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

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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 state¹,² 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 \(\geq 7.30\), serum
bicarbonate \geq 15 \text{ mmol/L}, \ BOHB < 1 \text{ 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 \ \sim 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 \ \geq 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 $\geq 7.0$. 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. In an analysis of more than 2100 children, 5% developed hypoxemia and 0.6% progressed to acute respiratory distress syndrome (ARDS). 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. Anecdotal evidence suggests that children with diabetes have not shown a different disease pattern or susceptibility when compared to children without diabetes.

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.

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. 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, 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, CDIC and LFAC 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 lispro23-26 and two (one pediatric) studies used aspart22, 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 insulin24-27 (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.\textsuperscript{26}

\textit{Published reviews on subcutaneous rapid-acting analogs for DKA}

One Cochrane and two systematic reviews published in the last ten years\textsuperscript{28-30} evaluated SC rapid-acting analogs for treatment of DKA (Supplementary Table 2). The Cochrane review\textsuperscript{28} analyzed the evidence from five RCTs\textsuperscript{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.\textsuperscript{29, 30} The cost difference noted in the single study\textsuperscript{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.\textsuperscript{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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Comparator/dose</th>
<th>Comparator group characteristics (n, mean age ± SD)</th>
<th>DKA severity</th>
<th>Inferiority</th>
<th>Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Razavi²²</td>
<td>SC aspart: 0.15 U/kg q2h</td>
<td>n=25 8.6±0.8 yrs</td>
<td>pH &gt;7.1</td>
<td>BG higher at end of treatment (p ns)</td>
<td>Shorter stay for moderate DKA (3.4 vs 4.4 days)</td>
</tr>
<tr>
<td>Della³³</td>
<td>SC lispro: 0.15 U/kg q2h, then q4h</td>
<td>n=30 median 11.3 yrs, range 3-17 yrs</td>
<td>pH &gt;7.0</td>
<td>Glucose control sub-optimal with q4h SC insulin</td>
<td>nil</td>
</tr>
<tr>
<td>Karoli²⁴</td>
<td>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 &lt;13.8 mmol/L</td>
<td>n=25 35±11 yrs</td>
<td>pH &gt;7.0</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td>Ersoz²⁵</td>
<td>SC lispro: IV regular insulin bolus 0.15 U/kg, then SC lispro 0.075 IU/kg q1h</td>
<td>n=10 38.7±19.7 yrs</td>
<td>pH &gt;7.0</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td>Umpierrez²⁶</td>
<td>SC lispro: SC Bolus 0.3 U/kg followed by 0.1 U/kg q1h until BG&lt;13.8 mmol/L, then 0.05 to 0.1 U/kg q1h</td>
<td>n=20 37±12 yrs</td>
<td>pH &gt;7.0</td>
<td>nil</td>
<td>Lower hospital cost in non-ICU SC group</td>
</tr>
<tr>
<td>Umpierrez²⁷</td>
<td>SC aspart-1 Bolus SC: 0.3 U/kg Then 0.1 U/kg q1h Then 0.05 U/kg q1h at BG&lt;13.8 mmol/l</td>
<td>n=15 in each group</td>
<td>pH &gt;7.0</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td></td>
<td>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&lt;13.8 mmol/l</td>
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</tbody>
</table>
### Supplementary Table 1: Studies on Subcutaneous Insulin in DKA: Study characteristics and levels of evidence

