Diabetic ketoacidosis and hyperosmolar crisis in adults

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Abstract

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) remain two of the most commonly encountered metabolic emergencies. They are potentially life-threatening when not managed correctly. DKA occurs most frequently in people with type 1 diabetes mellitus, but is increasingly found in those with type 2 diabetes. HHS (formerly known as hyperosmolar non-ketotic state) occurs most frequently (but not exclusively) in older people with type 2 diabetes, who have insufficient insulin concentrations to lower blood glucose, but enough to prevent ketone production. Diabetes can present for the first time as DKA or less commonly as HHS; however, these occur more frequently in people known to have diabetes, the most common causes being infection and other intercurrent illnesses, or non-concordance with medication. The initial treatment of DKA and HHS differs because they are biochemically dissimilar. In DKA with increasing access to bedside plasma ketone monitors, the emphasis of treatment is reduction of β-hydroxybutyrate concentrations rather than blood glucose. In HHS, glucose lowering should be undertaken predominantly using fluid rehydration, with insulin being gently introduced only when the rate of glucose lowering has stabilized.

Keywords Diabetes; diabetic ketoacidosis; hyperosmolar hyperglycaemic state; metabolic emergency; treatment

Key points

- Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) remain among the most commonly encountered metabolic emergencies
- The diagnosis of DKA requires all three components to be present — hyperglycaemia or a history of diabetes ('D'), raised plasma ketone concentration ('K') and low pH, or low bicarbonate ('A'). In some cases, however, glucose concentrations remain in the normal range (euglycaemic ketoacidosis)
- There is no formal definition of HHS, but raised plasma osmolality, high glucose concentrations and absence of acidosis is usually sufficient. However, acidosis caused by associated morbidity (infection, myocardial infarction, etc.) can be encountered, as can a mixed picture of DKA and HHS
- Although fluid rehydration remains key to the initial management of both conditions, subsequent management differs
- DKA requires a fixed-rate, weight-based intravenous insulin infusion from the start; a similar regimen is required in HHS only when the glucose concentration stops falling with adequate fluid rehydration

Introduction

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) are acute severe metabolic complications of uncontrolled diabetes mellitus. They are potentially life-threatening and require swift recognition and treatment.[1] Although each can be seen in 'pure' form, features of the two disorders can coexist and present with a mixed picture.

Diabetic ketoacidosis

Definition and pathophysiology[1,2]

DKA is defined by the presence of all three components: 'D' — a blood glucose >11.0 mmol/litre or known diabetes mellitus; 'K' — ketonaemia >3.0 mmol/litre or >2+ ketonuria on standard urine sticks; and 'A' — a serum bicarbonate <15.0 mmol/litre and/or venous pH <7.3 (usually with a raised anion gap). It is important to remember, however, that the glucose may not be particularly raised in DKA. This is known as euglycaemic DKA, a condition that occurs more frequently with the use of the sodium glucose co-transporter 2 (SGLT2) inhibitors, in pregnancy and with prolonged starvation or excess alcohol intake. A good history helps determine the cause.

DKA usually occurs as a consequence of absolute or relative insulin deficiency, accompanied by an increase in counter-regulatory hormone secretion.[3] This leads to unrestrained hydrolysis of triglycerides (triacylglycerols) in adipose tissue, increasing delivery to the liver of free fatty acid, which serves as a ketogenic substrate. Ketones include β-hydroxybutyrate, acetoacetate and acetone. Concurrently, inappropriate hepatic glycogenolysis and gluconeogenesis result in hyperglycaemia that can be severe. Figure 1 shows the pathways involved in the development of DKA, and how it differs from HHS.

Dehydration is a cardinal feature of DKA, resulting initially from osmotic diuresis caused by hyperglycaemia, and worsened later by vomiting, and eventually by an inability to take in fluid as a result of impaired consciousness. A clinical threat is also posed by hyperkalaemia, which occurs at presentation as a consequence of acidosis and loss of insulin-driven uptake of potassium into cells, as well as being aldosterone driven. Hypokalaemia can occur during rehydration and intravenous insulin treatment.

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Competing interests: KD is the lead author on the Joint British Diabetes Societies (JBDS) Guidelines on the Management of Diabetic Ketoacidosis in Adults and one of the lead authors on the JBDS guideline on management of the hyperosmolar hyperglycaemic state. He has received travel expenses and honoraria for speaking about these, and for other JBDS guidelines he has co-authored.

