

## Diabetic ketoacidosis

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#### 50 **Abstract**

51 Diabetic ketoacidosis (DKA) is the most common acute hyperglycaemic emergency in people  
52 with diabetes mellitus. A diagnosis of DKA is confirmed when all of the three criteria are present  
53 —‘D’, either elevated blood glucose levels or a family history of diabetes mellitus; ‘K’, the  
54 presence of high urinary or blood ketoacids; and ‘A’, a high anion gap metabolic acidosis. Early  
55 diagnosis and management is paramount to improve patient outcome. The mainstays of  
56 treatment include restoration of circulating volume, insulin therapy, electrolyte replacement and  
57 treatment of any underlying precipitating event. Without optimal treatment, DKA remains a  
58 condition with an appreciable, although largely preventable morbidity and mortality. In this  
59 Primer, we discuss the epidemiology, pathogenesis, risk factors and diagnosis of DKA, as well  
60 as we provide practical recommendations for management of DKA in adults and children.

61

62

## [H1] Introduction

Diabetic ketoacidosis (DKA) is the most common acute hyperglycaemic emergency in people with diabetes mellitus. DKA is the consequence of an absolute (that is, total absence of) or relative (that is, levels insufficient to suppress ketone production) lack of insulin and concomitant elevation of counter-regulatory hormones, usually resulting in the triad of hyperglycaemia, metabolic acidosis and ketosis (elevated levels of ketones in the blood or urine; serum ketone concentration of  $>3.0\text{mmol/l}$ ), often accompanied by varying degrees of circulatory volume depletion [G]. DKA occurs mostly in people with uncontrolled type 1 diabetes mellitus (T1DM, which results from the autoimmune destruction of the  $\beta$ -cells of the islets of Langerhans), but can also occur in adults with poorly controlled type 2 diabetes mellitus (T2DM, a result of impaired insulin secretion or action) under stressful conditions such as acute medical or surgical illnesses and, in adolescents, new onset T2DM (also known as ketosis-prone T2DM) (Figure 1). Although any illness or physiological stress can precipitate DKA, the most frequent causes are infections, particularly urinary tract infections and gastroenteritis<sup>1,2</sup>.

DKA was previously considered to be a key clinical feature of T1DM, but has been documented in children and adults with newly diagnosed T2DM<sup>2,3</sup>. Although ketosis-prone T2DM can occur in all populations, epidemiological data suggest that people of African or Hispanic origin seem to be at greater risk<sup>2</sup>. This predisposition likely has a genetic component, but this has yet to be elucidated. Most often individuals with ketosis-prone T2DM have obesity and a strong family history of T2DM and evidence of insulin resistance. Despite presenting with DKA and decreased insulin concentrations, on immunological testing these individuals have the same frequency of the typical autoimmune markers of T1DM such as islet cell, insulin, glutamic acid decarboxylase, and protein tyrosine phosphatase autoantibodies as those who present with HHS and their  $\beta$ -cell function recovers with restoration of insulin secretion quickly after treatment<sup>2</sup>. Thus, individuals with ketosis-prone T2DM can often go back to oral glucose-lowering medication, without the need for continuing insulin therapy. DKA is associated with significant morbidity and utilization of health care resources, accounting for 4–9% of all hospital discharges among those with a diagnosis of diabetes as the primary cause for their acute hospital admission<sup>4</sup>. DKA remains an expensive condition to treat. In the USA, a single episode of DKA is estimated to cost ~\$26,566 (Ref<sup>5</sup>). In the UK, the cost of one DKA episode is estimated to be £2,064 in adults and £1,387 in adolescents (11–18 years of age)<sup>6,7</sup>.

96  
97 The criteria used to define DKA differ in different parts of the world (Table 1). In 2001, the  
98 American Diabetes Association (ADA) expanded the definition of DKA to include mild metabolic  
99 acidosis, hyperglycaemia and positive ketone tests<sup>8,9</sup> (Table 1). Although all the definitions of  
100 DKA concur by saying that all three components need to be present, the glucose concentrations  
101 and method of documenting ketosis vary. Additionally, all guidelines agree that venous or arterial  
102 pH should be <7.30. Early diagnosis and treatment are paramount to improve patient outcomes.  
103 In developed countries, the risk of death resulting from DKA is <1% in children and adults<sup>10,11</sup>  
104 whereas in developing countries, mortality rates are much higher, with reported rates as high as  
105 3–13% in children<sup>12</sup>. Among adults, DKA-related deaths occur primarily in older persons (>60  
106 years of age) or in those with severe precipitating illnesses<sup>1</sup>. In children, the majority of DKA-  
107 related deaths result from cerebral injuries or cerebral oedema. Evidence-based treatment  
108 strategies include correction of fluid deficits, insulin therapy, potassium repletion and correction of  
109 the precipitating factor.

110  
111 The other hyperglycaemic emergency that occurs is hyperosmolar hyperglycaemic state, which  
112 has a distinct pathophysiology to DKA (Box 1).

113  
114 This Primer aims to provide up to date knowledge on the epidemiology, pathophysiology, clinical  
115 presentation, management of DKA. In addition, we also discuss prevention measures after  
116 discharge in adults and children with DKA.

## 117 118 **[H1] Epidemiology**

119  
120 As the majority of people with DKA are hospitalized, most epidemiological data comes from  
121 hospital discharge coding. Among adults, two-thirds of episodes of DKA occur in people  
122 diagnosed with T1DM and one-third occur in those with T2DM<sup>3,11,13</sup>. In children (<18 years of  
123 age), DKA commonly occurs at the initial diagnosis of T1DM, with incidence varying in different  
124 populations from 13% to 80%<sup>14-16</sup>. Adolescents with T2DM also present with DKA, although less  
125 frequently than children with T1DM<sup>14</sup>. In addition, the frequency of DKA at diagnosis correlates  
126 inversely with the frequency of T1DM in the population, suggesting that the more frequent T1DM  
127 occurs in the general population, the more likely that symptoms of new onset are recognised  
128 before it becomes an episode of DKA<sup>17-19</sup>. DKA occurs as the earliest presentation of diabetes in  
129 children <5 years of age, and in people who do not have easy access to medical care for

130 economic or social reasons<sup>20-22</sup>. Among individuals ( between 4.6 to 19.8 years of age), who were  
131 antibody negative and with median BMI z-score [G] 2.3 (2.0, 2.6), 11% presented with ketosis-  
132 prone T2DM<sup>23</sup>. The percentage of adults with ketosis-prone T2DM is unknown; however, since  
133 the early 2000s, the prevalence of ketosis-prone T2DM worldwide has increased<sup>3,13</sup>. Studies  
134 investigating autoimmunity in ketosis-prone T2DM that have suggested an association between  
135 developing the condition and full-length tyrosine phosphatase IA-2 antibody (IA-2FL) or its  
136 extracellular domain (IA-2EC)<sup>24</sup>. Thus, individuals with genetic predisposition might be at greater  
137 risk of developing ketosis-prone T2DM.

138  
139 Epidemiological studies in the USA and Europe revealed increasing hospitalizations for DKA in  
140 adults<sup>10,13,25</sup>. In 2014, the US Centers for Disease Control and Prevention reported a total of  
141 188,950 cases of DKA<sup>10</sup>. Between 2000 and 2009, an average decline of 1.1% in the annual age-  
142 adjusted DKA hospitalization rate was noted among people with any form of diabetes mellitus  
143 between<sup>10</sup>. However, the estimated average annual hospitalization rate increased to 6.3%  
144 between 2009 and 2014, that is, a rise of 54.9% in this period (from 19.5 to 30.2 per 1,000  
145 persons). This increase was observed across all age groups and sexes. The highest  
146 hospitalization rates were in individuals <45 years of age, which might be attributed to poor  
147 control (44.3 per 1,000 persons in 2014) and lowest in persons >65 years of age for reasons  
148 unknown (<2.0 per 1,000 persons in 2014)<sup>10</sup>. The causes of increased DKA hospitalizations are  
149 not clear, but might relate to changes in DKA definition<sup>8,9</sup>, use of new medications associated with  
150 increased DKA risk and lower thresholds for hospitalization (that is, admission of individuals with  
151 less serious disease)<sup>10,13</sup>.

152  
153 The rise in hospitalizations for DKA in the USA parallels the increased trend observed in the UK,  
154 Australia, New Zealand and Denmark<sup>11,26,27</sup>. A study from the UK examined nationally  
155 representative data in those with existing T1DM and T2DM using the Clinical Practice Research  
156 Datalink and the Hospital Episode Statistics databases between 1998 and 2013 (Ref<sup>11</sup>). The  
157 study found that the incidence of DKA was highest in adults between 18 and 24 years of age  
158 within 1 year of diagnosis, potentially suggesting a need for greater education on managing their  
159 diabetes at the time of diagnosis. In agreement with these reports, a systematic review<sup>25</sup> reported  
160 worldwide incidence of 8–51.3 cases per 1,000 patient-years in individuals with T1DM, which has  
161 shown to be the highest in men between 15 to 39 years of age<sup>28</sup>. These data made no distinction  
162 between first or recurrent (an individual presenting with >1 episode at any time after their first  
163 event) episodes of DKA. Furthermore, the Guangdong Type 1 Diabetes Translational Study

164 Group reported a much higher incidence across China (263 per 1,000 patient-years), which the  
165 investigators attributed to differences in national health care systems where people with T1DM  
166 have limited access to routine health care as well as infrequent self-monitoring of blood  
167 glucose<sup>29</sup>. However, in jurisdictions such as Taiwan, Germany and Italy, DKA hospitalization rates  
168 have decreased<sup>30-32</sup>. The reasons for this decrease are unknown, but might be due to  
169 improvements in access to healthcare and/or increased recognition of the early signs of  
170 hyperglycaemia and DKA.

171  
172 Recurrent DKA accounts for a substantial portion of the hospitalizations amongst adults with  
173 diabetes mellitus; 66% for T1DM and 35% for T2DM in the UK<sup>11</sup>. However, a study in the USA  
174 reported recurrent DKA in 21.6% of adults with T1DM or T2DM between 18 and 89 years of age.  
175 Of those with recurrent DKA, 16% had been hospitalized at more than one hospital<sup>33</sup>, implying  
176 that patients do not get continuity of care and that their care is fragmented. Recurrent DKA often  
177 occurs in a small number of adults or children who have behavioural, social or psychological  
178 problems who make up a disproportionate number of DKA admissions<sup>33,34</sup>.

179  
180 In developed countries, hospital case-fatality rates have declined over time with current reported  
181 mortality rates of <1% were observed across all age groups and sexes<sup>10,35</sup>. However, DKA is the  
182 leading cause of mortality among children and adults <58 years old with T1DM, accounting for  
183 >50% of all deaths in children with diabetes mellitus<sup>36</sup>. Mortality increases substantially in those  
184 with comorbidities and with ageing, reaching 8–10% in those >65–75 years of age<sup>1,37</sup>. The  
185 highest rates of DKA have been suggested to occur in regions least able to afford healthcare<sup>38</sup>.  
186 Mortality might also be higher in these populations, for example, data from India showed a 30%  
187 mortality in those presenting with DKA<sup>39</sup> and studies from sub-Saharan Africa have reported  
188 similarly high mortality (26–41.3%), whereas a study from Jamaica reported a mortality of 6.7%<sup>39-  
189 41</sup>. Limited resources in the treating hospital, late presentation or higher case load in larger  
190 institutions might contribute to the higher mortality.