<table>
<thead>
<tr>
<th>Study</th>
<th>Participant characteristics</th>
<th>Insulin regimens</th>
<th>Time until resolution of DKA (hours)</th>
<th>Time to resolution of hyperglycemia (hours)</th>
<th>Total dose of insulin to correct acidosis</th>
<th>Duration of hospital stay (days)</th>
<th>Hypoglycemia</th>
<th>Remarks/Mortality/Other adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Razavi et al 2018&lt;sup&gt;3&lt;/sup&gt;</td>
<td>RCT</td>
<td>SC aspart (ward) n=25, 8.6 ± 0.8 MILD/mod DKA: 12/13</td>
<td>SC aspart: 0.15 U/kg q2h&lt;br&gt;IV regular: 0.05 - 0.1 U/kg/h infusion</td>
<td>Mild DKA: SC: 10.4 ± 4.2, IV: 10.5 ± 5.9, p = 0.9&lt;br&gt;Moderate DKA: SC: 13.2 ± 5.4, IV: 16.7 ± 5.7, p = 0.09</td>
<td>SC: 1.02 ± 0.4 U/kg&lt;br&gt;IV: 3.01 ± 0.23 U/kg, p &lt; 0.001</td>
<td>NA</td>
<td>No metabolic complications</td>
<td>No deaths&lt;br&gt;Recurrence of DKA within 48 h: SC: 3/25 patients IV: 1/25 patients</td>
</tr>
<tr>
<td>Della Manna et al 2005&lt;sup&gt;3&lt;/sup&gt;</td>
<td>RCT, n=60 (57 in ED, 3 in ICU)</td>
<td>SC lispro n=30, median 11.3 yrs (3-17)&lt;br&gt;pH: 7.17 ± 0.10</td>
<td>SC lispro: 0.15 U/kg q2h until BG &lt; 13.8 mmol/L, then q4h for next 24 h&lt;br&gt;IV regular: 0.1 U/kg/h infusion</td>
<td>SC: 12 h after BG ≥ 13.8 mmol/L&lt;br&gt;IV: 6 h after BG ≥ 13.8 mmol/L&lt;br&gt;P=0.05</td>
<td>Rate of fall of BG similar&lt;br&gt;SC: 2.9 mmol/L/h&lt;br&gt;IV: 2.6 mmol/L/h, p=0.05</td>
<td>Insulin dose in first 6h&lt;br&gt;SC: 0.28± 0.19 U/kg&lt;br&gt;IV: 0.37± 0.24 U/kg</td>
<td>NA</td>
<td>MILD hypoglycemia (&lt;3.3 mmol/l)&lt;br&gt;IV regular, n = 6; SC lispro, n = 4, p NA.</td>
</tr>
<tr>
<td>Cohen et al 2016&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Chart review n=76, 11.6±4.0&lt;br&gt;pH: 7.22 ± 0.05</td>
<td>SC regular insulin 0.13 to 0.17 U/kg q4h&lt;br&gt;Increased or decreased stepwise by 10-20% based on BGL</td>
<td>10.3 (5.5, 14.2)</td>
<td>NA</td>
<td>0.05 (0.04 - 0.06) U/kg/h</td>
<td>NA</td>
<td>n=1</td>
<td>None transitioned to IV insulin or to ICU hypokalemia, mostly mild n=14, No cardiac arrhythmias, cerebral edema, or mortality</td>
</tr>
</tbody>
</table>
### Adult studies