Morbidity and mortality

Mortality rates have fallen significantly in the last 25 years from approximately 8% to <1%.[3] It is likely that the standardized guidelines, including on insulin administration and close monitoring of fluid and electrolyte status, have driven this fall. The main causes of mortality in the adult population include the underlying co-morbidity that may have precipitated the DKA, such as pneumonia, acute myocardial infarction or sepsis, and the severity of any hypokalaemia arising during treatment of DKA. Other complications, such as adult respiratory distress syndrome, are now much rarer causes of death.

DKA represents the most the most common cause of death in children and adolescents with type 1 diabetes, and the most common reason remains cerebral oedema, the causes of which remain undetermined.[3] Children and adolescents are not considered further in this chapter.

Management of DKA

The principles of managing DKA centre on:

- replenishing the fluid deficit, which serves to reduce counter-regulatory hormones as well as enhancing organ perfusion
- delivering adequate insulin to suppress lipolysis and ketone production
- identifying and treating precipitants
- restoring euvolaemia, euglycaemia and normal pH without inducing iatrogenic hypokalaemia or hypoglycaemia.

With recent technological advances, the delivery and monitoring of treatment have evolved in several ways. Thus, measurement of blood ketones, venous (rather than arterial) pH and serum bicarbonate are recommended as key treatment markers, with ketones and glucose measured using bedside meters when available and operating within their quality assurance range. Electrolytes are commonly analysed on near-patient blood gas analysers with only intermittent laboratory confirmation. Widely used variable-rate intravenous insulin infusions have been replaced by weight-based, fixed-rate intravenous insulin infusions (FRIIIs), starting at 0.1 U/kg per hour. Long-acting basal insulin (human or analogue) is either continued in patients already taking it, or started at a dose of 0.25 U/kg subcutaneously once daily in those for whom DKA is the first presentation of type 1 diabetes.

Resolution of DKA is defined as a venous pH >7.3, serum bicarbonate >15.0 mmol/litre and blood ketones <0.6 mmol/