## 191 192 **[H2] Risk factors**

193 In adults with known diabetes mellitus, precipitating factors for DKA include infections,  
194 intercurrent illnesses such as acute coronary syndrome, insulin pump issues (for example,  
195 dislodgement or blockage of infusion sets), and poor adherence and noncompliance with insulin  
196 therapy (Table 2)<sup>1,35</sup>. Several new studies have emphasized the impact of poor treatment  
197 adherence on the incidence of DKA. For example, in the USA, among urban Afro-Caribbean

198 populations and in underinsured people, noncompliance was the principal cause for the  
199 development of DKA<sup>42</sup>. As a result, poor adherence to insulin treatment accounted for >50% of  
200 DKA admissions to a large urban hospital<sup>33,42</sup>. A study reported that persons without health  
201 insurance or with Medicaid alone (in the USA) had hospitalisation rates 2–3 times higher for DKA  
202 than those with private insurance. A study examining two community hospitals in Chicago, IL,  
203 identified that most cases of DKA were caused by people with diabetes mellitus omitting their  
204 insulin (failure to administer insulin as directed) and medical illness accounted for less than one-  
205 third of admissions<sup>33</sup>. In the UK, the most frequent cause of DKA was infection, followed by non-  
206 compliance<sup>35</sup>. Other conditions that are known to precipitate DKA include myocardial infarction,  
207 cerebrovascular accidents, pancreatitis, alcohol misuse, pulmonary embolism and trauma<sup>1,8,35</sup>.  
208 The risk factors for recurrent DKA include low socioeconomic status, adolescence, female sex  
209 (possibly due to a higher incidence of deliberate insulin omission, psychological issues, eating  
210 disorders, and body dysmorphia<sup>43</sup>), high glycated haemoglobin (HbA1c), previous episodes of  
211 DKA and a history of mental health problems<sup>44-49</sup>.

212  
213 In children, lack of prompt recognition of new-onset T1DM by healthcare providers increases the  
214 risk of DKA at diagnosis<sup>50</sup>. Among children with known T1DM, the majority of DKA episodes are  
215 caused by insulin omission with a minority of episodes occurring in association with infections —  
216 most often gastrointestinal infections with vomiting and an inability to keep hydrated<sup>51</sup>. Risk  
217 factors for DKA in children with known diabetes mellitus include poor diabetes control, previous  
218 episodes of DKA, unstable or challenging family or social circumstances; adolescent age, being a  
219 peripubertal girl, and having limited access to medical services<sup>52,53</sup>. A study showed that in the  
220 USA and in India, a small proportion (5.5% and 6.6%, respectively) of people aged ≤19 years  
221 who are eventually diagnosed with T2DM present with DKA<sup>54</sup>. Whether this is ketosis-prone  
222 T2DM is unknown as genetic analyses on these individuals is unavailable.

223  
224 Psychological factors also influence the likelihood of developing DKA<sup>55,56</sup>. A report of ~350  
225 adolescent girls and women (aged 13–60 years) suggested that disordered eating and was a  
226 contributing factor in ~20% of recurrent episodes of DKA<sup>57</sup>. Furthermore, ~30% of young women  
227 (15 ± 2 years of age) with T1DM have been suggested to have an eating disorder<sup>58</sup>. When  
228 questioned, the women omitted insulin because of a fear of weight gain with good glycaemic  
229 control, diabetes-related distress, fear of hypoglycaemia, and rebellion from authority<sup>59</sup>.

230

231 **[H3] Pharmacological risk factors.**

232 As mentioned, insulin mismanagement or omission can lead to DKA. Most often treatment  
233 involves insulin given in a multiple dose regimen. However, data from the UK National  
234 Paediatric Diabetes Audit shows that insulin pump use is also associated with an increased  
235 risk of DKA in the <18 year old population<sup>60</sup>. DKA has also been reported in people with  
236 diabetes mellitus treated with sodium–glucose transport protein 2 (SGLT2) inhibitors. Results  
237 from randomized controlled trials (RCTs) have indicated that DKA is rare in patients with  
238 T2DM treated with SGLT2 inhibitors (incidence of 0.16–0.76 events per 1,000 patient-  
239 years<sup>61</sup>). Several RCTs, however, have reported a higher risk of SGLT2 inhibitor-associated  
240 ketosis in adults with T1DM (5–12%)<sup>62-64</sup> and an incidence of DKA in ~3–5% in those with  
241 T1DM treated with SGLT2 inhibitors<sup>62,65</sup>. The incidence of DKA in those receiving placebo in  
242 these RCTs of people with T1DM was 0–1.9%<sup>64</sup> and DKA occurred despite the use of  
243 measures designed to minimize the risk of ketosis. These risk mitigation strategies have  
244 been described elsewhere<sup>66,67</sup>. With the regulatory approval of SGLT2 inhibitors for use in  
245 patients with overweight and T1DM in Europe<sup>68</sup>, the actual rates of DKA outside of a clinical  
246 trial setting remain to be determined. The only other drug licensed in the USA for use in  
247 people with T1DM is pramlintide<sup>69</sup>. The use of this drug is not associated with the  
248 development of DKA, but is seldom used because it needs to be injected at each meal as a  
249 separate injection to insulin, causes nausea, and hypoglycaemia might occur if the insulin to  
250 carbohydrate ratio is incorrect. Thus, there is a need to develop better adjunctive treatments  
251 alongside insulin for people with T1DM.

252  
253 Data from the T1DM exchange registry in the USA has shown that cannabis use is associated  
254 with an increased risk of developing DKA<sup>70</sup>. In addition, drugs that affect carbohydrate  
255 metabolism such as corticosteroids, sympathomimetic agents (used in nasal decongestants)  
256 and pentamidine (an antimicrobial agent most frequently used to treat protozoal infection or  
257 pneumonia) can precipitate the development of DKA<sup>1,9</sup>. Atypical antipsychotic agents have been  
258 associated with weight gain and T2DM, but are also associated with DKA, which occur acutely  
259 even in the absence of weight gain<sup>71,72</sup>. Cancer treatment using immune check-point inhibitors  
260 (ICIs), such as those that block CTLA-4, and PD-1 or its ligand PD-L1 (Refs<sup>73,74</sup>), have been  
261 linked to new-onset autoimmune T1DM<sup>54,75,76</sup>. The WHO database of individual case safety  
262 reports described a total of 283 cases of new-onset diabetes with >50% of patients with ICI-  
263 induced diabetes mellitus presenting with DKA<sup>75,76</sup>. Additionally, a case series involving large  
264 academic medical centres estimated an incidence of 1% of new-onset T1DM with a median time  
265 of 49 days to onset and 76% of the cases presented with DKA<sup>74,76,77</sup>.

266

## 267 **[H1] Mechanisms/pathophysiology**

268

269 In T1DM or T2DM, when there is absolute or relative insulin deficiency or in times of acute  
270 illness, which is associated with an increase in the counter-regulatory hormones, cortisol,  
271 growth hormone, glucagon and catecholamines, DKA may occur. These alterations in hormone  
272 levels and the subsequent inflammatory response form the basis of the pathophysiological  
273 mechanisms involved in DKA. The changes in hormone concentrations lead to alterations in  
274 glucose production and disposal, as well as increased lipolysis and ketone body production  
275 (Figure 2). Intercurrent illness can lead to the production of counter regulatory hormones leading  
276 to hyperglycaemia and the pro-inflammatory state resulting from an infection precipitate DKA.

277

## 278 **[H2] Gluconeogenesis and hyperglycaemia**

279 In diabetes mellitus, insulin deficiency leads to increased gluconeogenesis (hepatic glucose  
280 production), which is simultaneously accompanied by impaired glucose uptake and use in  
281 peripheral tissues<sup>78,79</sup>, resulting in hyperglycaemia. In healthy individuals, ~20% of total  
282 endogenous glucose production also comes from the kidneys as a result of a combination of  
283 gluconeogenesis and glycogenolysis<sup>80</sup>. Endogenous renal glucose production has been  
284 speculated to be increased in DKA because data from the 1970's suggest that the presence of  
285 an acidosis increase renal glucose output, whilst impairing hepatic gluconeogenesis<sup>81</sup>. In T1DM  
286 and T2DM, increased hepatic gluconeogenesis results from the increased availability of  
287 gluconeogenic precursors such as lactate, glycerol and several gluconeogenic amino acids  
288 including alanine, glycine and serine. Furthermore, low insulin concentrations lead to catabolism  
289 of protein from muscles, liberating amino acids that are gluconeogenic and ketogenic such as  
290 tyrosine, isoleucine and phenylalanine, or purely ketogenic such as lysine and leucine.  
291 Catabolism of isoleucine, lysine and tryptophan lead to the formation of acetyl coenzyme A  
292 (acetyl CoA); catabolism of phenylalanine and tyrosine lead to the formation of acetoacetate;  
293 and leucine leads to the production of  $\beta$ -Hydroxy- $\beta$ -methylglutaryl-CoA (HMG-CoA) — all of  
294 which feed into the production of ketone bodies. High glucagon, catecholamine and cortisol  
295 concentrations relative to insulin levels stimulate gluconeogenic enzyme activity, in particular  
296 phosphoenol pyruvate carboxykinase, fructose-1,6-bisphosphatase and pyruvate carboxylase,  
297 all of which augment hyperglycaemia<sup>79,82,83</sup>.

298

299 **[H3] Ketogenesis.** The increase in counter-regulatory hormone concentrations associated with

300 severe insulin deficiency activates hormone-sensitive lipase in adipose tissue. Lipolysis of  
301 endogenous triglycerides by this enzyme releases large quantities of free fatty acids (FFAs) and  
302 glycerol into the circulation<sup>84</sup>. These FFAs are oxidized to ketone bodies in the hepatic  
303 mitochondria, a process mediated by high glucagon concentrations. Glucagon reduces the  
304 hepatic concentrations of malonyl CoA, which is the first committed intermediate in the lipogenic  
305 pathway<sup>85</sup>. Malonyl CoA is also a potent inhibitor of fatty acid oxidation and inhibits the enzyme,  
306 carnitine palmitoyltransferase 1 (CPT1). CPT1 regulates the uptake of FFAs into the  
307 mitochondria for  $\beta$ -oxidation<sup>86</sup>, causing an accumulation of acetyl CoA. Under normal  
308 circumstances, acetyl CoA enters the tricarboxylic acid (TCA) cycle (also known as Krebs cycle)  
309 and, subsequently, the mitochondrial electron transport chain to synthesize ATP. However,  
310 when acetyl CoA production exceeds the levels that can be metabolized by the TCA cycle, two  
311 molecules of acetyl CoA condense to form acetoacetyl-CoA, which can condense with another  
312 acetyl CoA molecule to form  $\beta$ -hydroxy- $\beta$ -methylglutaryl-CoA (HMG-CoA). The enzyme HMG-  
313 CoA synthase is stimulated by glucagon and inhibited by insulin, therefore, in times of fasting or  
314 insulin deprivation, the enzyme actively produces HMG-CoA. HMG-CoA within the mitochondria  
315 is lysed to form acetoacetate (as opposed to in the cytosol, where it is involved in cholesterol  
316 synthesis), which can further spontaneously degrade to form acetone or be metabolized to  $\beta$ -  
317 hydroxybutyrate<sup>87</sup>. The acetone, acetoacetate and  $\beta$ -hydroxybutyrate constitute the three ketone  
318 bodies produced by the liver. The exhaled acetone is what gives the classic 'fruity' breath in  
319 people presenting with DKA. Of these, acetoacetate and  $\beta$ -hydroxybutyrate are acidic, that is,  
320 they are ketoacids having pKa [G] values of 3.6 and 4.7 respectively. Concurrent with increased  
321 ketone body production, the clearance of  $\beta$ -hydroxybutyrate and acetoacetate is reduced.  
322 Acidosis occurs due to the buffering of the protons produced by the dissociation of ketoacids  
323 that occurs at physiological pH. The reduced clearance of ketones contributes to the high  
324 concentration of anions in the circulation, which also contributes to the development of DKA<sup>88</sup>.  
325 However, the reason for this decreased clearance remains uncertain<sup>79,89</sup>.

