

PREVALENCE

Diabetic ketoacidosis is defined as **[D]¹**:

- hyperglycaemia (> 14 mmol/l)
- metabolic acidosis (pH < 7.35 or bicarbonate < 15 mmol/l)
- high anion gap (anion gap = Na + K - HCO₃) **[C]²**
- ketonaemia.

Hyperglycaemic hyperosmolar non-ketosis **[D]¹** is different:

- blood glucose is higher (often > 33 mmol/l)
- no acidosis
- one plus ketonuria at the most on urine dipstick
- higher Na⁺ (often > 150 mmol/l).

DKA is relatively common **[B]³** in patients with diabetes and is often recurrent **[B]⁴**. Roughly one in seven patients with hyperglycaemia who feel unwell have DKA **[C]²**.

Note

- 8.9% of patients with diabetes have an episode of DKA in 1 year (95% CI: 7.7% to 10%) **[B]³**.
- 42% of patients with DKA have another episode (95% CI: 32% to 52%) **[B]⁴**.
- 14% of patients with a blood glucose > 11 mmol/l and any complaint have DKA (95% CI: 12% to 17%) **[C]²**.

Up to a quarter of cases are patients with new-onset diabetes **[C]⁸**.

Note

- 27% of patients with DKA have new-onset diabetes (95% CI: 22% to 33%).

CAUSES

Common causes of DKA include **[B]³ [B]⁴ [C]⁵ [C]⁶**:

- infection
- treatment error
- new-onset diabetes
- other medical illness

but it is often of unknown aetiology.

Why? The cause of many cases of DKA is unknown	
[B]³ [B]⁴ [C]⁵ [C]⁶	<i>Prevalence</i>
Unknown	19%–38%
Infection	27%–38%
Treatment error	12%–28%
Other medical illness	11%
■ pancreatitis	2%–3%
■ myocardial infarction	1%–7%
■ GI bleed	1%
■ heart failure	2%
Affected by drugs or alcohol	9%
Newly diagnosed diabetes	10%–27%

CLINICAL FEATURES

Ask about:

- known diabetes mellitus **[B]³ [B]⁴:**
- previous episodes of DKA **[B]³ [B]⁴**
- current medication **[A]⁷**, and any recent changes or mistakes **[B]³ [B]⁴**
- recent illness **[B]³ [B]⁴**
- polyuria, polydipsia and weakness **[D]**.

Why do this?						
<ul style="list-style-type: none"> ■ Patients who have intensive insulin therapy are at increased risk of ketoacidosis; however, there is no clear effect on mortality [A]⁷. ■ In particular, patients on continuous insulin infusions are at increased risk of ketoacidosis. There is no clear increase in ketoacidosis for patients on multiple daily injections [A]⁷. 						
Intensive insulin regimens, particularly insulin pumps, increase the risk of DKA						
<i>Patient</i> [A]⁷	<i>Treatment</i>	<i>Comparator</i>	<i>Outcome</i>	<i>CER</i>	<i>OR</i>	<i>NNH</i>
Insulin-dependent diabetes	Intensified insulin regimen	Standard insulin regimen	DKA at 2–6 years	6.4%	2.88 (2.38 to 3.48)	4 (3 to 5)
Insulin-dependent diabetes	Insulin pump	Standard insulin regimen	DKA at 2–6 years	0.86%	5.76 (2.88 to 11.50)	26 (12 to 64)

Look for evidence of **[B]³ [B]⁴:**

- dehydration
- infection (e.g. lobar pneumonia, urinary tract infection)
- associated disease (e.g. MI, pancreatitis).


Think about acidosis in any hyperventilating patient **[D]⁸**.

INVESTIGATIONS

Take a capillary blood glucose **[A]**.


Take a urine sample and test for:

- ketones **[C]²**
- leucocytes or nitrites: if abnormal send for culture **[D]**.


 Why? No ketones on urine dipstick make DKA very unlikely						
Patient [C]²	Target disorder (reference standard)	Diagnostic test	LR+(95% CI)	Post-test probability	LR-(95% CI)	Post-test probability
Suspected DKA (pre-test probability 14%)	DKA (elevated glucose, metabolic acidosis and ketonaemia)	Positive urine ketone dipstick	3.2 (2.9 to 3.7)	35%	0.015 (0.0021 to 0.10)	0.24%

Take the following blood tests:

- blood glucose
- urea and electrolytes, creatinine **[C]⁹**


 Why?	
■ 40% of patients with DKA have abnormal potassium levels: 28% hyperkalemia; 12% hypokalaemia [C]⁹ .	