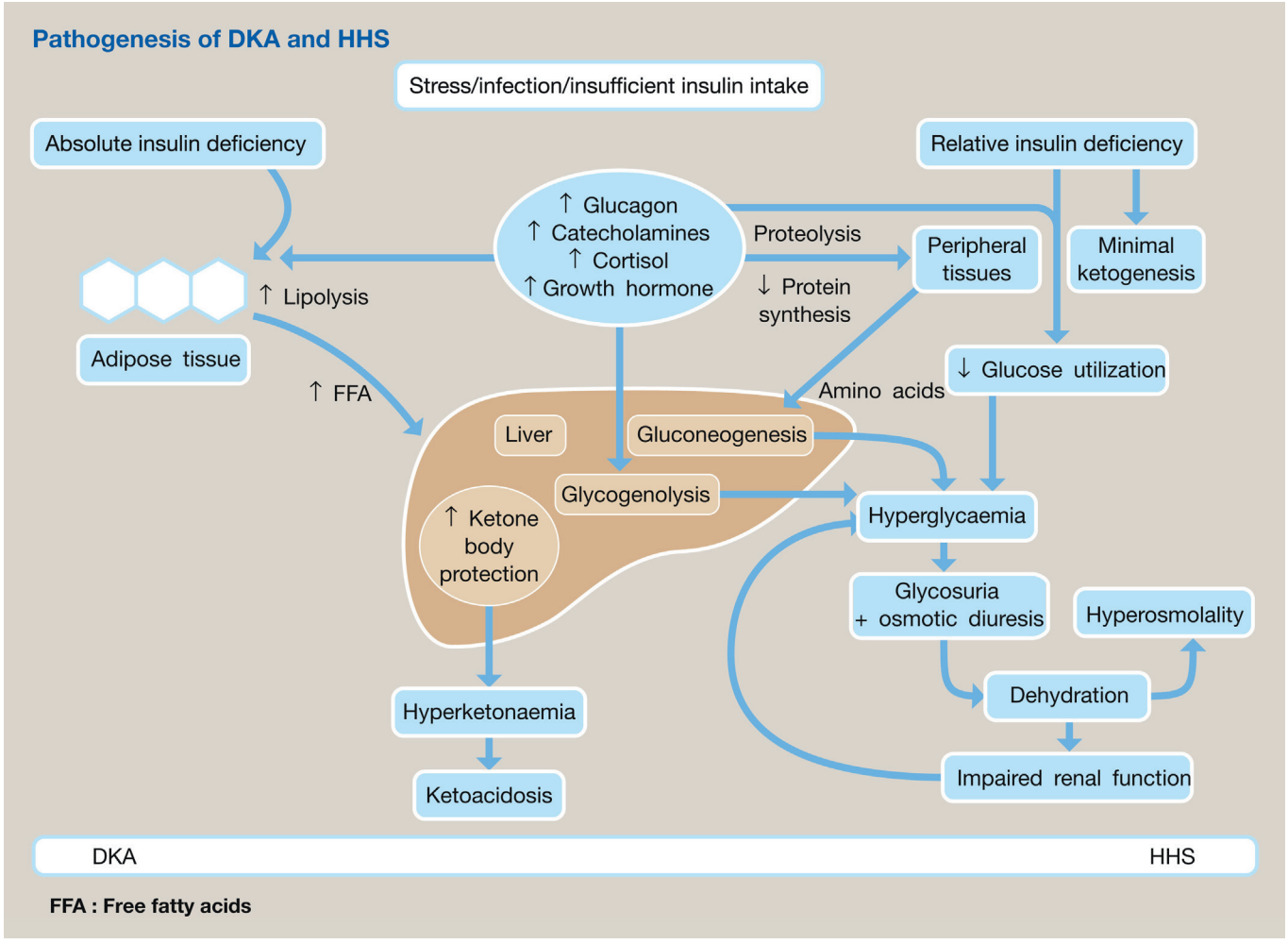

Figure 1 Reproduced from English P, Williams G. Hyperglycaemic crises and lactic acidosis in diabetes mellitus. *Postgrad Med J* 2004; **80**: 253–261, with permission from BMJ Publishing Group Ltd.

litre (beware the low bicarbonate from hyperchloraemic metabolic acidosis caused by high volumes of infused 0.9% sodium chloride solution).

Initial assessment focuses on resuscitation, determining the severity of fluid deficit and acidosis, and a search for likely precipitants such as sepsis or myocardial infarction. The presence of any of the following on admission to hospital indicate admission to a level 2/high-dependency unit (HDU) environment:

- severe ketoacidosis (blood ketones >6.0 mmol/litre; serum bicarbonate <5.0 mmol/litre; venous or arterial pH <7.0; anion gap >16 mmol/litre)
- hypokalaemia (<3.5 mmol/litre)
- impaired consciousness (e.g. abnormal Glasgow Coma Scale (GCS) score or AVPU (Alert, Voice, Pain, Unresponsive) score)
- oxygen saturation <92% when breathing air (if baseline respiratory function is normal)
- haemodynamic compromise (systolic blood pressure <90 mmHg and/or heart rate >100 or <60 beats per minute).

If systolic blood pressure is >90 mmHg, vigorous fluid replacement should be commenced, using a regimen such as that illustrated in Table 1. Insulin should be delivered intravenously using a weight-based FRIII. The FRIII should use an infusion pump with human soluble insulin 50 U made up to 50 ml with sodium chloride 0.9% solution. It should be infused at an initial rate of 0.1 U/kg per hour. If the person's exact weight is not known, it can be estimated. If the individual is pregnant, her present weight should be used and senior advice sought urgently. A bolus dose of subcutaneous or intravenous insulin should be used only if there is a delay in setting up an FRIII. If the patient normally takes a long-acting basal insulin (human or analogue) subcutaneously, this should be continued at the usual dose and usual time to reduce the problem of rebound hyperglycaemia after withdrawal of the intravenous infusion.

Hyperkalaemia is common at presentation of DKA, and, if severe, should be treated as an emergency. However, high serum potassium masks a deficiency of intracellular potassium in DKA, and because potassium is driven into cells by treatment with insulin and fluids, serum potassium can fall sharply; it should be replaced proactively to avoid dangerous hypokalaemia. Serum potassium should be checked regularly, ideally using a near-patient venous blood gas machine. A typical replacement regimen is shown in Table 2. When the glucose concentration drops to <14.0 mmol/litre consider reducing the rate of intravenous insulin infusion to 0.05 units/kg per hour to reduce the risk of developing hypoglycaemia and/or hypokalaemia.

After admission, regular — initially hourly — clinical and biochemical assessment is mandatory to ensure continued improvement after initial therapy. The use of urine ketone sticks is discouraged, because although β-hydroxybutyrate is found predominantly in the blood — and this is detected by the point-of-care bedside plasma ketone meters — urine ketone sticks detect only acetoacetate, which is the predominant ketone in urine. Thus, because β-hydroxybutyrate is converted to acetoacetate, if urine sticks are used, it can give the (false) impression that the DKA is not resolving. In addition, because the urine tests are an average of acetoacetate concentrations since the bladder was last emptied, their use can prolong treatment.