326

327 Accumulation of ketoacids leads to a decrease in serum bicarbonate concentration and  
328 retention of these 'fixed acids' leads to the development of high anion gap metabolic acidosis.  
329 The anion gap is a calculation of the difference between the cations and anions in the serum  
330 and the difference can be used as a guide to the cause of the excess acidity. If there is a large  
331 difference that is not accounted for by the anions and cations in the equation, then alternative  
332 causes for the difference must be found. The most frequently used equation to calculate anion  
333 gap is  $([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$ , although some investigators do not include potassium

334 ion concentration owing to its negligible effect on the overall result. In healthy individuals, the  
335 reference range is most frequently 10–14 mmol/l<sup>90-92</sup>. The relationship between the change in  
336 the anion gap and the change in serum bicarbonate concentration is not always 1:1, as was  
337 previously postulated, which might be owing to the contribution of unmeasured cations (UC) (for  
338 example, Ca<sup>2+</sup> and Mg<sup>2+</sup>) and unmeasured anions (UA) (for example, HPO<sub>4</sub><sup>-</sup>, SO<sub>4</sub><sup>2-</sup>). Thus, the  
339 true equation for anion gap can be expressed as [Na<sup>+</sup>] + [K<sup>+</sup>] + UC = [Cl<sup>-</sup>] + [HCO<sub>3</sub><sup>-</sup>] + UA,  
340 which can be arranged as [Na<sup>+</sup>] + [K<sup>+</sup>] – [Cl<sup>-</sup>] + [HCO<sub>3</sub><sup>-</sup>] = UA – UC = anion gap. Thus, the  
341 difference between the UAs and UCs also constitutes the anion gap<sup>90</sup>. Other components of the  
342 plasma, in particular albumin, can affect the relationship between the severity of the acidosis,  
343 the bicarbonate and anion gap and this relationship is discussed in more detail elsewhere<sup>90,93</sup>.  
344 The measure of acidity is important because as pH falls <7.35, intracellular biological systems  
345 begin to fail, leading to irreversible damage at ~pH <6.8. This low pH can lead to neurological  
346 dysfunction, leading the coma, and if severe or prolonged enough, death.

347

## 348 [H2] Osmotic diuresis

349 The severity of hyperglycaemia and the high concentrations of acetoacetate and β-  
350 hydroxybutyrate cause osmotic diuresis leading to hypovolaemia (state of extracellular volume  
351 depletion) with contraction of arterial blood volume. The osmotic diuresis also leads to a  
352 decreased glomerular filtration rate [G], therefore, reducing the ability to excrete glucose. The  
353 hypovolaemia leads to further increases in the levels of counter-regulatory hormones, further  
354 aggravating hyperglycaemia<sup>94</sup>. The resulting low circulating volume leads to generalised  
355 hypoperfusion and can also lead to a rise in lactic acid. Owing to lack of perfusion, peripheral  
356 tissues become deprived of oxygen and switch to anaerobic respiration, thereby generating  
357 lactate, worsening the acidaemia (the state of low blood pH). The lack of renal perfusion can  
358 lead to pre-renal renal failure. This lack of renal perfusion means that there is an inability to  
359 adequately excrete acids such as sulphate, phosphate or urate, further exacerbating the high  
360 anion gap acidaemia. The osmotic diuresis, as well as the associated vomiting and inability to  
361 take fluid orally or a lower conscious level lead to worsening of the dehydration. The  
362 hyperglycaemia might be worsened by the ingestion of sugar sweetened beverages to quench  
363 the thirst experienced by these individuals.

364

## 365 [H2] Electrolyte disturbance

366 Insulin maintains the potassium (a predominantly intracellular cation) concentrations within the  
367 intracellular fluid. Thus, the lack of insulin causes potassium to move into the extracellular

368 space. As the plasma pH falls due to the rise in ketone concentrations, plasma bicarbonate ions  
369 act as one of the main buffers to maintain the physiological pH (that is, pH 7.4). As acidaemia  
370 progresses and the pH falls further, the bicarbonate concentration drops because it buffers [G]  
371 the increase in hydrogen ion concentration, and further tissue buffering becomes crucial. To  
372 achieve this, extracellular hydrogen ions from the ketoacids are exchanged for intracellular  
373 potassium ions. In addition, the extracellular hypertonicity [G] causes movement of water from  
374 the intracellular space to the extracellular space leading to further loss of intracellular  
375 potassium. Furthermore, owing to the osmotic diuresis, the circulating volume decreases and  
376 aldosterone concentration increases. Aldosterone works by conserving sodium reabsorption in  
377 the kidney by excreting potassium in the urine, leading to further potassium loss. The end effect  
378 of these physiological attempts at maintaining buffering capacity and electrical neutrality is  
379 hyperkalaemia. A study from 1956 showed that for each 0.1 unit fall in pH, serum potassium  
380 concentration increased by 0.6mmol/l<sup>95</sup>. Thus in the acute stage before fluid and insulin  
381 treatment is started, serum potassium can be as high as  $\geq 7.0$ mmol/l, yet because of the renal  
382 loss, total body potassium stores are usually substantially depleted, which is estimated to be 3–  
383 5mmol/Kg<sup>9</sup>.

384

## 385 [H2] Inflammation

386 Severe hyperglycaemia and the occurrence of ketoacidosis result in a pro-inflammatory state,  
387 evidenced by an elevation of oxidative stress markers and increased concentrations of pro-  
388 inflammatory cytokines<sup>96-99</sup>. This increase in inflammatory cytokines leads to white adipose  
389 tissue dysfunction by inhibiting insulin signalling or increasing lipolysis, thereby leading to  
390 greater transport of FFAs to the liver, which act as ketogenic substrates<sup>100-102</sup>. In diabetic  
391 conditions, impaired insulin signalling that results in severe hyperglycaemia can induce the liver  
392 to produce CRP (a pro-inflammatory marker) under the influence of activated macrophages that  
393 secrete pro-inflammatory cytokines such as, IL-6, IL-1 $\beta$ , and TNF. These cytokines, in turn, can  
394 impair insulin secretion and reduce insulin action further exacerbating DKA<sup>97,98,103,104</sup>. The  
395 elevated FFAs also induce insulin resistance and at the same time cause endothelial  
396 dysfunction by impairing nitric oxide production in endothelial cells<sup>105,106</sup>. Together, the  
397 inflammatory response induces oxidative stress and the subsequent generation of reactive  
398 oxygen species lead to capillary endothelial disruption and damage of cellular lipids, proteins,  
399 membranes, and DNA<sup>97,99</sup>. The inflammatory state caused by has also been hypothesized to be  
400 involved in causing complications of DKA in children, particularly cerebral oedema and cerebral  
401 injury<sup>107-109</sup>. The cerebral oedema in DKA is vasogenic (that is, resulting from the disruption of

402 the blood–brain barrier) but the mechanism remains undetermined.

403

404 The reasons for coma or reduction in cognitive ability in DKA are yet to be elucidated. Given  
405 that some people are fully alert and orientated with a pH of 6.9, whereas others are obtunded at  
406 a pH of 7.2 suggests that an element of ‘physiological reserve’ might be involved. However, the  
407 degree of circulatory volume depletion, high glucose concentrations and rapid shift of  
408 electrolytes between the intracellular and extracellular spaces might also play a part.

## 409 **[H2] SGLT2 inhibitor-induced ketoacidosis**

410

411 By promoting a glycosuria, the SGLT2 inhibitors lower circulating glucose concentrations<sup>110</sup>.  
412 As glucose concentrations drop, insulin concentrations also drop and glucagon rises.  
413 Together these changes promote lipid  $\beta$ -oxidation, and ketoacid production occurs<sup>111-113</sup>. In  
414 patients already using insulin, as glucose concentrations drop, insulin doses may be  
415 reduced, but ketogenesis is not prevented. As ketone concentrations continue to rise, DKA  
416 may occur – but crucially, as the circulating glucose concentrations are low, euglycaemic  
417 DKA occurs more frequently in these individuals<sup>114,115</sup>. The mechanism for the development  
418 of DKA with SGLT2 inhibitors has been discussed in detail elsewhere<sup>114,115</sup>.

419

420

## 421 **[H2] Alcoholic ketoacidosis**

422 Alcoholic ketoacidosis has a different pathogenesis from DKA and develops in people with  
423 chronic alcohol abuse who have binged, resulting in nausea, vomiting and acute  
424 starvation<sup>116,117</sup>. Blood glucose concentration is the key diagnostic feature that differentiates  
425 DKA and alcohol-induced ketoacidosis. Acute alcohol withdrawal can cause counter-regulatory  
426 hormone release and any accompanying starvation will be associated with low insulin secretion,  
427 which, in turn, causes lipolysis and ketogenesis. Furthermore, the enzyme, alcohol  
428 dehydrogenase, metabolizes ethanol to acetaldehyde, which is metabolized to acetic acid and  
429 transported into the mitochondria, where it is converted into acetyl CoA that subsequently  
430 condenses to acetoacetate<sup>118</sup>. In contrast to DKA that usually presents with severe  
431 hyperglycaemia, the presence of ketoacidosis without hyperglycaemia in an alcoholic patient is  
432 virtually diagnostic of alcoholic ketoacidosis<sup>117,119</sup>.

433

## 434 **[H2] Starvation ketosis**

435 Starvation ketosis occurs when a person has a prolonged reduced calorie intake of

436 <500Kcal/day<sup>120</sup>. With little or no carbohydrate intake, insulin secretion is decreased, leading to  
437 lipolysis and ketogenesis. However, starvation ketosis differs from DKA; in healthy individuals or  
438 in individuals with obesity without diabetes who starve,  $\beta$ -hydroxybutyrate concentrations can  
439 reach 5–6mmol/l, but this takes several days of absolute starvation with almost very little or no  
440 caloric intake<sup>121,122</sup>, or 4–5mmol/l after 10 days of starvation<sup>123</sup>. For comparison, in a healthy,  
441 non-starving individual,  $\beta$ -hydroxybutyrate concentrations should be <0.3mmol/l. An individual is  
442 able to adapt to prolonged fasting by increasing brain and muscle ketone clearance as well as  
443 renal compensation by increasing acid excretion, in particular ammonia<sup>121,124</sup>. As this condition  
444 develops over many days, electrolyte imbalance (for example, low bicarbonate concentrations)  
445 is less likely to occur due to the ability of the kidney to compensate. However, if electrolyte  
446 intake is also limited, then eventually electrolyte disturbances will occur<sup>124</sup>. Thus, as a result of  
447 renal compensation, starvation-induced ketosis is unlikely to present with a serum bicarbonate  
448 concentration <18.0mmol/L<sup>120</sup>. This serum bicarbonate corresponds to a mean  $\beta$ -  
449 hydroxybutyrate concentration of 5.68 ( $\pm$ 1.5) mmol/l in the UK national survey of DKA; it is likely  
450 that it took only a few hours of insulin deprivation to achieve that ketone concentration in  
451 patients with DKA<sup>35</sup>.