<table>
<thead>
<tr>
<th>Study</th>
<th>SC lispro</th>
<th>SC bolus</th>
<th>Hours to BG</th>
<th>SC</th>
<th>No. of events</th>
<th>SC lispro</th>
<th>SC bolus</th>
<th>Hours to BG</th>
<th>SC</th>
<th>No. of events</th>
<th>SC lispro</th>
<th>SC bolus</th>
<th>Hours to BG</th>
<th>SC</th>
<th>No. of events</th>
<th>SC lispro</th>
<th>SC bolus</th>
<th>Hours to BG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karol et al 2011</td>
<td>SC lispro n=25, 0.2 U/kg after 1 h, then 0.2 U/kg q2h. Reduced to 0.1 U/kg q2h if BG &lt;13.8 mmol/L.</td>
<td>Hours to BG</td>
<td>SC</td>
<td>10 ± 3</td>
<td>Hours to BG</td>
<td>SC</td>
<td>10 ± 3</td>
<td>Hours to BG</td>
<td>SC</td>
<td>10 ± 3</td>
<td>Hours to BG</td>
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<tr>
<td>IV: n=25, (ED)</td>
<td>4 ± 13 yrs pH: 7.18 ± 0.04</td>
<td>12 ± 2 h</td>
<td>4 ± 13</td>
<td>7.2 ± 6.2</td>
<td>14 ± 12</td>
<td>6 ± 1.5</td>
<td>2 ± 5</td>
<td>4 ± 13</td>
<td>7.2 ± 6.2</td>
<td>14 ± 12</td>
<td>6 ± 1.5</td>
<td>2 ± 5</td>
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<tr>
<td>Erosz et al 2006</td>
<td>SC lispro: IV regular bolus 0.15 U/kg, followed by continuous infusion</td>
<td>Hours to BG</td>
<td>SC</td>
<td>11.2 ± 4.9</td>
<td>Hours to BG</td>
<td>SC</td>
<td>11.2 ± 4.9</td>
<td>Hours to BG</td>
<td>SC</td>
<td>11.2 ± 4.9</td>
<td>Hours to BG</td>
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<td>IV: n=10, (Adm Unit NA)</td>
<td>19.7</td>
<td>15.3 ± 8.7</td>
<td>15.3 ± 8.7</td>
<td>15.3 ± 8.7</td>
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<tr>
<td>IV: n=10, (Adm Unit n.r.)</td>
<td>8 ± 3.0</td>
<td>8 ± 3.0</td>
<td>12.7 ± 7.5</td>
<td>12.7 ± 7.5</td>
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<td></td>
<td>pH: 7.18 ± 0.12</td>
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<tr>
<td>Umpher rez et al 2004</td>
<td>SC lispro: IV regular bolus 0.15 U/kg, followed by continuous infusion</td>
<td>Hours to BG</td>
<td>SC</td>
<td>10 ± 3</td>
<td>Hours to BG</td>
<td>SC</td>
<td>10 ± 3</td>
<td>Hours to BG</td>
<td>SC</td>
<td>10 ± 3</td>
<td>Hours to BG</td>
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<td>IV: n=20, (ward)</td>
<td>37.1 ± 7.2</td>
<td>11 ± 4</td>
<td>11 ± 4</td>
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<td>pH: 7.17 ± 0.10</td>
<td>p-n</td>
<td>p-n</td>
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<tr>
<td>Umpher rez et al 2004</td>
<td>SC aspart-2: 0.3 U/kg, then 0.2 U/kg q1h following by 0.2 U/kg q1h at BG=13.8 mmol/L</td>
<td>Hours to BG</td>
<td>SC aspart-1:</td>
<td>10 ± 3</td>
<td>Hours to BG</td>
<td>SC aspart-1:</td>
<td>10 ± 3</td>
<td>Hours to BG</td>
<td>SC aspart-1:</td>
<td>10 ± 3</td>
<td>Hours to BG</td>
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<td>SC aspart-1:</td>
<td>36 ± 8 yrs pH: 7.14 ± 0.09</td>
<td>12 ± 2 h</td>
<td>12 ± 2 h</td>
<td>12 ± 2 h</td>
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<td>SC aspart-2:</td>
<td>n=15, 38 ± 12</td>
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<td>SC aspart-2:</td>
<td>pH: 7.15 ± 0.12</td>
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<td>IV regular:</td>
<td>n=15, 40 ± 13 pH: 7.11 ± 0.17</td>
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</tbody>
</table>

### Notes
- No mortality
- No recurrence of DKA
- No venous thrombosis, respiratory distress syndrome, or hyperchloremic acidosis
- No need for IV insulin treatment due to inadequate response
- No mortality
- No recurrence of DKA.
- 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.
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.25, 27
### Supplementary Table 2: Published reviews on subcutaneous insulin in DKA

