous insulin in DKA

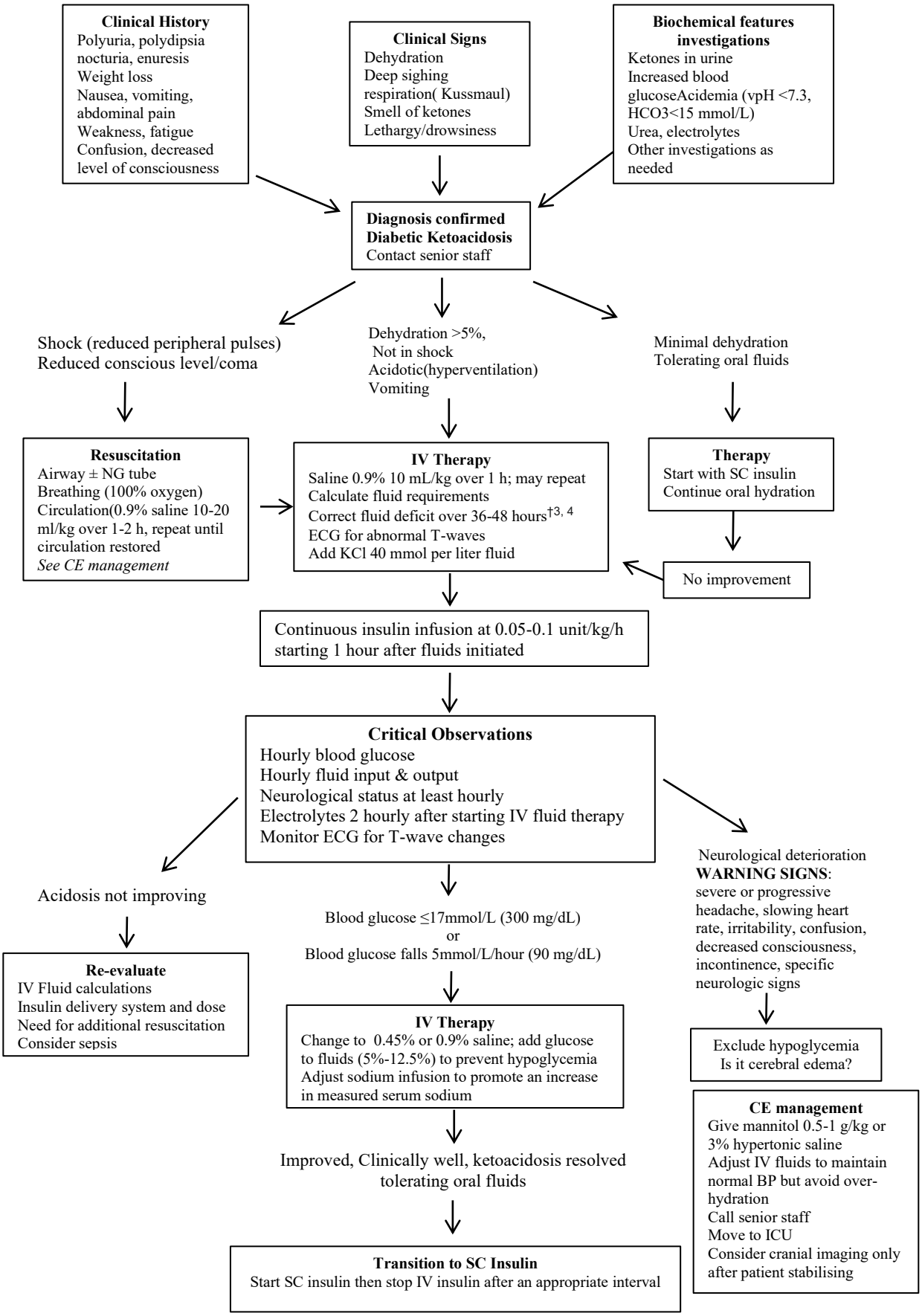
Study	Study characteristics	Pooled outcomes/conclusions			Summary
		Time until resolution of DKA (hours)	Hypoglycemia	Duration of hospital stay (days)	
Andrade-Castellanos 2016[28]	5 RCTs (to 2015) SC analogs vs IV infusion [23-27] 4 adult, 1 pediatric 4 lispro, 1 aspart n=201; 110 to SC, 91 to IV DKA; pH>7.0	*SC lispro*: mean difference (MD) 0.2 h (95% CI -1.7 to 2.1); P = 0.81 *SC aspart:*MD -1 h; 95% CI -3.2 - 1.2 very low-quality evidence	*SC lispro*:: risk ratio (RR) 0.59 (95% CI 0.23 to 1.52); P = 0.28 *SC aspart*: RR 1.00 (95% CI 0.07 to 14.55); P = 1.0 low-quality evidence	*SC lispro*:: MD of -0.4 days (95% CI -1 to 0.2); P = 0.22; *SC aspart*: 1.1 days (95% CI -3.3 to 1.1); P = 0.32; low-quality evidence	Mainly data on adults No deaths No trial reported on adverse events other than hypoglycemic episodes No trial investigated patient satisfaction. Conclusion: Neither advantageous nor disadvantageous in SC vs IV (Mostly low- to very low-quality evidence)
Cohn 2015[29]	5 RCTs (to 2015) SC analogs vs IV infusion [23-27] 4 adult, 1 pediatric 4 lispro, 1 aspart DKA; pH>7.0	No difference in the duration of therapy until resolution of DKA with either group	Incidence of hypoglycemia was low p-ns	-	Initial bolus omitted in children Amount of nursing time required would increase with SC insulin Costs are increased due to ICU charges. The authors questioned the necessity of ICU in uncomplicated mild to moderate DKA.
Vincent 2013[30]	4 RCTs (to 2013) SC lispro only vs IV infusion [23-26] 4 adult, 1 pediatric	No difference in outcomes SC versus IV	Rare, and of mild severity	-	SC insulin feasible alternative to IV Larger, appropriately powered studies needed