452  
453  
454

## 455 [H1] Diagnosis, screening and prevention

456

## 457 [H2] Presentation

458 DKA frequently presents with a short history, with symptoms developing usually over a few  
459 hours. These include the classic symptoms of hyperglycaemia — polyuria (excessive urine  
460 production), polydipsia (excessive thirst) and, in those for whom DKA is the first presentation of  
461 diabetes, weight loss (Figure 3). Polyphagia (excessive hunger) has been reported in children,  
462 but remains rare in adults<sup>125</sup>. Gastrointestinal symptoms such as nausea, vomiting and  
463 generalized abdominal pain are reported in >60% of patients<sup>1,126</sup>. Abdominal pain, sometimes  
464 mimicking an acute abdomen, is especially common in children and in patients with severe  
465 metabolic acidosis. Abdominal pain typically resolves during the first 24 hours of treatment and  
466 lack of resolution of abdominal pain within this time frame should prompt a search for other  
467 causes<sup>126</sup>. Although the cause of the gastrointestinal complaints has not been fully elucidated,  
468 delayed gastric emptying, ileus (that is, lack of movement in the intestines that leads to a delay  
469 in transit), electrolyte disturbances and metabolic acidosis have been implicated<sup>1,126</sup>.

470  
471 Physical examination of adults and children usually reveals signs of circulatory volume  
472 depletion, including dry mucous membranes and tachycardia. Mental status on admission varies  
473 from full alertness to lethargy and stupor, with <20% of adults hospitalized showing loss of  
474 consciousness<sup>127</sup>. As pH drops, respiratory compensation for the metabolic acidosis, that is,  
475 excreting acidic carbon dioxide in an attempt to maintain plasma pH, leads to Kussmaul  
476 respirations (a deep and laboured breathing pattern) in individuals with DKA and the breath  
477 might have a classic fruity odour owing to acetone exhalation. Most adults and children are  
478 normothermic or even hypothermic at presentation even in the presence of infection.  
479 Hypotension might be observed in adults but is rarely present in children. In fact, for reasons  
480 unknown, studies have documented a high frequency of hypertension in children with DKA, in  
481 spite of substantial volume depletion<sup>128</sup>. Therefore, it is important not to rely on blood pressure  
482 as a marker of DKA severity in children.

483

## 484 **[H2] Diagnosis**

485 The diagnosis of DKA is based on the triad of hyperglycaemia, ketosis and metabolic  
486 acidosis<sup>129</sup>. Although the ADA, Joint British Diabetes Societies and the International Society of  
487 Pediatric and Adolescent Diabetes agree that the main diagnostic feature of DKA is the  
488 elevation in circulating total blood ketone concentration, the other diagnostic criteria such as  
489 serum glucose and bicarbonate concentrations differ (Table 1)<sup>8,9,52,130</sup>. Studies have shown that  
490 between 3–8.7% of adults who present with DKA have normal or only mildly elevated glucose  
491 concentrations (<13.9mmol/l [250mg/dl]) — a condition known as euglycaemic DKA<sup>131-133</sup>.  
492 Euglycaemic DKA has been reported during prolonged starvation, with excessive alcohol intake,  
493 in partially treated individuals (i.e. those receiving inadequate doses of insulin), during  
494 pregnancy and in those who use an SGLT-2 inhibitor<sup>65,133,134</sup>. In those taking SGLT-2 inhibitors  
495 who may present with DKA but without severe hyperglycaemia, a thorough medication history is  
496 key to confirming the diagnosis.

497

498 When individuals present with euglycaemic DKA, the admission biochemistry is relatively non-  
499 specific and might be affected by the degree of respiratory compensation, the coexistence of a  
500 mixed acid–base disturbance or other comorbidities<sup>116</sup>. Studies from the 1980s documented  
501 high anion gap acidosis in 46% of people (14–55 years of age) admitted for DKA, whilst 43%  
502 had mixed anion gap acidosis and hyperchloraemic metabolic acidosis, and 11% develop  
503 hyperchloraemic metabolic acidosis<sup>135</sup>, however, current data do not describe patterns of

504 acidosis on admission and these differing categories have no impact on the diagnosis or  
505 immediate treatment of DKA. The fact that not all people fall into a single category indicated the  
506 heterogeneity of the biochemical abnormalities observed in DKA. The hyperchloraemic  
507 metabolic acidosis is most frequently observed in those given large volumes of 0.9% sodium  
508 chloride solution, during the recovery phase of the admission<sup>136</sup>.

509  
510 Assessment of ketonaemia (that is, blood ketone concentration) can be performed by the  
511 nitroprusside reaction in urine or serum or by direct measurement of  $\beta$ -hydroxybutyrate in  
512 capillary blood using point-of-care testing or by the hospital laboratory<sup>8,88</sup>. Although easy to  
513 perform, the nitroprusside test measures acetoacetate and does not detect  $\beta$ -hydroxybutyrate,  
514 the main ketone in DKA<sup>79,137</sup>. As plasma or urine acetoacetate concentration only accounts for  
515 15–40% of the total ketone concentration, relying on acetoacetate using urine ketone testing  
516 alone is likely to underestimate the severity of ketonaemia<sup>52,138</sup>. In addition, several sulfhydryl  
517 drugs (for example, captopril) or medications such as valproate that are taken for comorbidities  
518 including hypertension or epilepsy, give false-positive nitroprusside urine tests<sup>52,87</sup>. Using  
519 expired or improperly stored test strips can give false-negative results, which can also occur  
520 when urine specimens are highly acidic, for example, after the consumption of large amounts of  
521 vitamin C<sup>87</sup>. In addition, unlike the ADA guidelines, the Joint British Diabetes Societies strongly  
522 discourages the use of urinary ketone tests<sup>8,88</sup> and recommends direct measurement of  $\beta$ -  
523 hydroxybutyrate from a blood sample to assess ketonaemia in ambulatory and hospital care. A  
524 more detailed explanation of the differences of urinary and plasma ketone tests can be found  
525 elsewhere<sup>88</sup>.

526  
527 Studies in adults and children with DKA have reported a good correlation between  $\beta$ -  
528 hydroxybutyrate and the severity of acidaemia measured from serum bicarbonate  
529 concentration<sup>139,140</sup>. A bicarbonate concentration of 18.0 and 15.0mmol/L corresponds to 3.0  
530 and 4.4mmol/L of  $\beta$ -hydroxybutyrate, respectively, suggesting that when plasma ketone tests  
531 are unavailable, a 'best guess' can be made according to the bicarbonate concentration.  
532 Measurement of  $\beta$ -hydroxybutyrate can also guide response to treatment. The UK guidelines  
533 recommends to intensify the treatment if the plasma concentration of  $\beta$ -hydroxybutyrate does  
534 not decrease by 0.5mmol/l per hour following fluid and intravenous insulin administration<sup>130</sup>.

535  
536 Many individuals with hyperglycaemic crises present with combined features of DKA and HHS  
537 (Box 1). Previous work has reported that among 1,211 patients who had a first admission with

538 hyperglycaemic crises criteria based on the ADA guidelines<sup>8</sup>, 465 (38%) had isolated DKA, 421  
539 (35%) had isolated HHS, and 325 (27%) had combined features of DKA and HHS. After  
540 adjustment for age, sex, BMI, ethnicity and Charlson Comorbidity Index score (which predicts  
541 the 1-year mortality of a patient with a range of comorbidities) with combined DKA–HHS had  
542 higher in-hospital mortality compared with patients with isolated DKA (adjusted OR 2.7; 95% CI  
543 1.4–4.9)<sup>141</sup>.

544

## 545 **[H2] Systemic assessment**

546 Upon hospital admission, immediate assessment of the haemodynamic state and level of  
547 consciousness, together with measurement of blood glucose, blood or urine ketones, serum  
548 electrolytes, venous blood gases and complete blood count should be performed. As part of the  
549 rapid assessment of the individual, precipitants for DKA should be sought, including an ECG to  
550 exclude acute coronary syndrome and repolarization abnormalities (that is, peaked T waves)  
551 due to hyperkalaemia.

552

553 The systemic effect of DKA in adults depends on the severity of the acidaemia and circulatory  
554 volume depletion (Table 1). However, one of the drawbacks of the ADA classification is that the  
555 degree of acidaemia is imperfectly correlated with the patient's level of consciousness<sup>8</sup>. Thus, it  
556 is unclear whether a patient who presents with a pH of <7.0, yet is fully conscious, or another  
557 who presents comatose with a pH of 7.26 are mild or severe. Other markers of severity  
558 including ketone concentrations (>6.0mmol/l), venous pH <7.0, hypokalaemia on admission  
559 (<3.5mmol/l), systolic blood pressure (<90mmHg), pulse rate (either >100bpm or <60bpm),  
560 oxygen saturations (<92%, assuming it is normal at baseline), and Glasgow Coma Scale Score  
561 (<12) have been suggested by the UK guideline<sup>130</sup>. The Glasgow Coma Scale comprises  
562 subscale scores for behaviours (such as eye opening and verbal and motor responses to  
563 stimuli), with a higher total score indicating a higher level of consciousness of the patient)<sup>142</sup>. If  
564 breathing is compromised due to lethargy or coma, then urgent airway management needs to  
565 be initiated with support of the intensive care team.

566

567 In adults, mortality is often due to the underlying precipitant such as infection or intercurrent  
568 illness. However, lack of access to treatment might be the cause of excess mortality in low-  
569 resource environments. In children, mortality resulting from DKA is mainly the result of cerebral  
570 oedema or cerebral injury. Thus, assessment of consciousness level is of particular importance.

571

## 572 [H2] Prevention

573 In individuals with known diabetes, prevention of DKA and hospital admission is feasible. ‘Sick  
574 day rules’ are a simple set of instructions that patients can follow when they are unwell for any  
575 reason. These rules state that — particularly in those with T1DM, insulin must never be  
576 stopped, even if the individuals do not consume solids or fluids<sup>143</sup>. Also, when unwell, blood  
577 glucose concentrations should be measured every few hours and blood or urine ketone  
578 concentrations should be measured at least twice a day. If ketones are detected, increased  
579 insulin doses should be administered. Maintaining good hydration is also important. If vomiting  
580 due to illness is persistent, then hospital admission is often necessary. One study reported that  
581 telephone consultations with nurses or diabetes educators can help prevent DKA admissions<sup>144</sup>.

582

## 583 [H1] Management

584

585 Most of the data regarding management of DKA come from North America, Europe and  
586 Australia. Data from other parts of the world show a lack of accessibility of treatments.  
587 Individuals living in areas of low socio-economic status have no or limited access to insulin  
588 owing to an inability to main ‘security of supply’<sup>145</sup>. Many studies have shown that in parts of  
589 Africa, DKA was the main cause of death in people who require insulin who were admitted to  
590 hospital<sup>41,146</sup>.

591

592 Insulin therapy and fluid and electrolyte replacement are the cornerstones of DKA treatment.  
593 The aim is to correct acidaemia, restore normal circulatory volume and normalize blood glucose  
594 concentrations and acid-base disturbances to restore normal levels of inflammatory and  
595 oxidative stress markers<sup>106,147</sup>.