- ketones **[A]**
- pH **[A]** from venous blood **[C]¹⁰**

 Why?	
■ Venous blood pH and bicarbonate levels correlate closely in patients with DKA [C]¹⁰ .	

- bicarbonate **[C]²**.

Calculate the anion gap ($\text{Na} + \text{K} - \text{HCO}_3$) **[C]²**.

 Why? A normal anion gap makes DKA unlikely, and a low bicarbonate makes it very likely						
Patient [C]²	Target disorder (reference standard)	Diagnostic test	LR+ (95% CI)	Post-test probability	LR-(95% CI)	Post-test probability
Suspected DKA (pre-test probability 14%)	DKA (elevated glucose, metabolic acidosis and ketonaemia)	Anion gap > 16 mmol/l	6.3 (5.1 to 7.6)	51%	0.096 (0.049 to 0.19)	1.5%
		Serum bicarbonate < 15 mmol/l	100 (42 to 240)	94%	0.16 (0.11 to 0.26)	2.6%

The following tests may help identify the cause:

- blood count **[D]**
- cardiac enzymes **[B]³ [B]⁴**
- amylase **[B]³ [B]⁴**
- blood cultures
- chest X-ray **[B]³ [B]⁴**
- 12-lead and continuous ECG **[B]³ [B]⁴**.

Repeat electrolytes and glucose levels **[C]⁹ [C]¹¹** at least hourly **[D]** until biochemical normality is achieved. A chart for vital signs, laboratory results and fluid balance is helpful **[D]**.

THERAPY

- Resuscitate and seek help if required **[D]**.
- Give intravenous fluids: initially 0.9% saline **[C]¹¹** (e.g. 1 litre over 30 min, 1 litre over 1 h, 1 litre over 2 h, 1 litre over 4 h).

If none of the following are present, fluids can safely be given more slowly if necessary **[D]¹²**:

- circulatory shock
- oliguria (< 30 ml/h) during the first 4 h of admission
- renal insufficiency (urea > 21 mmol/l or creatinine > 350 µmol/l).



Why do this?

- If there is no evidence of severe dehydration, normal saline given at 500 ml/h for 4 h followed by 250 ml/h for 4 h does not clearly affect time to normalised biochemistry compared with normal saline 1 litre/h for 4 h followed by 500 ml/h for 4 h **[D]¹²**.

In dehydrated or comatose patients, consider **[D]**:

- a urinary catheter
 - a central venous line.
- Monitor electrolytes **[C]⁹ [C]¹¹** and capillary glucose **[D]** frequently.
Give potassium supplementation **[A]** after insulin therapy has begun if $K^+ < 5.5$ mmol/l **[D]**.
Provide 10–30 mmol/h **[C]⁹**.

? **Why do this?**

- Potassium abnormalities are common: 28% of patients have hyperkalaemia on admission (95% CI: 10% to 46%) and 12% have hypokalaemia (95% CI: 0% to 25%) **[C]⁹**.
- Patients require on average 30–40 mmol of potassium per litre of fluid to keep serum potassium normal during rehydration **[C]⁹**.
- A patient whose serum sodium concentration falls or fails to rise during rehydration is at increased risk of developing cerebral oedema. A failure to rise suggests rehydration with excess free water **[C]¹¹**.

A failure of sodium to rise on rehydration increases the risk of cerebral oedema

Patient [C]¹¹	Prognostic factor	Outcome	Control rate	RR (95% CI)	NNF+ (95% CI)
DKA	No rise in serum sodium on rehydration <i>not independent</i>	Cerebral oedema	2.3% (0.0% to 5.5%)	6.56 (1.56 to 27.53)	8 (2 to 76)

- Give broad-spectrum antibiotics if there is evidence of infection **[A]**.
- Give soluble insulin **[A]** in low doses (e.g. 5–10 units/h) **[A]¹³** intravenously **[D]** at regular intervals or continuously **[D]**.

? **Why do this?**

- A low-dose insulin regimen is less likely to cause hypoglycaemia or hypokalaemia than a high-dose regimen **[A]¹³**.
- There is no clear difference in the time taken to return to biochemical normality **[A]¹³**.

A low-dose insulin regimen reduces the risk of hypoglycaemia or hypokalaemia

Patient	Treatment	Comparator	Outcome	CER	RRR	NNT
DKA	Low-dose insulin	High-dose insulin	Hypoglycaemia (< 2.8 mmol/l) at 12 h	25%	100%	4 (2 to 13)
			Hypokalaemia (< 3.4 mmol/l) at 12 h	29%	86% (-7% to 98%)	4 (2 to 19)

- The route used to administer insulin in patients has no clear effect on the time taken to return to biochemical normality or the amount of insulin required **[D]¹⁴ [D]¹⁵**.
- A continuous insulin infusion is not clearly more likely to cause a faster fall in glucose levels nor shorten the time to reach a glucose < 14 mmol/l than a bolus followed by regular injections **[D]¹⁶**.