DKA: Diabetic Ketoacidosis; RCT: randomised controlled trial; SC: subcutaneous; IV: Intravenous; h: hour; ICU: intensive care unit

Supplementary Table 3: Characteristis of studies using intramuscular insulin for treatment of DKA

Study	N Age (yrs)	Inclusion criteria	Exclusion criteria	Insulin regimens	Time to resolution of DKA (hours)	Total insulin dose to correct acidosis	Duration of hospital stay (days)	Remarks/Mortality/ Other adverse events
Pediatric studies								
Moseley 1975[31]	Case series n=12 1.5 to 14	DKA (all severity)	n.r.	IM regular insulin 0.25 U/kg Followed by 0.1 U/kg q1h IM until resolution of ketoacidosis and BG< 11.1 mmol/l. Follow by q4h SC	n.r.	n.r.	n.r.	No mortality
Adult studies								
Basetty 2017[32]	Chart review n=34 48.3 ±10.3	DKA or DK (without acidosis: Bicarbonate <15)	Severe DKA Incomplete data	Bolus : 0.15 U/kg IV regular insulin added to the IVF plus 0.15 U/kg IM Followed by : 0.1 U/kg q1h IM If BG drop <3-4 mmol/L/h 0.2 U/kg q1h At BG < 13.8 mmol/L, dextrose saline infusion with 8 U regular insulin started.	With precipitating factors 34.7 ±30.1 Without precipitating factors 30.12 ±8.2	With precipitating factors 83.4 ± 48.5U Without precipitating factors 56 ±18U	DKA 5.29 ±3.0 DK 4.2 ±2.6	Safe; no mortality, no hypoglycemia, Economical
Fisher 1977[10]	IM regular n=15, 40.7(19-64) SC regular n=15, 44.3(28-75) IV regular n=15, 37.2(21-69)	DKA	n.r.	IM regular: 0.33U/kg SC regular: 0.33U/kg IV regular: 0.33U/kg Repeat loading dose was given hourly till less than 10% decline in BG, Followed by 7 units q1h by respective routes	n.r.	94 ±15 U 85± 8 U 100± 11 U ns	n.r.	IM: 40% needed 2, 15% needed 3 loading doses SC: 20% needed 2 loading doses IV: 13% needed 2 loading doses, had fastest initial response No hypoglycemia Recommended IV bolus followed by IM regular insulin for DKA management

DKA: diabetic ketoacidosis; DK: diabetic ketosis; RCT: randomised controlled trial; SC: subcutaneous; IV: intravenous; IM: intramuscular; h: hour; ICU: intensive care unit; n.r.: not reported