596

597 Careful monitoring of the patient’s response to DKA treatment and appropriate adjustments in  
598 treatment based on this response are essential. Monitoring should include tracking of blood  
599 pressure, pulse and respiratory rate as well as accurate documentation of fluid intake and  
600 output. For most patients, glucose levels should be monitored hourly and electrolytes (sodium,  
601 potassium, chloride and bicarbonate), urea nitrogen, creatinine and venous pH should be  
602 measured every 2–4 hours. Levels of phosphate, calcium and magnesium are measured less  
603 frequently (generally every 4–6 hours). Neurological status should be monitored hourly using  
604 the Glasgow Coma Scale<sup>142</sup> or similar assessments, for example, AVPU (Alert, Voice, Pain,  
605 Unresponsive) scale<sup>148</sup>. More frequent monitoring (that is, every 30 minutes) might be

606 necessary for children with DKA and impaired cognitive status. There should be a low threshold  
607 for moving individuals presenting with altered cognitive status or severe metabolic derangement  
608 and those who fail to improve after initial treatment to an intermediate care unit (high  
609 dependency) or critical care unit in the hospital<sup>1,149</sup>. Alternatively, people with the ADA-classified  
610 mild DKA (Table 1) who have normal cognition and are able to eat and drink can be treated with  
611 oral fluids and subcutaneous insulin in an acute care setting, potentially avoiding  
612 hospitalization<sup>1,149</sup>.

613  
614 The criteria for the resolution of a DKA episode should be a combination of a blood glucose of  
615 <200mg/dL (11.1mmol/l), a serum bicarbonate level of  $\geq 18.0$ mmol/l, a venous pH >7.30 and a  
616 calculated anion gap of  $\leq 14.0$ mmol/l<sup>8</sup>. A serum  $\beta$ -hydroxybutyrate <1.0mmol/l can also be used  
617 to determine resolution of DKA. In settings where  $\beta$ -hydroxybutyrate measurements are  
618 unavailable, normalization of the anion gap is the best indicator of DKA resolution<sup>8</sup>.

## 619 620 **[H2] Volume correction**

621 Administration of intravenous fluid is the key to intravascular volume correction, thereby  
622 improving renal perfusion. The concomitant decrease in circulating counter-regulatory hormone  
623 concentrations also reduces insulin resistance<sup>150</sup>. In adults with DKA, the ADA and UK  
624 guidelines recommend normal saline (0.9% sodium chloride solution) for the initial fluid  
625 replacement<sup>8,130</sup>, administered at an initial rate of 500–1000 ml/hour during the first 2–4 hours.  
626 In an attempt to understand the best resuscitation fluid to use in DKA, a study comparing  
627 intravenous infusion of normal saline with Ringer's lactate (a mixture of sodium chloride, sodium  
628 lactate, potassium chloride and calcium chloride) found no difference in the time to resolution of  
629 DKA, although hyperglycaemia resolved later in the Ringer's lactate group<sup>151,152</sup>. A potential  
630 'trap' for the unwary is the development of hyperchloraemic metabolic acidosis owing to  
631 excessive chloride resulting from the administration of high volumes of saline. This is because  
632 0.9% saline contains a higher concentration of chloride ions than serum (154mmol/l compared  
633 with 100mmol/l)<sup>9</sup>. Although there are generally no acute adverse effects of hyperchloraemic  
634 metabolic acidosis, the development of hyperchloraemic metabolic acidosis can delay transition  
635 to subcutaneous insulin treatment if the serum bicarbonate concentration is used as an indicator  
636 of DKA resolution. After restoration of intravascular volume, the serum sodium concentration  
637 and state of hydration assessed by blood pressure, heart rate and fluid balance should  
638 determine whether the rate of normal saline infusion can be reduced to 250 ml/hour or changed  
639 to 0.45% sodium chloride (250–500 ml/h)<sup>8</sup>. A study has proposed different approaches for

640 individualizing fluid treatment based on calculations of sodium and fluid deficits<sup>153</sup>. Plasma  
641 glucose concentrations typically decrease to <200mg/dl (11.1mmol/l) before ketoacidosis  
642 resolves. Thus, once the plasma glucose concentration is ~200mg/dL (11.1mmol/L), the  
643 replacement fluids should contain 5–10% dextrose (to prevent hypoglycaemia) to allow  
644 continued insulin administration until ketonaemia is corrected<sup>1</sup>.

645  
646 In children (<18 years of age) with DKA, fluid deficits can vary between 30 and 100 ml/Kg,  
647 depending on the duration of symptoms and ability to maintain hydration. Clinical assessments  
648 (using capillary refill time, skin turgor and other aspects of the physical exam) to estimate the  
649 degree of fluid deficit are frequently inaccurate in children with DKA<sup>154-156</sup>, therefore, average  
650 fluid deficits of ~70 ml/Kg should be assumed for most children. An initial bolus of 10–20 ml/Kg  
651 of 0.9% normal saline or other isotonic fluid should be administered promptly over 30–60  
652 minutes to help restore organ perfusion. In children with hypovolaemic shock, the initial fluid  
653 administration should be 20 ml/kg over 15–30 minutes. Fluid boluses can be repeated if  
654 necessary based on the haemodynamic state. Such bolus fluid administration is preferred in  
655 children to ensure more rapid tissue perfusion than can be achieved than by slower continuous  
656 fluid infusion. Following the initial fluid bolus, the remaining fluid deficit should be replaced over  
657 24–48 hours, using 0.45–0.9% sodium chloride. In the 1980s and early 1990s, slower  
658 administration of intravenous fluids was recommended in paediatric patients with DKA to  
659 prevent cerebral oedema<sup>157,158</sup>. A large RCT (the Pediatric Emergency Care Applied Research  
660 Network FLUID Study), however, found no differences in acute or post-recovery neurological  
661 outcomes in children with DKA treated with rapid versus slower volume correction<sup>159</sup> or between  
662 the use of 0.9% versus 0.45% sodium chloride. In a sub-analysis involving children with severe  
663 acidosis and cognitive impairment resulted in improved mental status during DKA treatment<sup>159</sup>.  
664 These findings are reassuring as they assure that variations in fluid treatment protocols are not  
665 the cause of cerebral oedema or cerebral injury during DKA.

666  
667 In both adult and paediatric DKA, the ‘two bag’ method of fluid replacement is often used,  
668 whereby two concurrent bags of fluid are used. Although both bags have identical electrolyte  
669 content (0.45% or 0.9% saline with potassium), only one bag contains 10% dextrose. The bag  
670 without dextrose is used initially as the resuscitation fluid and the dextrose infusion is added  
671 when the glucose drops to 200–250mg/dl (11.0–13.9mmol/l). The two bag method prevents the  
672 need to continually change infusion fluids according to glucose concentrations<sup>160-162</sup>.

673

674 The measured serum sodium concentration at presentation reflects relative losses of sodium  
675 and extracellular free water as well as the osmotic effect of hyperglycaemia. Most adults and  
676 children with DKA have mild hyponatraemia at presentation, which gradually returns to the  
677 normal range of 135–145mmol/l as blood glucose levels decline and water moves back into  
678 intracellular space. The measured sodium concentration has been proposed to decline by  
679 1.6mmol/l for every 100mg/dl (5.5mmol/L) rise in the serum glucose concentration above the  
680 normal range such that a ‘corrected’ sodium concentration can be calculated as the measured  
681 serum sodium concentration + 1.6 × [(glucose concentration in mg/dL – 100)/100]. This  
682 theoretically determined correction factor was found to correlate well with empirical data from a  
683 study of children with DKA<sup>163</sup> that enables a better assessment of sodium deficit (and therefore,  
684 requirements for replacement) can be made. Alternative correction factors have also been  
685 proposed and tracking the corrected sodium concentration during treatment can be useful for  
686 monitoring the adequacy of relative rates of fluid and sodium administration<sup>164,165</sup>.

687

## 688 **[H2] Insulin administration**

689 Most people with DKA will be treated initially with an intravenous insulin infusion until the DKA  
690 has resolved and the patients are eating and drinking normally, at which time they will be  
691 transferred to subcutaneous insulin.

692

693 **[H3] Intravenous infusion.** In most adults with DKA, a continuous intravenous infusion of  
694 regular (soluble) insulin is the treatment of choice. In many hospitals, the intravenous fluids are  
695 administered whilst the intravenous insulin infusion is being prepared<sup>35</sup>. In adults, many  
696 treatment protocols recommend the administration of insulin (0.1 unit per kg body weight) bolus  
697 intravenously or intramuscularly if a delay in getting venous access is anticipated, which is  
698 immediately followed by fixed rate intravenous insulin infusion at 0.1 unit/kg/hour. Once the  
699 blood glucose concentration is ~200mg/dl (11.0mmol/l) the insulin infusion rate is adjusted to  
700 between 0.02–0.05 units/kg/hour and an of 5% dextrose is added to the infusion, to maintain  
701 glucose concentrations at 140–200mg/dL (7.8–11.0mmol/l) until resolution of ketoacidosis<sup>8</sup>.

702

703 For treatment of DKA in children, the International Society for Pediatric and Adolescent  
704 Diabetes (ISPAD) guidelines recommend intravenous administration of regular insulin as a  
705 continuous infusion at 0.1units/kg/hour<sup>22</sup>, which should be started immediately after the initial  
706 intravenous fluid bolus(es). Intravascular volume expansion before insulin administration is  
707 particularly important in children who present with very high glucose levels and hyperosmolality

708 because intravascular volume will decline substantially as the hyperosmolar state resolves. An  
709 initial bolus of insulin is not necessary as continuous intravenous insulin infusion rapidly  
710 achieves steady state serum insulin levels<sup>166,167</sup>. A few small studies reported that insulin  
711 infused at 0.05unit/kg/hour can resolve hyperglycaemia over a similar time frame compared with  
712 the standard dosage of 0.1units/kg/hour<sup>168-170</sup>. This lower dosage might be considered for very  
713 young children (< 6 years old) or others with greater insulin sensitivity for whom the standard  
714 dosage might not be necessary<sup>168</sup>. In general, intravenous insulin is recommended for treating  
715 children with DKA due to unreliable subcutaneous insulin absorption in the volume-depleted  
716 state. However, subcutaneous administration can be used in children with mild DKA (Table 1)or  
717 in situations when intravenous administration is not possible. When the serum glucose  
718 concentration decreases to ~250mg/dL (13.9mmol/L), intravenous fluids containing dextrose  
719 should be used to maintain the serum glucose concentration at ~100-150mg/dl (5.5 to  
720 8.3mmol/l) while maintaining the total fluid infusion rate<sup>22</sup>.

721

### 722 ***[H3] Maintenance insulin therapy.***

723 Once biochemical resolution of DKA is achieved and the patient is eating and drinking normally,  
724 subcutaneous insulin therapy can be started in adults as well as children. Adults with newly  
725 diagnosed diabetes mellitus or those who have not previously received insulin should be started  
726 on total insulin dosage of 0.5–0.6 units/kg/day. Patients who were already on subcutaneous  
727 insulin prior to DKA admission should resume their previous insulin regimens.

728

729 For most adults, a basal bolus regimen (that is, rapid-acting insulin given with each meal as well  
730 as a once or twice daily administered long-acting basal insulin) is preferred over the use of  
731 regular insulin because of the lower rate of in-hospital hypoglycaemia despite similar glucose  
732 control<sup>171</sup>. In children, insulin regimens differ depending on the centre; however, basal-bolus  
733 regimens are generally preferred. Previous work has shown that the administration of frequent  
734 doses of subcutaneous rapid-acting insulin analogues (given every 1–2 hours), can be an  
735 acceptable alternative to an intravenous insulin infusion as both treatments resolve DKA in  
736 similar time<sup>172-174</sup>. In adults and children, subcutaneous rapid-acting insulin is given as a bolus of  
737 0.2unit/kg at the start of treatment, followed by 0.1–0.2unit/kg every 1–3 hours until the blood  
738 glucose concentration is <250mg/dl (13.9mmol/l), then the dose is reduced by half and  
739 continued every 1–2 hours until resolution of DKA<sup>172,175</sup>. The total insulin daily dose is generally  
740 0.7–0.8unit/Kg/day in the prepubertal child and 1.0–1.2unit/Kg/day in the pubertal adolescent<sup>176</sup>.

