

# Supplemental file to Understanding the Disease: Management of Diabetic Ketoacidosis

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## Summary

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## Diagnosis

The diagnosis of diabetic ketoacidosis (DKA) is usually made from a combination of hyperglycemia (>250 mg/dL, >14 mmol/l), ketosis and acidosis (pH <7.3 and/or bicarbonate <15 mEq/L). No clinical feature *per se* enables a diagnosis of DKA. Hyperglycemia may not always be present and is not diagnostic of DKA without accompanying acidosis. Ketosis may be demonstrated either through ketonemia (>3 mmol/L) or high intensity ketonuria. Ketonemia is more specific than ketonuria to diagnose ketoacidosis [1] and may be more helpful as an early point-of-care test for DKA [2]. It should be stressed that ketosis will also occur with starvation and patients may not have eaten for many hours or even days at presentation. Of note, laboratory and bedside meters for testing blood ketones mainly measure  $\beta$ -hydroxybutyrate, the predominant ketone produced in DKA whereas the urine dip test measures acetoacetate. As  $\beta$ -hydroxybutyrate is usually oxidised to acetoacetate as the ketosis resolves, there may be a paradoxical rise in urine ketones despite a decreasing concentration of blood  $\beta$ -hydroxybutyrate [3]. Finally, blood gases with accompanying electrolyte measurements (sodium, potassium, and chloride) are needed to diagnose acidosis and the existence of a high anion-gap (or the Na-Cl difference as an easy-to-observe surrogate which should normally be 35-40 mEq/L), the hallmark feature of DKA.

Beyond diagnosing DKA, it is important to evaluate the patient for triggers of DKA such as infection, tissue ischemia and surgical stress, and other possible causes such as new-onset type 1 diabetes or withdrawal of insulin for some reason by the patient. Such evaluation is beyond the scope of this short article on pathophysiology and management of DKA.

## Diagnostic criteria for DKA

As mentioned in the main manuscript, diagnostic criteria for DKA are not uniform [4-6]. The only common concept is that acidemia is necessary for diagnosis with a pH <7.3 AND either low bicarbonate levels OR an enlarged anion gap. Furthermore, either a positive urine nitroprusside reaction to check for ketonuria OR increased blood levels of ketones should be demonstrated. Of note:

- 1) AACE recommendations do not consider hyperglycemia in their diagnostic criteria because of the increasingly common SGLT-2 inhibitor-associated euglycemic DKA.
- 2) Blood ketone levels are not necessary to diagnose DKA, although they can be used where available.

Table S1 presents diagnostic criteria recommended by three major societies who have made a position statement on DKA diagnosis and treatment.

**Table S1:** Comparison of diagnostic criteria for diabetic ketoacidosis in adults

Criterion	ADA	JBSD	AACE
<b>Plasma glucose concentration</b>	> 250 mg/dL (14 mmol/L)	> 200 mg/dL (11 mmol/L)	n/a
<b>pH</b>	< 7.3	< 7.3	< 7.3
<b>Bicarbonate (mEq/L)</b>	< 18	< 15	n/a
<b>Anion-gap</b>	> 10	n/a	> 10
<b>Urine acetoacetate (nitroprusside reaction)</b>	Positive	Positive	Positive
<b>Blood <math>\beta</math>-hydroxybutyrate (mmol/L)</b>	NA	$\geq$ 3 mmol/L (31 mg/dL)	$\geq$ 40 mg/dL (3.8 mmol/L)

ADA: American Diabetes Association; JBSD: Joint British Societies of Diabetes; AACE: American Academy of Clinical Endocrinologists; n/a: not applicable

## DKA resolution

The goal of DKA management is to allow its safe resolution and avoid iatrogenesis. Ultimately, correction of acidosis is the primary biochemical target for DKA resolution, although ADA guidelines stress the need to correct hyperglycemia [6]. However, since hyperglycemia is not always a hallmark of DKA, euglycemia is neither necessary nor a unique aspect of DKA resolution. The JBSD stresses this point, specifically that titration of insulin and its cessation should not be done solely based on glycemia [4] .

Ketonemia is another area of controversy. UK guidelines recommend this should be targeted throughout treatment, but this has never been properly studied and can distract from what is important. Other surrogate endpoints for anion-gap closure are readily available, e.g. the Na-Cl difference trending towards normality (35-40 mEq/L) [7].

As shown in Table S2, the two common criteria for DKA resolution among guidelines are the pH criteria and the anion-gap (the surrogate for ketonemia). We suggest Na-Cl trends are enough to assess for gap closure in most patients. As mentioned earlier, urine acetoacetate should not be used as a criterion for DKA resolution due to its paradoxical rise in the face of conversion of  $\beta$ -hydroxybutyrate to acetoacetate during treatment.

Once resolution is achieved:

- Start a rapid acting SC insulin
- Maintain IV insulin for 30-60 minutes before discontinuation
- Commence (or reconcile) a full insulin schedule as currently recommended for hospitalized type I diabetes patients (basal + prandial + correction doses)

Table S2: Comparison of criteria for DKA resolution in adults

	ADA	JBSD
<b>Set of criteria</b>	Glucose criteria AND 2/3 of pH, bicarbonate or anion-gap criteria	pH criteria AND ketonemia criteria
<b>Plasma glucose concentration</b>	< 200 mg/dL (11 mmol/L)	n/a
<b>pH</b>	> 7.3	> 7.3
<b>Bicarbonate (mEq/L)</b>	> 15	n/a
<b>Anion-gap</b>	≤ 12	n/a
<b>Urine acetoacetate (nitroprusside reaction)</b>	Not recommended	Not recommended
<b>Blood β-hydroxybutyrate (mmol/L)</b>	n/a	< 0.6 mmol/L (10 mg/dL)

ADA: American Diabetes Association; JBSD: Joint British Societies of Diabetes; n/a not applicable

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