

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?				
	<ul style="list-style-type: none"> ■ 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?					
	<ul style="list-style-type: none"> ■ 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)
	<ul style="list-style-type: none"> ■ 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	
Number of subsequent episodes of DKA [B] ⁴	% of patients
0	58%
1	23%
2	10%
≥3	9%
<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

REFERENCES

<i>No</i>	<i>Level</i>	<i>Citation</i>
1	5	Kitabchi AE, Wal BM. Diabetic ketoacidosis (narrative review). <i>Med Clin North Am</i> 1995; 79: 9–37
2	4	Schwab TM, Hendey GW, Soliz TC et al. Screening for ketonemia in patients with diabetes. <i>Ann Emerg Med</i> 1999; 34: 342–6
3	2c	Snorgaard O et al. Diabetic ketoacidosis in Denmark: epidemiology, incidence rates, precipitating factors and mortality rates. <i>J Intern Med</i> 1989; 226: 223–8
4	2c	Johnson DD et al. Diabetic ketoacidosis in a community-based population. <i>Mayo Clin Proc</i> 1980; 55: 83–8
5	4	Westphal SA: The occurrence of diabetic ketoacidosis in non-insulin-dependent diabetes and newly diagnosed diabetic adults: <i>Am J Med</i> 1996; 101: 19–24
6	4	Basu A, Close CF, Jenkins D et al. Persisting mortality in diabetic ketoacidosis. <i>Diabet Med</i> 1993; 10: 282–4
7	1a	Egger M, Davey Smith G, Stettler C et al. Risk of adverse effects of intensified treatment in insulin dependent diabetes mellitus: a meta-analysis. <i>Diabet Med</i> 1997; 14: 919–28
8	5	Treasure RA et al. Misdiagnosis of diabetic ketoacidosis as hyperventilation syndrome (case report). <i>BMJ</i> 1987; 294: 630
9	4	Soler NG et al. Potassium balance during the treatment of diabetic ketoacidosis. <i>Lancet</i> 1972; ii: 665–7
10	4	Brandenburg MA, Dire DJ. Comparison of arterial and venous blood gas values in the initial emergency department evaluation of patients with diabetic ketoacidosis. <i>Ann Emerg Med</i> 1998; 31: 459–65
11	4	Harris GD et al. Minimizing the risk of brain herniation during treatment of diabetic ketoacidosis: a retrospective and prospective study. <i>J Pediatr</i> 1990; 117: 22–31
12	1b –	Adrogué HJ, Barrero J, Eknayan G. Salutory effects of modest fluid replacement in the treatment of adults with diabetic ketoacidosis. Use in patients without extreme volume deficit. <i>JAMA</i> 1989; 262: 2108–13
13	1b	Kitabchi AE, Ayyagari V, Guerra SM. The efficacy of low dose versus conventional therapy of insulin for treatment of diabetic ketoacidosis. <i>Ann Intern Med</i> 1976; 84: 633–8
14	1b –	Fisher JN et al. Diabetic ketoacidosis: low-dose insulin therapy by various routes. <i>N Engl J Med</i> 1977; 297: 238–41
15	1b –	Sacks HS et al. Similar responsiveness of diabetic ketoacidosis to low-dose insulin by intramuscular injection and albumin-free solution. <i>Ann Intern Med</i> 1979; 90: 36–42
16	1b –	Heber D, Molitch ME, Sperling MA. Low-dose continuous insulin therapy for diabetic ketoacidosis: prospective comparison with ‘conventional’ insulin therapy. <i>Arch Intern Med</i> 1977; 137: 1377–80

<i>No</i>	<i>Level</i>	<i>Citation</i>
17	1b	Wiggam MI et al. Treatment of diabetic ketoacidosis using normalization of blood 3-hydroxybutyrate concentration as the endpoint of emergency management. <i>Diabetes Care</i> 1997; 20: 1347–51
18	4	Morris LR, Murphy MB, Kitabchi AE. Bicarbonate therapy in severe diabetic ketoacidosis. <i>Ann Intern Med</i> 1986; 105: 836–40
19	4	Hale PJ, Crase J, Nattrass M. Metabolic effects of bicarbonate in the treatment of diabetic ketoacidosis. <i>BMJ</i> 1984; 289: 1035–8
20	1b	Keller U, Berger W. Prevention of hypophosphatemia by phosphate infusion during treatment of diabetic ketoacidosis and hyperosmolar coma. <i>Diabetes</i> 1980; 29: 87–95
21	1b –	Wilson HK, Keuer SP, Lea AS et al. Phosphate therapy in diabetic ketoacidosis. <i>Arch Intern Med</i> 1982; 142: 517–20
22	1b –	Fisher JN, Kitabchi AE. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. <i>J Clin Endocrinol Metab</i> 1983; 57: 177–80
23	1b –	Krentz AJ, Hale PJ, Singh BM et al. The effect of glucose and insulin infusion on the fall of ketone bodies during treatment of diabetic ketoacidosis. <i>Diabet Med</i> 1989; 6: 31–6
24	1b	Koproski J et al. Effects of an intervention by a diabetes team in hospitalized patients with diabetes. <i>Diabetes Care</i> 1997; 20: 1553–5
25	2c	Hamblin PS et al. Deaths associated with diabetic ketoacidosis and hyperosmolar coma 1973–1988. <i>Med J Aust</i> 1989; 151: 439–44
26	4	Kent LA, Gill GV, Williams G. Mortality and outcome of patients with brittle diabetes and recurrent ketoacidosis. <i>Lancet</i> 1994; 344: 778–81
27	4	Tattersall R et al. Course of brittle diabetes: 12 year follow-up. <i>BMJ</i> 1991; 302: 1240–3