741

742 Clinical trials and meta-analyses that compared continuous subcutaneous insulin infusion (CSII)  
743 with discrete subcutaneous insulin doses (for example, basal bolus regimens) have shown  
744 small but significant reductions in HbA1c and risk of severe hypoglycaemia in those receiving  
745 CSII. In addition, these studies have found an increased risk of developing ketoacidosis with  
746 CSII primarily due to device malfunction and/or catheter occlusion<sup>177-179</sup>, a finding confirmed  
747 by the UK National Diabetes Pump Audit<sup>60</sup>. However, the use of frequent home glucose  
748 monitoring has reduced this complication considerably<sup>178</sup>. In adults and children, intramuscular  
749 administration of rapid-acting insulin is also effective. However, this route is more painful than  
750 subcutaneous injections and potentially would be contraindicated in those taking  
751 anticoagulants<sup>1,180,181</sup>.

752

## 753 **[H2] Potassium replacement**

754 Nearly all patients with DKA have substantial potassium deficits at the time of presentation and  
755 potassium replacement is almost always required (Box 2). At presentation, serum potassium  
756 concentrations are frequently normal or slightly elevated in spite of total body deficits. As insulin  
757 treatment starts, ketone production is suppressed, and the acidosis begins to resolve. In  
758 addition, insulin drives potassium back into the cell, and the individual can become profoundly  
759 hypokalaemic. Hypokalaemia occurs frequently despite aggressive potassium replacement<sup>35,141</sup>  
760 and frequent monitoring of potassium during the first few hours of treatment is an essential part  
761 of managing DKA<sup>8,130</sup>. Because of potentially rapid shifts in potassium and the possible risk of  
762 developing cardiac arrhythmias, continuous cardiac monitoring is recommended in all cases  
763 where potassium is being administered at >10mmol/hr.

764 Two studies showed that within 24–48 hours of admission, potassium levels declined on  
765 average from  $4.8 \pm 1.0$  and  $4.9 \pm 1.1$  to  $3.65 (\pm 0.66)$  and  $3.66 (\pm 0.6)$  mmol/l, respectively,  
766 among adults with DKA<sup>35,141</sup>. The development of severe hypokalaemia (<2.5 mmol/l) was  
767 associated with increased mortality (OR 3.17; 95% CI 1.49–6.76)<sup>141</sup>. The association between  
768 hypokalaemia within 48 hours and mortality remained significant after adjusting for demographic  
769 variables and metabolic parameters on admission suggesting that hypokalaemia is most likely  
770 the cause of increased mortality and not any other confounding factors.

771 In patients who develop symptomatic hypokalaemia (muscle weakness and cardiac arrhythmia),  
772 potassium replacement should be started and insulin administration should be delayed until the  
773 potassium concentration has risen to >3.3mmol/l. A survey of the management of DKA in the

774 UK showed that an intravenous insulin infusion rate of 0.1unit/Kg/hour was associated with 55%  
775 of adults developing hypokalaemia<sup>35</sup>. Although no harm was associated with this hypokalaemia,  
776 it provides support for the practice of reducing the insulin infusion rate to 0.05unit/Kg/hr after  
777 glucose levels decline.

778  
779 Similar to adults, hypokalaemia is rarely present in children before DKA treatment. In these rare  
780 cases, earlier and more aggressive potassium replacement is necessary and the insulin infusion  
781 should be delayed until urine output is documented and serum potassium has been restored to  
782 a near normal concentration<sup>22</sup>. Serum potassium levels should be monitored every 2–4 hours  
783 and the potassium concentration in intravenous fluids adjusted to maintain normal potassium  
784 levels. A cardiac monitor or frequent ECGs should be considered during intravenous potassium  
785 replacement.

786  
787 The choice of potassium salts to use for replacement has been a subject of debate. Adult  
788 protocols typically recommend potassium chloride alone, but paediatric protocols often  
789 recommend using a mixture of potassium chloride and potassium phosphate or potassium  
790 acetate<sup>22</sup> to reduce the chloride load thereby diminishing the risk of hyperchloraemic acidosis.

791  
792 **[H2] Bicarbonate administration**

793 Treatment with intravenous bicarbonate is not routinely recommended for adults or children with  
794 DKA. Time to biochemical resolution, length of hospitalisation or mortality have not been shown  
795 to improve with bicarbonate treatment<sup>182-185</sup>. Bicarbonate therapy might increase the risk of  
796 hypokalaemia, slow the resolution of ketosis, cause paradoxical increases in cerebral acidaemia  
797 due to an increase in tissue pCO<sub>2</sub> and increase the risk of cerebral injury<sup>186,187</sup>. Some  
798 commentaries have suggested that specific subsets of adults with DKA might benefit from  
799 bicarbonate administration, however, data from randomized trials are lacking<sup>93</sup>.

800  
801 **[H2] Phosphate replacement**

802 Similar to potassium, serum phosphate concentrations are typically normal at presentation but  
803 intracellular depletion is present and serum concentrations decline during DKA treatment.  
804 Phosphate replacement is necessary in those with serum phosphate concentration <1.0–  
805 1.5mg/dl (0.3–0.5mmol/l)<sup>8</sup>. Inclusion of phosphate in the infusion has been proposed to diminish  
806 the risk of hypophosphataemia, which has been associated with severe complications in some  
807 patients including rhabdomyolysis (breakdown of skeletal muscles), renal failure, respiratory

808 failure, arrhythmias and haemolytic anaemia<sup>98,188-191</sup>. Thus, for individuals with cardiac  
809 dysfunction, anaemia or respiratory depression, phosphate replacement should be strongly  
810 considered. Concern over phosphate replacement mainly centres on an increased risk of  
811 hypocalcaemia; however, studies documenting hypocalcaemia with phosphate replacement  
812 used more aggressive phosphate replacement than recommended in current protocols<sup>192</sup>.  
813 Studies in the 1980s found increases in red blood cell 2,3-disphosphoglycerate (DPG, which  
814 liberates oxygen from haemoglobin in peripheral tissues) levels with phosphate replacement but  
815 did not detect any beneficial effect of phosphate replacement on clinical outcomes<sup>193,194</sup>. The  
816 sample size for these studies, however, was very small and statistical power to detect  
817 differences in outcomes was very limited. Phosphate levels should be monitored during  
818 treatment at least every 4–6 hours, although more frequent monitoring (every 2–3 hours) is  
819 recommended for those not receiving phosphate replacement.

820

## 821 [H2] Cerebral injury

822 Among the severe complications of DKA, cerebral injury is the most well recognized (Table 3).  
823 Although rare in adults, severe cerebral injury occurs in 0.3–0.9% of DKA episodes in  
824 children<sup>186,195,196</sup> and is associated with high rates of mortality (21–24%) and permanent  
825 neurological morbidity (20–26%)<sup>186,195,196</sup>. Risk factors for cerebral injury include severe  
826 acidaemia and severe deficits in circulatory volume<sup>186,195,196</sup>. Younger children (<5 years) are at  
827 greater risk for DKA-related cerebral injury, reflecting the greater severity of DKA at presentation  
828 in this age group in whom symptoms of diabetes can be less apparent and  $\beta$ -cell destruction is  
829 often aggressive. Although severe cerebral injury occurs in <1% of children with DKA, mild  
830 cerebral injury occurs much more commonly – possibly in the majority of children<sup>197,198</sup>. Subtle  
831 deficits in memory, attention and intelligence quotient have been reported in children with T1DM  
832 with a history of DKA compared with children with T1DM without DKA history<sup>199-201</sup>. These  
833 differences persist after adjusting for HbA1c and demographic factors. Microstructural and  
834 macrostructural alterations, such as increased total white matter volume and other changes in  
835 the in the frontal, temporal, and parietal white matter in the brain have also been associated with  
836 DKA in children<sup>199</sup>.

837

838 Cerebral injury can exist at the time of presentation, before starting treatment, but is more  
839 common during the first 12 hours of treatment<sup>186,196,202</sup>. Changes in mental status, onset of  
840 headache during DKA treatment and recurrence of vomiting are indicative of cerebral injury<sup>203</sup>.  
841 Cerebral oedema may be found on imaging studies, but many individuals have no detectable

842 imaging abnormalities at the time of neurological deterioration, suggesting that cerebral oedema  
843 and/or infarction can develop hours or days after treatment has started<sup>203</sup>. For this reason,  
844 treatment for DKA-related cerebral injury should not be delayed while awaiting imaging studies.  
845 Treatment involves administration of mannitol or hypertonic saline, both of which induce osmotic  
846 shifts of fluid from within the intracellular space into the vascular compartment.

847

## 848 **[H2] The precipitating illness**

849 The most common precipitant of DKA in adults is infection, which vary from gastrointestinal  
850 upset, with diarrhoea and vomiting, to chest or urinary tract infections. These precipitating  
851 illnesses need to be treated at the same time as the DKA. In addition, non-infectious illnesses,  
852 such as acute coronary syndrome that precipitate DKA need to be evaluated and addressed at  
853 the time of presentation. In children, episodes of DKA generally occur at onset or time of  
854 diagnosis of diabetes or because of insulin omission. Serious intercurrent illnesses are rarely  
855 present and routine investigation for precipitating causes of DKA is unnecessary.

856

## 857 **[H1] Quality of Life**

858 The UK National Institute for Health and Care Excellence (NICE) systematically reviewed the  
859 evidence for the management of DKA and found no studies in adults that evaluated quality of  
860 life<sup>204</sup>. However, fear of DKA is one of the factors affecting the quality of life in those with  
861 T1DM<sup>205</sup>. Of note, despite the lower quality of life experienced by those with T1DM, recurrent  
862 DKA does not contribute to further reductions<sup>42</sup>. The development of any systemic or  
863 neurological injury can also lead to a reduction in quality of life and prevention of these  
864 complications remains a priority<sup>206</sup>. As mentioned previously, DKA remains an expensive  
865 condition to treat<sup>5-7</sup>. These costs place huge burdens on those who have to pay themselves and  
866 on society in general.

867

## 868 **[H2] Other complications**

869 DKA is associated with a wide range of complications. For example, hypokalaemia and  
870 hypoglycaemia are the most frequent complications of DKA treatment, but are generally mild  
871 and easily treated with ongoing careful biochemical monitoring<sup>22,35</sup>. Other important  
872 complications of DKA include the development of a hypercoagulable state with increased risk of  
873 deep venous thromboses, particularly when central venous catheters are used to gain  
874 intravenous access if peripheral access was not possible due to severe dehydration<sup>207</sup>. DKA also  
875 frequently causes acute kidney injury (AKI) in children. In one study, 64% of children with DKA

876 were found to have AKI; >50% had stage 2 or stage 3 AKI, suggesting renal tubular injury,  
877 rather than simply pre-renal uraemia due to circulatory volume depletion with renal  
878 hypoperfusion<sup>208</sup>. Other complications of DKA are rare (Table 3).