Recommended rates of change of blood ketones, bicarbonate and glucose are shown in Table 3. Detailed management of DKA beyond 60 minutes is described in the UK national guidelines (https://abcd.care/sites/abcd.care/files/site_uploads/JBDS_Guidelines_Current/JBDS_02%20_DKA_Guideline_amended_v2_June_2021.pdf). These are used by >90% of all UK hospitals. It is crucial to longer term management, and to pre-empt future admissions, that the diabetes specialist team be involved as soon as possible after admission.

Hyperosmolar hyperglycaemic state

Definition and pathophysiology:[4] HHS is a condition characterized by severe dehydration, hyperglycaemia in the absence of ketoacidosis, and hyperosmolarity. Diagnostic criteria adopted in the UK require the presence of hypovolaemia and severe hyperglycaemia (>30.0 mmol/litre), with serum osmolality usually >320 mOsm/kg and an absence of significant ketonaemia (<3.0 mmol/litre). HHS is believed to result from the presence of sufficient insulin to suppress hepatic ketone production, but not to suppress hepatic and renal gluconeogenesis. The ensuing hyperglycaemia leads to osmotic diuresis, which itself leads to dehydration and haemoconcentration, and a vicious cycle begins. The pathophysiology of HHS is illustrated in Figure 1.

HHS usually presents in elderly people and can be the first presentation of type 2 diabetes mellitus. It can be precipitated by intercurrent illness and the subsequent release of counter-regulatory hormones, or the use of drugs that induce hyperglycaemia (e.g. corticosteroids). However, because type 2 diabetes is being diagnosed in ever-younger adults and teenagers, it is increasingly likely that HHS will present in younger age groups

Typical fluid replacement regimen for DKA if systolic blood pressure is >90 mmHg

Fluid	Volume
Sodium chloride 0.9% 1 litre	1000 ml over first hour
Sodium chloride 0.9% 1 litre with potassium chloride	1000 ml over next 2 hours
Sodium chloride 0.9% 1 litre with potassium chloride	1000 ml over next 2 hours
Sodium chloride 0.9% 1 litre with potassium chloride	1000 ml over next 2 hours
Sodium chloride 0.9% 1 litre with potassium chloride	1000 ml over next 4 hours
Sodium chloride 0.9% 1 litre with potassium chloride	1000 ml over next 4 hours

Reassessment of cardiovascular status at 12 hours is mandatory, as further fluid may be required.
If the blood glucose concentration drops to <14 mmol/litre, 10% dextrose should be added to provide a substrate for the insulin. This should be in addition to the sodium chloride 0.9%, which acts as the resuscitation fluid.
The fixed-rate intravenous insulin infusion should be continued until the ketonaemia resolves, i.e. <0.6 mmol/litre.

Table 1

Recommended potassium replacement regimen in DKA and HHS

Serum potassium in first 24 hours (mmol/litre)	Potassium concentration in infusion solution (mmol/litre)
>5.5	0
3.5–5.5	40
<3.5	>40 (requires senior clinical review)

Table 2

Recommended metabolic targets in the management of DKA

- Reduction of blood ketone concentration by 0.5 mmol/litre per hour
- Increase in venous bicarbonate concentration by 3.0 mmol/litre per hour
- Reduction of capillary blood glucose by 3.0 mmol/litre per hour
- Maintenance of serum potassium between 4.5 and 5.5 mmol/litre

Table 3

as well. Unlike DKA, which usually evolves over a matter of hours, HHS evolves over many days, and consequently the dehydration and metabolic disturbances are more extreme. However, a mixed picture of HHS and DKA can occur and can be a trap for the unwary. If they occur together, they should be treated like an episode of DKA.

Hyperglycaemia induces osmotic diuresis and renal losses of water in excess of sodium and potassium. Fluid losses are estimated to be severe, at 100–220 ml/kg.[1] Despite this, typical patients with HHS may not look as dehydrated as they are, because of a redistribution of body water resulting from blood hypertonicity and preservation of intravascular volume.

Morbidity and mortality

Because patients with HHS tend to be older than those with DKA they often have other co-morbidities and are thus at greater risk of developing the complications of not only diabetes, but also its treatment. Atherosclerosis, thrombosis and foot ulceration pose particular risks. The reported mortality of HHS has fallen from around 40% to 5–16%, which is still 10-fold higher than for DKA.