<table>
<thead>
<tr>
<th>Study</th>
<th>Study characteristics</th>
<th>Pooled outcomes/conclusions</th>
<th>Hypoglycemia</th>
<th>Duration of hospital stay (days)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrade-Castellanos</td>
<td>5 RCTs (to 2015) SC</td>
<td>SC <strong>lispro</strong>: mean difference (MD) 0.2 h (95% CI -1.7 to 2.1); P = 0.81</td>
<td>SC <strong>lispro</strong>: risk ratio (RR) 0.59 (95% CI 0.23 to 1.52); P = 0.28</td>
<td>0.4 days (95% CI -1 to 0.2);</td>
<td>Mainly data on adults No deaths No trial reported on adverse events other than hypoglycaemic episodes No trial investigated patient satisfaction. Conclusion: Neither advantageous nor disadvantageous in SC vs IV (Mostly low- to very low-quality evidence)</td>
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<tr>
<td></td>
<td>analogs vs IV infusion</td>
<td>SC <strong>aspart</strong>: MD -1 h; 95% CI -3.2 to 1.2 very low-quality evidence</td>
<td>SC <strong>aspart</strong>: RR 1.00 (95% CI 0.07 to 14.55); P = 1.0 low-quality evidence</td>
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<td>4 adult, 1 pediatric</td>
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<td>4 lispro, 1 aspart</td>
<td>n=201; 110 to SC, 91 to IV DKA; pH&gt;7.0</td>
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<tr>
<td>Cohn</td>
<td>5 RCTs (to 2015) SC</td>
<td>No difference in the duration of therapy until resolution of DKA with either group</td>
<td>Incidence of hypoglycaemia was low</td>
<td></td>
<td>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.</td>
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<tr>
<td></td>
<td>analogs vs IV infusion</td>
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<td>p-nS</td>
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<td>4 adult, 1 pediatric</td>
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<td></td>
<td>4 lispro, 1 aspart</td>
<td>DKA; pH&gt;7.0</td>
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<tr>
<td>Vincent</td>
<td>4 RCTs (to 2013) SC</td>
<td>No difference in outcomes SC versus IV</td>
<td>Rare, and of mild severity</td>
<td></td>
<td>SC insulin feasible alternative to IV Larger, appropriately powered studies needed</td>
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<tr>
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<td>lispro only vs IV</td>
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<td>infusion</td>
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<td>23-38</td>
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<td>4 adult, 1 pediatric</td>
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</tbody>
</table>

DKA: Diabetic Ketoacidosis; RCT: randomised controlled trial; SC: subcutaneous; IV: Intravenous; h: hour; ICU: intensive care unit
### Supplementary Table 3: Characteristics of studies using intramuscular insulin for treatment of DKA

<table>
<thead>
<tr>
<th>Study</th>
<th>N Age (yrs)</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Insulin regimen</th>
<th>Time to resolution of DKA (hours)</th>
<th>Total insulin dose to correct acidosis</th>
<th>Duration of hospital stay (days)</th>
<th>Remarks/Mortality/Other adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moseley 1975&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Case series n=12 1.5 to 14</td>
<td>DKA (all severity)</td>
<td>n.r.</td>
<td>IM regular insulin 0.25 U/kg Followed by 0.1 U/kg q1h IM until resolution of ketoadosis and BG&lt; 11.1 mmol/L. Follow by q4h SC</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>No mortality</td>
</tr>
<tr>
<td>Basetty 2017&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Chart review n=34 48.3 ± 10.3</td>
<td>DKA or DK (without acidosis: Bicarbonate &lt;15)</td>
<td>Severe DKA Incomplete data</td>
<td>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 &lt;3-4 mmol/L/h 0.2 U/kg q1h At BG &lt; 13.8 mmol/L, dextrose saline infusion with 8 U regular insulin started.</td>
<td>With precipitating factors 34.7 ±30.1 Without precipitating factors 30.12 ±8.2</td>
<td>With precipitating factors 83.4 ±48.5U Without precipitating factors 56 ±18U</td>
<td>DKA 5.29 ±3.0 DK 4.2 ±2.6</td>
<td>Safe; no mortality, no hypoglycemia, Economical</td>
</tr>
<tr>
<td>Fisher 1977&lt;sup&gt;10&lt;/sup&gt;</td>
<td>IM regular n=15, 40.7(19-64) SC regular n=15, 44.3(28-75) IV regular n=15, 37.2(21-69)</td>
<td>DKA</td>
<td>n.r.</td>
<td>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</td>
<td>n.r.</td>
<td>94 ±15 U 85± 8 U 100± 11 U ns</td>
<td>n.r.</td>
<td>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</td>
</tr>
</tbody>
</table>

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
Clinical History
Polyuria, polydipsia nocturia, enuresis
Weight loss
Nausea, vomiting, abdominal pain
Weakness, fatigue
Confusion, decreased level of consciousness

Clinical Signs
Dehydration
Deep sighing respiration (Kussmaul)
Smell of ketones
Lethargy/drowsiness

Biochemical features investigations
Ketones in urine
Increased blood glucose/acidemia (pH < 7.3, HCO3 < 15 mmol/L)
Urea, electrolytes
Other investigations as needed

Diagnosis confirmed Diabetic Ketoadicosis
Contact senior staff

Shock (reduced peripheral pulses)
Reduced conscious level/coma

Resuscitation
Airway ± NG tube
Breathing (100% oxygen)
Circulation/0.9% saline 10-20 ml/kg over 1-2 h, repeat until circulation restored
See CE management