†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]

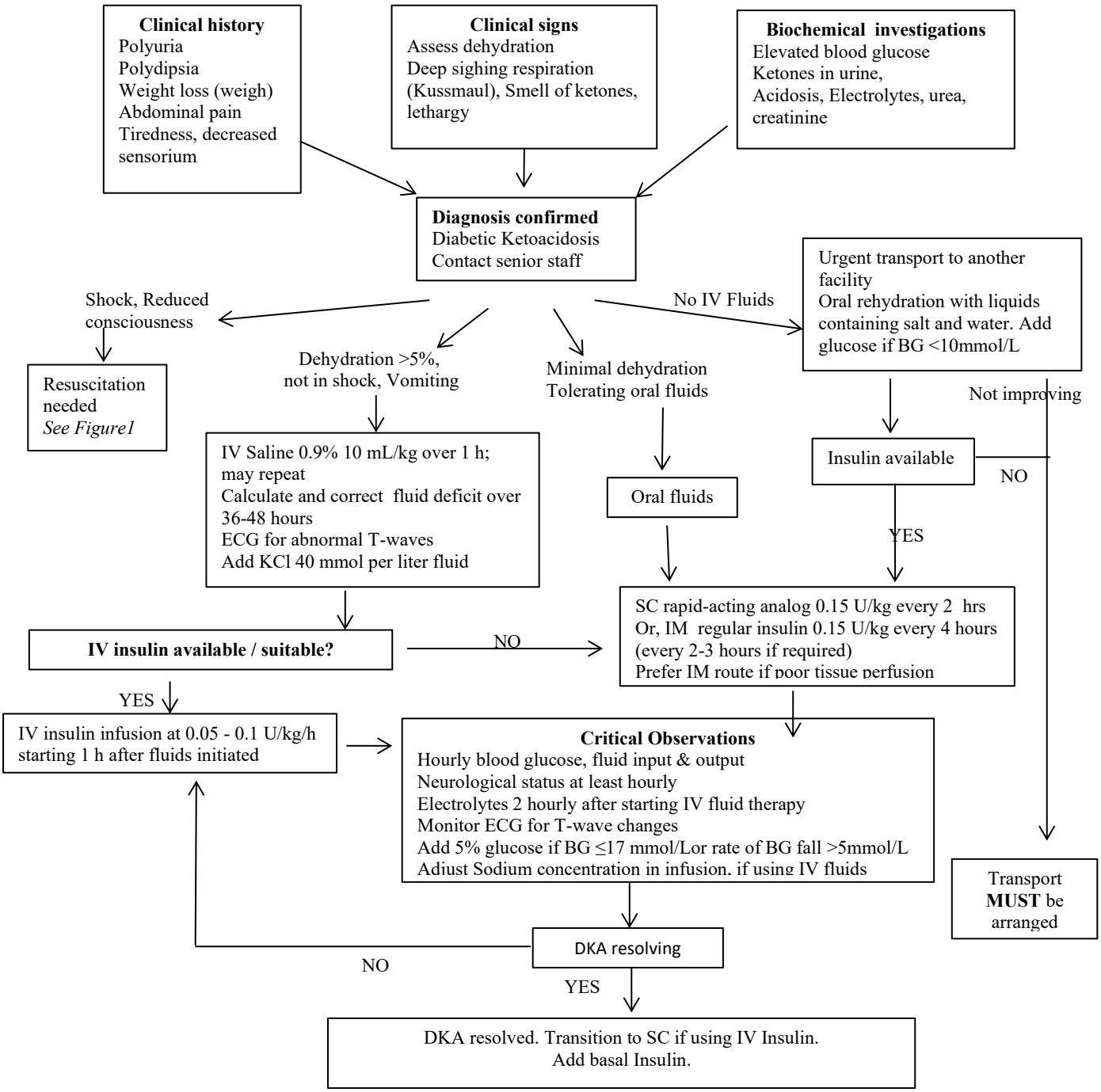


Figure 2: Algorithm for management of DKA outside the ICU or in the setting of limited care. [1, 2, 6]

IV: intravenous; SC: subcutaneous; IM: intramuscular; BG: blood glucose; HCO3: serum bicarbonate

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