Management of HHS

Clinical assessment should determine the extent of dehydration, evaluate mental state and look for evidence of a precipitating cause, for example infection, sepsis, myocardial infarction or a recent change in medication. The recent addition of high-dose glucocorticoids is a prime example of the latter. Risk of foot ulceration should also be assessed at the time of admission and daily afterwards, with obtunded or uncooperative patients assumed to be at particularly high risk.

Investigations should determine the biochemical severity of hyperglycaemia and acidosis, and should include calculation of osmolarity (e.g. $2Na^+$ + glucose + urea). End-organ damage, in particular acute kidney injury, should be looked for.

Immediate aims of management are to:

- replace approximately 50% of the estimated fluid loss within the first 12 hours and the remainder in the following 12 hours – the rate is determined by the initial severity, degree of renal impairment and associated co-morbidities, particularly heart failure
- achieve a target blood glucose of 10.0–15.0 mmol/litre
- treat the underlying cause
- prevent complications such as arterial or venous thrombosis, cerebral oedema, central pontine myelinolysis and foot ulceration.

Complete correction of electrolytes and osmolality can take up to 72 hours. The presence of any of the following on admission to hospital indicates admission to a level 2/HDU environment:

- serum osmolality >350 mOsm/kg and/or serum sodium >160 mmol/litre venous/arterial pH <7.1
- severely deranged serum potassium (<3.5 or >6.0 mmol/litre)
- impaired consciousness (e.g. GCS <12 or abnormal AVPU score)
- oxygen saturation <92% when breathing air (if baseline respiratory function is normal)
- haemodynamic compromise (systolic blood pressure <90 mmHg and/or heart rate >100 or <60 beats/minute)
- hypothermia
- acute or serious co-morbidity (e.g. myocardial infarction, congestive cardiac failure or cerebrovascular accident)
- urine output <0.5 ml/kg/hour or other evidence of acute kidney injury.

If there is a problem obtaining intravenous access, critical care support should be requested immediately. Fluid resuscitation should be guided by clinical state and co-morbidity, but often starts with giving sodium chloride 0.9% 1 litre over 1 hour. If the osmolality is no longer declining despite adequate fluid replacement with 0.9% sodium chloride solution *and* an adequate rate of fall of plasma glucose is not being achieved, 0.45% sodium chloride solution should be substituted. It is usually mandatory to insert a urinary catheter to monitor hourly urine output and calculate fluid balance.

A monitoring regimen appropriate to the patient should be established – this is usually hourly determination of blood glucose, serum sodium, potassium and urea and calculated osmolarity for the first 6 hours, and then 2-hourly osmolarity if the response is satisfactory (ideally a fall in 3–8 mOsm/litre per hour).

Fluid replacement alone lowers blood glucose, which reduces osmolality, causing a shift of free water into the intracellular space. This inevitably results in a rise in serum sodium – another trap for the unwary, because even though the sodium concentration can rise, the corresponding fall in glucose and urea should result in a fall in the calculated serum osmolarity. Serum sodium concentrations should be monitored frequently, and the concentration of sodium in infusion fluids adjusted to promote a gradual decline in corrected serum sodium. Although there are no data to indicate an optimal rate of decline in serum sodium, a rate of 0.5 mmol/litre per hour has been recommended for

hypernatraemic dehydration. Potassium should be replaced as in DKA (Table 2).

Significant ketonaemia (β-hydroxybutyrate >1.0 mmol/litre) indicates relative hypoinsulinaemia, so insulin should be started at once. If significant ketonaemia is not present (β-hydroxybutyrate <1.0 mmol/litre), insulin is not indicated. Fluid replacement alone, with sodium chloride 0.9%, reduces blood glucose; therefore, because most patients with HHS are insulin sensitive, there is a risk of lowering osmolality dangerously and quickly, resulting in central pontine myelinolysis (osmotic demyelination). Insulin treatment before adequate fluid replacement can result in cardiovascular collapse as water moves out of the intravascular space, with an attendant decline in intravascular volume. A fall of blood glucose of <5.0 mmol/litre per hour is ideal. Once blood glucose has ceased to fall after initial fluid resuscitation, fluid intake and renal function should be reassessed. Insulin can be started at this point using an FRIII given at 0.05 U/kg per hour.