- Continue giving insulin by this route until **[A]¹⁷**:
 - glucose < 10 mmol/l, and
 - ketones are cleared (3-hydroxybutyrate < 0.5 mmol/l).

If glucose < 10 mmol/l but ketones are still raised, continue insulin infusion with 20% glucose iv to maintain glucose 5–10 mmol/l.



Why do this?

- Patients with DKA who receive an extended insulin regimen have a more rapid fall in ketones than those on a conventional regimen (~16 h difference) **[A]**¹⁷.

- Once patients have stabilised, swap to subcutaneous insulin. Give 5% glucose and insulin infusion (at 8 units/h), with subcutaneous insulin as necessary to maintain blood glucose < 10 mmol/l until patients are eating **[C]**¹⁷. Give the first subcutaneous dose before stopping the infusion **[D]**.

There is no clear benefit from:

- sodium bicarbonate **[D]**¹⁸ **[D]**¹⁹



Why?

- Patients with severe DKA who receive bicarbonate do not clearly return more quickly to biochemical stability **[D]**¹⁸ **[D]**¹⁹.
- The effect on hypokalaemic or hypoglycaemic episodes is unclear **[D]**¹⁸ **[D]**¹⁹.

- routine phosphate supplementation **[A]**²⁰



Why?

- It reduces the risk of hypophosphataemia but increases the risk of infection, and has no clear effect on mortality **[A]**²⁰.
- Patients do not recover consciousness more quickly nor leave hospital sooner **[A]**²⁰.
- It has no clear effect on pH, phosphate, calcium or glucose levels at 24 h **[D]**²¹ **[D]**²².

- hypertonic glucose **[D]**²³.



Why?

- Patients with a glucose < 14 mmol/l do not clearly have a faster improvement in biochemical markers following 10% glucose and insulin rather than 5% glucose and insulin **[D]**²³.


PREVENTION

- Refer your patient to the diabetes team and educate the patient about diabetes **[A]**²⁴.




Why do this?

- It improves glycaemic control and reduces readmissions **[A]**²⁴.
- There is no clear effect on length of hospital stay **[A]**²⁴.


 Why do this? A diabetic team improves glycaemic control and reduces hospital readmissions						
Patient [A] ²⁴	Treatment	Comparator	Outcome	CER	RRR	NNT
Inpatient with diabetes	Diabetic team intervention	No intervention	Good glycaemic control at 1 month	46%	65 % (28% to 112%)	3 (2 to 6)
			Readmission at 3 months	32%	52 % (14% to 73%)	6 (3 to 22)

PROGNOSIS

Watch for cerebral oedema during resuscitation of patients aged < 30 years, particularly in patients whose serum sodium concentration fails to rise during rehydration **[C]**¹¹.


 Note
<ul style="list-style-type: none"> ■ Around 10% of patients with DKA suffer complications of brain swelling (mostly minor); 3% die [C]¹¹.

Few patients die: death is mainly from associated disease **[B]**³ **[B]**²⁵.

 Note
<ul style="list-style-type: none"> ■ 3–5% with DKA die during admission; 15% of patients with hyperosmolar coma die [B]³ [B]²⁵. ■ The commonest causes of death are pneumonia, MI and bowel or limb ischaemia [B]²⁵.

Recurrent episodes are common **[B]**⁴.

Patients with recurrent episodes are at increased risk of dying or having diabetic complications **[C]**²⁶ **[C]**²⁷.

 Note Half of patients have another episode										
<table border="1"> <thead> <tr> <th>Number of subsequent episodes of DKA [B]⁴</th> <th>% of patients</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>58%</td> </tr> <tr> <td>1</td> <td>23%</td> </tr> <tr> <td>2</td> <td>10%</td> </tr> <tr> <td>≥3</td> <td>9%</td> </tr> </tbody> </table>	Number of subsequent episodes of DKA [B] ⁴	% of patients	0	58%	1	23%	2	10%	≥3	9%
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2	10%									
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<ul style="list-style-type: none"> ■ 20% of women with recurrent DKA are dead within 10 years [C]²⁶ [C]²⁷. ■ Two-thirds have a diabetic complication and ~75% have a pregnancy complication in this time [C]²⁶ [C]²⁷. ■ Only 10% still have recurrent DKA after 10 years [C]²⁶ [C]²⁷. 										

Guideline writers: Richard Hardern, Christopher Ball

CAT writers: Richard Hardern, Chris Ball

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