879 Patients with DKA with chronic poor glycaemic control are uniquely susceptible to rhinocerebral  
880 or pulmonary mucormycosis<sup>209</sup>, which is frequently fatal. Acidotic conditions decrease iron  
881 binding to transferrin, creating conditions that support fungal growth. Some rare complications of  
882 DKA include cardiac arrhythmias due to electrolyte derangements, intestinal necrosis,  
883 pulmonary oedema and pneumomediastinum (abnormal presence of air in the mediastinum),  
884 which might be associated with pneumothorax and is thought to be caused by protracted  
885 vomiting and hyperventilation<sup>210,211</sup>. Multiple organ dysfunction syndrome is another rare  
886 complication of DKA causing multiple organ failure, which may be associated with  
887 thrombocytopenia in children; reported cases in adults often involve elevated liver enzymes,  
888 elevated pancreatic enzymes and renal dysfunction<sup>212-214</sup>. Peripheral neuropathy has been  
889 reported in children, and might occur in association with other DKA complications including  
890 cerebral injury or disseminated intravascular coagulation<sup>215-219</sup>. Other isolated case reports have  
891 described rare neurological complications including cerebellar ataxia, movement disorder  
892 (choreiform movements and pill rolling tremor) and hemiparesis in children<sup>219</sup>.

893

## 894 **[H1] Outlook**

895 Increasing numbers of DKA hospitalizations highlight the need for targeted programmes to  
896 prevent DKA at new-onset of diabetes and recurrent episodes of DKA in children and adults  
897 with previously diagnosed diabetes. Education and the implementation of protocols aimed at  
898 maintenance insulin administration after discharge might reduce lapses in treatment and are a  
899 cost-effective way to reduce future risk of hospitalization for hyperglycaemic emergencies<sup>220</sup>.  
900 Several strategies including early screening, close follow-up of high-risk individuals (for  
901 example, those with multiple admissions), availability of telephone support from diabetes  
902 specialist nurses, and education of parents and communities have been proposed<sup>13,144</sup>. Studies  
903 have reported a lower incidence of DKA when parents were made aware of the higher risk of  
904 diabetes in their children (due to the presence of autoantibodies)<sup>221</sup>. Similarly, another study  
905 showed close follow-up of high-risk children in the prediabetes stage reduced hospitalizations  
906 for DKA<sup>222</sup>. In Italy, a prevention programme educating parents, paediatricians and school staff  
907 reduced the number of children presenting with DKA at initial diagnosis of diabetes<sup>223</sup>. In 1991,  
908 when the study started, this programme cost \$23,470 to deliver, and led to a reduction of DKA

909 as the presenting feature of diabetes from 78% to 12.5% over the 8 years of follow up. Thus,  
910 delivering targeted education to those who have most contact with children might be beneficial.

911  
912

## 913 **[H2] Clinical priorities**

914 More intensive coordination of care with patients and greater family engagement are some of  
915 the additional strategies for prevention of recurrent episodes of DKA. The Novel Interventions in  
916 Children's Healthcare programme uses care coordination with family and telemedicine in an  
917 attempt as a part of the preventive strategy to engage young people with multiple  
918 hospitalizations for DKA<sup>224</sup>. This work used text messages and other forms of communication  
919 with the adolescents and showed that daily communication decreased DKA readmissions.  
920 Furthermore, the Type 1 Diabetes Exchange programme showed that the use of new  
921 technology such as insulin pumps and real-time continuous glucose monitoring could be useful  
922 in preventing recurrent DKA<sup>225-227</sup>.

923

924 In the 1990s, the use of CSII or insulin pumps was associated with increased risk of DKA in  
925 children and adults with T1DM<sup>228</sup>. A series from 2017, however, reported a low incidence of 1.0  
926 case/100 patient years<sup>229</sup>. An analysis of 13,487 participants (aged 2–26 years) in the T1DM  
927 Exchange clinic registry found that a lower incidence of DKA in those treated with CSII than in  
928 patients treated with multi-dose subcutaneous insulin injections<sup>230</sup>. However, as these  
929 individuals were looked after in specialist diabetes centres in the USA, rates of DKA amongst  
930 those cared for in other centres may be higher. Similarly, in a German study in children with  
931 T1DM, those who used CSII had lower rates of DKA than those receiving insulin by injection  
932 (2.29 versus 2.80 per 100 patient-years)<sup>231</sup>, suggesting that increasing CSII use might be an  
933 alternative method for reducing DKA incidence. However, pump use is expensive and requires  
934 access to specialist centres with appropriate expertise.

935

936 Patients with treatment adherence problems account for a disproportionate number of recurrent  
937 DKA episodes. In the USA, 50% of first episodes of DKA in adults with T2DM and ~80% of  
938 recurrent DKA episodes are caused by poor compliance with therapy<sup>42</sup>. In the UK, adults who  
939 had attended a structured diabetes education programme and were on a flexible basal-bolus  
940 insulin dosing regimen based on individualizing carbohydrate ratios at each meal experienced a  
941 61% reduction in risk for DKA<sup>232</sup>. Similarly, a multidisciplinary, multi-pronged approach  
942 incorporating more flexible intensive insulin regimens, standardizing diabetes education and

943 empowering community engagement, reported a 44% reduction in DKA admissions in those  
944 with T1DM<sup>233</sup>. Future strategies to increase treatment adherence combining increased  
945 education, motivational interviews, patient support technology (continuous glucose monitoring,  
946 CSII, telephone support, text and e-mail messaging) are needed to improve adherence to  
947 therapy and to reduce the risk of DKA.

948

949 In less developed parts of the world, efforts need to be made to ensure easy availability of  
950 insulin at an affordable price. Insulin and 0.9% saline solution are on the WHO list of essential  
951 medicines<sup>234</sup>. Education of local health care providers also remains key to the recognition of  
952 DKA as well as prompt access to health care facilities with the ability to administer appropriate  
953 care.

954

## 955 **[H2] Unmet needs and areas for future research**

956

957 To date, many of the guidelines used to treat DKA have evolved over time, which are largely  
958 based on consensus and opinion. Thus, large RCTs are needed to help determine the best  
959 management options including optimizing electrolyte content of intravenous fluids (for example,  
960 Ringer's lactate versus 0.9% saline)<sup>151,152,235</sup>. In addition, further investigations are necessary to  
961 determine the optimal rates and optimal technique of insulin administration <sup>236</sup>. Additional  
962 studies are also needed to determine the ideal combination of potassium salts for replacement.  
963 In essence, most stages of the patient journey from the time of diagnosis and admission to the  
964 time of discharge has areas of uncertainty that need good quality data to help improve overall  
965 patient management. Furthermore, the advent of closed loop systems for those with T1DM  
966 where the subcutaneously implanted interstitial glucose sensor is wirelessly linked to an insulin  
967 pump and other 'artificial intelligence' systems may also improve outcomes. They have been  
968 shown to improve time in glucose range, and thus, the likelihood of developing hyperglycaemia  
969 and subsequent DKA may be reduced<sup>237,238</sup>. However, this has yet to be determined

970

971

972 Table 1: Diagnostic Criteria for DKA.

973

Severity	Glucose (mg/dl) (mmol/L)	Arterial or venous pH	Bicarbonate (mmol/L)	Urine or serum ketones (nitroprusside test)	$\beta$ -hydroxy butyrate (mmol/L)	Anion gap (mmol/L)	Mental status	Refs
American Diabetes Association criteria for adults								
Mild	>250 (13.8)	7.25-7.30	15–18	Positive	>3.0	>10	Alert	8
Moderate	>250 (13.8)	7.24-7.0	10–15	Positive	>3.0	>12	Alert/drowsy	
Severe	>250 (13.8)	<7.0	<10	Positive	>3.0	>12	Stupor/coma	
Joint British Diabetes Societies								
NA	>200 (11.1)	<7.30 <sup>a</sup>	<15	Positive	>3.0	NA	NA	130
International Society of Pediatric and Adolescent Diabetes								
Mild	>200 (11.1)	<7.30 <sup>a</sup>	<15	Positive	>3.0	NA	NA	22
Moderate	>200 (11.1)	<7.2 <sup>a</sup>	<10	Positive	>3.0	NA	NA	
Severe	>200 (11.1)	<7.1 <sup>a</sup>	<5	Positive	>3.0	NA	NA	

974

975 Adapted from Refs<sup>8,22,130</sup>. The ADA criteria recommends the use of arterial pH be for diagnosis  
 976 and venous pH as a guide to evaluate the need for bicarbonate therapy and to measure  
 977 resolution. Note that severity of DKA is defined by the degree of acidosis and level of  
 978 consciousness, not by the degree of hyperglycaemia or ketonaemia. NA, not applicable.

979 <sup>a</sup>Venous pH can be used to diagnose DKA.

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Table 2: Precipitating causes of diabetic ketoacidosis in adults by region.

Region	New-onset diabetes mellitus (%)	Infection (%)	Poor treatment adherence (%)	Other (%)	Unknown (%)
Australia	5.7	28.6	40	25.7	NR
Brazil	12.2	25	39	15	8.8
China	NR	39.2	24	10.9	25.9
Indonesia	3.3	58.3	13.3	17.1	8
South Korea	NR	25.3	32.7	11.2	30.8
Nigeria	NR	32.5	27.5	4.8	34.6
Spain	12.8	33.2	30.7	23.3	NR
Syria	NR	47.8	23.5	7.8	20.9
Taiwan	18.2	31.7	27.7	6.2	16.2
UK	6.1	44.6	19.7	10.9	18.7
USA	17.2–23.8	14.0–16.0	41.0–59.6	9.7–18.0	3.0–4.2

985 Adapted from<sup>1,35</sup>. NR, not reported. Other causes include the use of medications that  
986 affect carbohydrate metabolism, insulin pump failure, or alcohol or drug misuse.

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Table 3: Complications of DKA<sup>a</sup>

Complication	Frequency	Description	Risk factors	Refs
Cerebral injury	0-3–0.9% of children, rare in adults	Cerebral oedema; cerebral thromboses, haemorrhage and infarction; posterior reversible encephalopathy syndrome has also been described	Impaired renal function, low pH, low pCO <sub>2</sub> , lack of rise in measured serum Na <sup>+</sup> during DKA treatment, low Na <sup>+</sup> at presentation, high K <sup>+</sup> at presentation	186,195,203,239-241
Acute kidney injury	30–64% of children, 50% of adults	Stage 1 (pre-renal) is most common but stage 2 and stage 3 occur in substantial numbers of patients (children); rare episodes of renal failure; some episodes of renal failure associated with rhabdomyolysis (adults and children)	High acidaemia (children), high heart rate (children), high corrected Na <sup>+</sup> concentration (children), older age, high glucose (adults), low serum protein (adults)	208,242,243
Large vessel thromboses	50% of children <sup>b</sup>	Rare reports in children of stroke and other thromboses not associated with central venous catheter use. Thrombophilia in some cases in children; fatal pulmonary thromboembolism as well as thromboses in other regions in adults	Central venous catheter use, DKA causes a hypercoagulable state	244-247
Subclinical interstitial pulmonary oedema	Common in children <sup>b</sup>	Generally subclinical but rare episodes of ARDS have been described; episodes of simultaneous pulmonary oedema and cerebral oedema are described in both adults and children	Hypokalaemia or hypophosphataemia in some cases in adults and children	248,249
Symptomatic pulmonary oedema	Rare in adults and children			
Pancreatic enzyme elevation	20–30% of children, 16–29% of adults	Acute pancreatitis, sometimes associated with hypertriglyceridaemia or alcohol; asymptomatic pancreatic enzyme elevation without acute pancreatitis is common in both children and adults; pancreatitis is rare in children	High acidaemia, impaired renal function, hypophosphataemia in adults and children	250-252
Pancreatitis	2% of children, 10–11% of adults			
Cardiac arrhythmias	47% of children <sup>b</sup>	Prolonged QTc occurs commonly but is asymptomatic; Brugada pattern of arrhythmia has been described in multiple adult and paediatric case reports; Electrolyte abnormalities including hypophosphataemia has been shown to cause rare episodes of arrhythmia	In adults and children high anion gap (QTc), hypokalaemia, hypophosphataemia and hyperkalaemia	253-258