HHS can be considered to be resolved when the following criteria are met: when measured or calculated serum osmolality falls to <300 mOsm/kg, hypovolaemia has been corrected (urine output ≥0.5 ml/kg/hour), cognitive status has returned to the pre-morbid state and blood glucose <15 mmol/litre.

Because of the increased risk of arterial and venous thromboembolism, all patients should be given prophylactic low-weight heparin for the duration of admission unless contra-indicated. Full-treatment-dose anticoagulation should be considered only in those with suspected thrombosis or acute coronary syndrome. Heel protectors should be applied in individuals with neuropathy, peripheral vascular disease or lower limb deformity, and the feet should be re-examined daily.

Longer term management of HHS is discussed in the UK national guidelines (https://abcd.care/resource/management-hyperosmolar-hyperglycaemic-state-hhs). ◆

KEY REFERENCES

1 Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009; **32:** 1335–43.

2 Joint British Diabetes Societies. JBDS 02 the management of diabetic ketoacidosis (DKA) in adults. 2021, https://abcd.care/sites/abcd.care/files/site_uploads/JBDS_Guidelines_Current/JBDS_02%20_DKA_Guideline_amended_v2_June_2021.pdf (accessed 10 June 2022).

3 Dhatariya KK, Glaser NS, Codner E, Umpierrez GE. Diabetic ketoacidosis. *Nat Rev Dis Primers* 2020; **6:** 40.

4 Joint British Diabetes Societies. JBDS 06 the management of hyperosmolar hyperglycaemic state (HHS) in adults. 2022, https://abcd.care/resource/management-hyperosmolar-hyperglycaemic-state-hhs (accessed 10 June 2022).

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 32-year-old woman was admitted with diabetic ketoacidosis. After 24 hours of appropriate treatment, her normal basal bolus insulin regimen was restarted. However, she continued to feel nauseated, and her blood glucose began to rise. Her urine ketones also began to rise, to >3+.

On clinical examination, her heart rate was 124 beats/minute, and blood pressure 100/60 mmHg.

Investigations

- Sodium 135 mmol/litre (137–144)
- Potassium 4.2 mmol/litre (3.5–4.9)
- Bicarbonate 14 mmol/litre (20–28)
- Creatinine 780 micromol/litre (60–110)
- Random plasma glucose 8.1 mmol/litre (3.0–11.0)

What is the most appropriate next step in management?

A. Give more subcutaneous basal insulin at bedtime
B. Give more subcutaneous bolus insulin with her meals
C. Restart a fixed-rate intravenous insulin infusion
D. Start Hartmann's solution with fixed-rate intravenous insulin
E. Start glucose 10% with fixed-rate intravenous insulin

Question 2

A 24-year-old man presented as an emergency feeling unwell. He was drowsy but was able to confirm that he had never previously been unwell. There was no record of him on the hospital computer system. On clinical examination, he was thin and unwell. His temperature was 35.2°C, heart rate 124 beats/minute, blood pressure 83/45 mmHg, and respiratory rate 20 breaths/minute. Oxygen saturations were 96% (94–98%) on air. Urine testing showed 3+ ketones.

Investigations

- Sodium 153 mmol/litre (137–144)
- Potassium 6.4 mmol/litre (3.5–4.9)
- Bicarbonate<5 mmol/litre (20–28)
- Urea 16.2 mmol/litre (2.5–7.0)
- Creatinine 154 micromol/litre (60–110)
- Random plasma glucose 32.7 mmol/litre (3.0–11.0)
- ECG showed slightly peaked T waves

In addition to insulin, what is the most appropriate infusion?

A. Calcium chloride 10%
B. Plasma-Lyte
C. Sodium bicarbonate 8.4%
D. Sodium chloride 0.45%
E. Sodium chloride 0.9%

Question 3

A 72-year-old woman presented after a collapse at home. She had no history of type 2 diabetes mellitus. Three weeks previously, she had started on prednisolone 40 mg for polymyalgia rheumatica.

On clinical examination, she was drowsy. Her heart rate was 132 beats/minute, and blood pressure 95/60 mmHg.

Investigations

- Sodium109 mmol/litre (137–144)
- Potassium 3.4 mmol/litre (3.5–4.9)
- Chloride 55 mmol/litre (95–107)
- Bicarbonate 24 mmol/litre (20–28)
- Urea 25.0 mmol/litre (2.5–7.0)
- Creatinine 311 micromol/litre (60–110)
- Random plasma glucose 119.0 mmol/litre (3.0–11.0)

What is her calculated anion gap?

A. 30
B. 31
C. 32
D. 33
E. 34