Dehydration >5%, Not in shock
Acidotic (hyperventilation)
Vomiting

Minimal dehydration
Tolerating oral fluids

IV Therapy
Saline 0.9% 10 mL/kg over 1 h; may repeat
Calculate fluid requirements
Correct fluid deficit over 36-48 hours
EGC for abnormal T-waves
Add KCl 40 mmol per liter fluid

Continuous insulin infusion at 0.05-0.1 unit/kg/h
starting 1 hour after fluids initiated

Critical Observations
Hourly blood glucose
Hourly fluid input & output
Neurological status at least hourly
Electrolytes 2 hourly after starting IV fluid therapy
Monitor ECG for T-wave changes

Acidosis not improving

Blood glucose ≤ 17 mmol/L (300 mg/dL)
or
Blood glucose falls 5 mmol/L/hour (90 mg/dL)

Re-evaluate
IV Fluid calculations
Insulin delivery system and dose
Need for additional resuscitation
Consider sepsis

IV Therapy
Change to 0.45% or 0.9% saline; add glucose to fluids (5%-12.5%) to prevent hypoglycaemia
Adjust sodium infusion to promote an increase in measured serum sodium

Improved, Clinically well, ketoacidosis resolved tolerating oral fluids

Transition to SC Insulin
Start SC insulin then stop IV insulin after an appropriate interval

No improvement

Neurological deterioration
WARNING SIGNS:
severe or progressive headache, slowing heart rate, irritability, confusion, decreased consciousness, incontinence, specific neurologic signs

Exclude hypoglycaemia
Is it cerebral edema?

CE management
Give mannitol 0.5-1 g/kg or 3% hypertonic saline
Adjust IV fluids to maintain normal BP but avoid overhydration
Call senior staff
Move to ICU
Consider cranial imaging only after patient stabilising

Infusion therapy
Subcutaneous insulin administration

Figure 1: Algorithm for management of DKA as per ISPAD 2018 guidelines

1Fluid deficit to be corrected over 36-48 hours
IV: intravenous; SC: subcutaneous; IM: intramuscular; BG: blood glucose; HCO3: serum bicarbonate
Clinical history
Polyuria
Polydipsia
Weight loss (weigh)
Abdominal pain
Tiredness, decreased sensorium

Clinical signs
Assess dehydration
Deep sighing respiration
(Kussmaul), Smell of ketones, lethargy

Biochemical investigations
Elevated blood glucose
Ketones in urine,
Acidosis, Electrolytes, urea, creatinine

Diagnosis confirmed
Diabetic Ketoacidosis
Contact senior staff

Shock, Reduced consciousness
Dehydration >5%, not in shock, Vomiting
Minimal dehydration Tolerating oral fluids

Resuscitation needed
See Figure1

IV Saline 0.9% 10 mL/kg over 1 h;
may repeat
Calculate and correct fluid deficit over
36-48 hours
ECG for abnormal T-waves
Add KCl 40 mmol per liter fluid

IV Saline 0.9% 10 mL/kg over 1 h;
may repeat
Calculate and correct fluid deficit over
36-48 hours
ECG for abnormal T-waves
Add KCl 40 mmol per liter fluid

IV insulin available / suitable?

IV insulin infusion at 0.05 - 0.1 U/kg/h
starting 1 h after fluids initiated

IV insulin infusion at 0.05 - 0.1 U/kg/h
starting 1 h after fluids initiated

No IV Fluids
Urgent transport to another facility
Oral rehydration with liquids containing salt and water. Add
glucose if BG <10mmol/L

Insulin available
SC rapid-acting analog 0.15 U/kg every 2 hrs
Or, IM regular insulin 0.15 U/kg every 4 hours
every 2-3 hours if required
Prefer IM route if poor tissue perfusion

Critical Observations
Hourly blood glucose, fluid input & output
Neurological status at least hourly
Electrolytes 2 hourly after starting IV fluid therapy
Monitor ECG for T-wave changes
Add 5% glucose if BG ≤17 mmol/L or rate of BG fall >5mmol/L
Adjust Sodium concentration in infusion, if using IV fluids

DAK resolving

D KA resolved. Transition to SC if using IV Insulin.
Add basal Insulin.

Transport MUST be arranged

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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