Subtle or asymptomatic diastolic dysfunction	47% of children <sup>b</sup>	Asymptomatic elevations of cardiac troponin I and CK-MB detected in children; might be associated with systemic inflammatory response; possibly associated with thiamine deficiency	High acidaemia; presence of the systemic inflammatory response	259-262
Symptomatic cardiomyopathy	Rare in adults and children			
Rhabdomyolysis	16% of adults, 10% of children	Often subclinical; occurs more frequently in HHS but also described in DKA; some cases are associated with hypophosphataemia. Severe rhabdomyolysis are mainly described in mixed DKA and HHS and in severe hypophosphataemia	Low pH, impaired renal function, High glucose and Na <sup>+</sup> , hypophosphataemia, increased osmolality	191,263-266
Asymptomatic hypophosphataemia	Up to 90% of adults <sup>c</sup>	Asymptomatic hypophosphataemia is common; case reports of severe hypophosphataemia causing rhabdomyolysis, renal failure, haemolytic anaemia, arrhythmia, respiratory failure	High acidaemia	98,188-191
Severe or symptomatic hypophosphataemia	Rare in adults and children			
Intestinal necrosis or GI bleeding	Rare in children, upper GI bleeding in 9% of adults	Intestinal necrosis thought to be related to hypoperfusion and microangiopathy; intestinal necrosis is described in children and adolescents but not adults, upper GI bleeding is frequent in adults, which might be related to acid reflux during DKA	Impaired renal function, high glucose	267,268

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<sup>a</sup>**Hypoglycaemia** and **hypokalaemia** are well known complications of DKA treatment that occur commonly and are not included here as they are discussed extensively in the text. <sup>b</sup>Rates in adults are unknown; <sup>c</sup>Rates in children unknown  
ARDS, acute respiratory distress syndrome; CK-MB, creatine kinase - myocardial band; DKA, diabetic ketoacidosis; GI, gastrointestinal; HHS, hyperglycaemic hyperosmolar state, pCO<sub>2</sub>, partial pressure of carbon dioxide; QTc, corrected QT interval.

12 **Figure legends**

13

14 **Figure 1. The history of DKA.**

15 The first reports of diabetic coma date back to the early 1800s and included isolated cases of  
16 children and adults with previously undiagnosed or established diabetes who presented with rapid  
17 onset symptoms of hyperglycaemia that led to coma and death<sup>269</sup>. In 1857, the presence of acetone  
18 was identified in the urine of an individual presenting in a diabetic coma<sup>270</sup>. Two decades later, the  
19 German physician Adolf Kussmaul reported severe dyspnoea (hyperventilation) in patients<sup>271</sup>. A  
20 decade later, Stadelmann reported that the urine of most patients with diabetic coma contained  
21 large quantities of  $\beta$ -hydroxybutyric acid, in addition to acetoacetate<sup>272</sup>. The mortality rate was >90%  
22 in the pre-insulin era<sup>273</sup> with only a few patients living longer than a few months. In subsequent  
23 decades, the mortality associated with DKA decreased to <1–2% since the 2010s in developed  
24 countries<sup>1,8</sup>. It was not until in the 1970s that it was established that low-dose intravenous insulin  
25 infusions were introduced following data to show that they lowered glucose and ketone  
26 concentrations just as well as higher doses<sup>274</sup>. The first American Diabetes Association (ADA)  
27 guideline was published in 2001 and the first edition of the UK guideline was published in 2011. In  
28 2018, the first randomized controlled trial of fluid replacement in children showed no differences in  
29 acute or post-recovery neurological outcomes in children with DKA treated with rapid versus slower  
30 volume correction using either 0.9% or 0.45% saline<sup>159</sup>.

31

32 **Figure 2: Pathogenesis of diabetic ketoacidosis.**

33

34 Hyperglycaemia develops in insulin deficiency because of three processes: increased  
35 gluconeogenesis, accelerated glycogenolysis, and impaired glucose utilization by peripheral  
36 tissues. The reduction in insulin concentration together with the increase in counter-regulatory  
37 hormones, leads to the activation of hormone sensitive lipase in adipose tissue with the  
38 subsequent breakdown of triglyceride into glycerol and free fatty acids (FFAs). In the liver, FFAs  
39 are oxidized to ketoacids, mainly under the influence of glucagon. FFAs undergo  $\beta$ -oxidation to  
40 form acetyl CoA. Excess acetyl CoA that does not enter the Krebs cycle generates acetoacetyl  
41 CoA, three molecules of which condense to form hydroxyl-3-methylgluturate-CoA (HMG-CoA).  
42 This in turn is cleaved to form acetoacetate and acetyl CoA. The acetoacetate is further reduced by  
43 NADH to form  $\beta$ -hydroxybutyrate. The two major ketoacids are  $\beta$ -hydroxybutyrate and  
44 acetoacetate. Accumulation of ketoacids leads to a high anion gap metabolic acidosis due to the

45 reduction in serum bicarbonate concentration and 'fixed acid' retention. Hyperglycaemia also  
46 activates macrophages to produce pro-inflammatory cytokines, and the liver to produce CRP,  
47 which in turn impair pancreatic  $\beta$ -cell function, as well as reducing endothelial nitric oxide, leading  
48 to endothelial dysfunction. Hyperglycaemia and high ketone levels cause an osmotic diuresis that  
49 leads to hypovolaemia, decreased glomerular filtration rate worsening hyperglycaemia. As a result  
50 of respiratory compensation for the metabolic acidosis, Kussmaul breathing characterized by deep,  
51 regular breaths (often with a 'fruity' odour) are taken by those in DKA as a way of excreting acidic  
52 carbon dioxide. Cerebral oedema is increased fluid content of the brain tissue that may lead to  
53 neurological signs and symptoms.

54

55 **Figure 3: Symptoms and signs of DKA.**

56 The osmotic diuresis of hyperglycaemia and ketonuria causes circulatory volume depletion. This in  
57 turn can cause the lethargy, stupor and coma. The metabolic acidosis stimulates respiratory  
58 compensation, with the classic hyperventilation ('air hunger') that is Kussmaul breathing — the  
59 volatile ketones can be smelt on the breath. Changes in visual acuity, which is thought to be due to  
60 changes in water content in the eye ball or the lens are also observed. Patients with diabetic  
61 ketoacidosis also experience abdominal pain, nausea and vomiting that resolve with treatment.

62

63

64 **Box 1. Hyperglycaemic hyperosmolar state**

65

66 Hyperglycaemic hyperosmolar state (HHS) is another commonly encountered hyperglycaemic  
67 emergency. HHS occurs less frequently than DKA (<1% of diabetes-related emergencies<sup>269</sup>), but  
68 has a substantial mortality of up to 20%<sup>149,269</sup>. HHS is characterized by severe hyperglycaemia and  
69 high serum osmolality (concentration of electrolytes and glucose in the serum) accompanied by  
70 circulatory volume depletion<sup>275</sup>. In HHS, insulin concentrations are adequate to inhibit ketogenesis,  
71 but not high enough to ensure adequate cellular glucose uptake. So, HHS is characterized by  
72 hyperglycaemia and an osmotic diuresis that perpetuates dehydration without ketosis. As with  
73 DKA, concurrent illness, such as infection or acute coronary syndrome can lead to an increase in  
74 counter-regulatory hormones, which exacerbates hyperglycaemia. Medications such as  
75 corticosteroids and atypical antipsychotics can also precipitate HHS<sup>276,277</sup>.

76

77

78 The UK and US guidelines for diagnosing HHS slightly differ from each other<sup>8,275</sup>. The UK  
79 guidelines define HHS as a glucose concentration  $\geq 30$ mmol/l, pH>7.3, bicarbonate >15mmol/l, and  
80 blood  $\beta$ -hydroxybutyrate <3.0mmol/l, and osmolality of >320mosmol/l<sup>275</sup>; US guidelines define HHS  
81 as glucose levels >33.3mmol/l, pH>7.3, bicarbonate >18mmol/l, with 'small' concentrations or  
82 urinary or serum ketones and osmolality of >320mosmol/l<sup>8</sup>. In addition to detecting and treating any  
83 precipitating cause, the management of HHS involves correction of fluid deficits including  
84 potassium replacement and reducing hyperosmolality. The administration of intravenous fluids,  
85 such as 0.9% saline will also lower glucose concentrations by addressing the haemoconcentration  
86 (an increase in the proportion of the blood that is cells, due to the loss of water) and restoring renal  
87 perfusion. Circulatory volume depletion is more severe in HHS than in DKA and higher rates of  
88 fluid administration are typically necessary. Consensus recommendations from various groups are  
89 slightly different owing to lack of trials<sup>8,275</sup>. Intravenous insulin is started immediately after the initial  
90 fluid bolus if there is evidence of a metabolic acidosis (DKA and HHS can frequently co-exist<sup>278</sup>).  
91 However, in the absence of acidosis, a weight-based fixed rate intravenous insulin infusion is  
92 started only after the glucose concentration ceases to decline with fluid replacement alone<sup>275</sup>, or  
93 after potassium levels have been corrected<sup>8</sup>.

94

95 **Box 2. Current potassium replacement guidelines**

96

97 **[H1] Adults**

98

- 99 •  $K^+ \geq 5.5$ mmol/l: no supplementation is required due to the risk of precipitating cardiac  
100 arrhythmias with additional potassium
- 101 •  $K^+ = 4.0$ – $5.0$ mmol/l: 20mmol/l of replacement fluid
- 102 •  $K^+ = 3.0$ – $4.0$ mmol/l: 40mmol/l of replacement fluid
- 103 •  $K^+ = <3.0$ mmol/l: 10–20mmol per hour until serum  $K^+ >3.0$ mmol/l, then add 40mmol/l to  
104 replacement fluid.

105

106

107 **[H1] Children**

108

- 109 •  $K^+ >5.0$ mmol/l: delay potassium administration until  $K^+ \leq 5.0$ mmol/l.
- 110 •  $K^+ 3.5$  –  $5.0$ mmol/l: add potassium 40 mmol/l to the infusion after administering the initial fluid  
111 replacement bolus.
- 112 •  $K^+ <3.5$ mmol/l: begin potassium replacement 40mmol/l as soon as possible and delay insulin  
113 administration until potassium level is normal.

114

115

116 **Glossary terms**

117

118 **BMI z-score**

119 Also known as the BMI standard deviation scores, the z-score is a measure of a child's relative  
120 weight adjusted for age and gender

121

122 **Buffering**

123 The ability of molecules in the circulation to stabilise the acid base balance in an attempt to  
124 maintain the pH

125

126 **pKa**

127 This is the negative base-10 logarithm of the acid dissociation constant ( $K_a$ ) of a solution. The  
128 lower the pKa, the stronger the acid.

129

130 **Circulatory volume depletion**

131 A reduction in intravascular and / or extracellular fluid volume, such that there may be an inability  
132 to adequately perfuse tissue.

133

134 **Glomerular filtration rate**

135 This is an estimate of how much blood passes through the renal glomeruli every minute. Is it often  
136 a calculation from the serum creatinine, age, gender and body weight

137

138 Hypertonicity – A state where the circulating extracellular fluid has a higher osmotic pressure, than  
139 would be observed in a healthy individual.

140

141 **Pre-renal renal failure**

142 The loss of kidney function as a result of poor renal or glomerular perfusion, e.g. haemorrhage,  
143 cardiac failure or hypovolaemia.

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