DKA - HHS UF HEALTH FLAGLER HOSPITAL PROTOCOL

As with any protocol, this protocol provides evidence-based, comprehensive recommendations to guide our multidisciplinary team in patient care, with the expectation that expert practitioners will modify and customize the present protocol to meet individual patient needs as necessary. This Protocol is not intended to replace the physician's judgment; it is intended to guide the physician for the group of patients described in this Protocol.

Current literature was reviewed including the more recent consensus report and updated guidelines from the American Diabetes Association (ADA) and the British Diabetes Societies (JBDS-IP) for inpatient management of diabetic ketoacidosis (DKA) and the hyperglycemic hyperosmolar state (HHS) in adults (1-3).

OBJECTIVE:

- To optimize the diagnosis and in-patient management of adults with DKA and HHS at UF Health Flagler Hospital.
- All patients admitted to the hospital with suspected or confirmed DKA or HHS will be eligible to be included in the protocol.

BACKGROUND:

Protocols and diabetes specialists' teams should always be involved as soon as possible and ideally within 24 hours because this has been demonstrated to be associated with a better experience for the patient with diabetes and reduced length of stay.

Clinical Presentation

Both DKA and HHS may present with polyuria, polydipsia, weight loss, vomiting, dehydration, and change in cognitive state. One in three hyperglycemic emergencies has a hybrid DKA/HHS presentation.

- Changes in cognitive state are usually present in patients with severe DKA and HHS.
- Nausea, vomiting, and abdominal pain are common in DKA (>50%) but are uncommon in HHS.
    - Abdominal pain could be either a result of DKA or an indication of a precipitating cause of DKA, particularly in the absence of severe metabolic acidosis.

Diagnosis

The diagnosis of **DKA** should be based on the presence of **all three criteria** and **HHS** of **all the four criteria** described below:

DKA	A. DKA Diagnostic Criteria	
	Diabetes/hyperglycemia	Glucose ≥200 mg/dL (11.1 mmol/L) OR prior history of diabetes
	Ketosis	β-Hydroxybutyrate concentration ≥3.0 mmol/L OR urine ketone strip 2+ or greater
	Metabolic Acidosis	pH <7.3 and/or bicarbonate concentration <18 mmol/L
HHS	B. HHS Diagnostic Criteria	
	Hyperglycemia	Plasma glucose ≥600 mg/dL (33.3 mmol/L)
	Hyperosmolarity	Calculated effective serum osmolality >300 mOsm/kg (calculated as [2xNa⁺ (mmol/L) + glucose (mmol/L)]), OR total serum osmolality >320 mOsm/kg [(2xNa⁺ (mmol/L) + glucose (mmol/L) + urea (mmol/L)]
	AbSence of significant ketonemia	β-Hydroxybutyrate concentration <3.0 mmol/L OR urine ketone strip less than 2+
	Absence of acidosis	pH ≥7.3 and bicarbonate concentration ≥15 mmol/L

Euglycemic DKA **(EDKA)** is the development of DKA in patients with diabetes but where the glucose is normal, or not particularly raised.

- EDKA is the reason for no cutoff value for patients with known diabetes.
- Usually seen in patients using sodium-glucose cotransporter 2 (SGLT2) inhibitors, infections, surgery, fasting, physiologic stress, and pregnancy

DKA can develop in patients with type 2 diabetes referred to as **"ketosis-prone type 2 diabetes"**

- The treatment for this condition is the same as for others with DKA, but patients often come off insulin quickly after the resolution of the DKA and underlying precipitating condition.

Assessment of DKA severity

The severity of DKA is classified as mild, moderate, or severe based on the magnitude of metabolic acidosis (blood pH, serum bicarbonate, and ketone levels, and the presence of altered mental status.

	Mild DKA	Moderate DKA	Severe DKA
"D": history of diabetes or elevated glucose level	Glucose ≥200 mg/dL (11.1 mmol/L)	Glucose ≥200 mg/dL (11.1 mmol/L)	Glucose ≥200 mg/dL (11.1 mmol/L)
"K": ketonemia	β-Hydroxybutyrate 3.0–6.0 mmol/L	β-Hydroxybutyrate 3.0–6.0 mmol/L	β-Hydroxybutyrate >6.0 mmol/L
"A": acidosis	• pH >7.25 to <7.30 or bicarbonate 15–18 mmol/L	• pH 7.0–7.25 • Bicarbonate 10 to <15 mmol/L	• pH <7.0 • Bicarbonate <10 mmol/L
Mental status	Alert	Alert/drowsy	Stupor/coma

The presence of **one or more** of the following may also indicate severe DKA:

- Hypokalemia on admission less than 3.5 mmol/L
- Glasgow Coma Score (GCS) less than 12
- Oxygen saturation below 92% on room air (assuming normal baseline respiratory function)
- Systolic BP below 90 mmHg
- Pulse over 100 or below 60 bpm

Resolution of DKA

- Defined as ketones less than 0.6 mmol/L and venous pH over 7.3 or bicarbonate >18 mmol/L
- Ideally, the blood glucose concentration should also be <200 mg/dL
- The anion gap should not be used as a criterion, as it may be misleading because of the common development of hyperchloremic metabolic acidosis caused by large volumes of IV fluids particularly normal saline

Resolution of HHS

- Defined as the presence of the following criteria:
    - Measured or calculated serum osmolality <300 mOsm/kg
    - Blood glucose <250 mg/dL
    - Cognitive status improvement

DKA differential diagnosis

- Alcoholic ketoacidosis
- Starvation ketosis
- Ketosis of pregnancy and hyperemesis

The distinction between alcoholic ketoacidosis from starvation ketosis and both of these conditions from DKA is a clinical judgment based upon the history, the severity of the disorder, and serum glucose concentration.

- People with chronic alcohol excess with a recent binge associated with vomiting and acute starvation may develop ketoacidosis with or without hyperglycemia.
    - Modest elevation of serum glucose can occur in alcoholic ketoacidosis
- Fasting ketosis rarely reduces the bicarbonate level below 17 mEq/L
- The vomiting of hyperemesis gravidarum leads to excess counterregulatory hormone concentrations, also predisposing to ketone formation.

SCREENING:

In all patients with suspected DKA and/or HHS, the initial approach will include:

- Place a large bore IV access and assess clinically
    - Vital signs and continuous O_2 saturation
    - Glasgow Coma Scale and physical examination
- Samples will be taken for CBC, CMP, magnesium, phosphorous, venous blood gases, blood ketone levels, high sensitivity troponin, EKG, and CXR.
- Urine culture and blood cultures if infection is suspected
- Pregnancy test in women of childbearing age

MONITORING AND MANAGEMENT

If a diagnosis of DKA and/or HHS is confirmed:

- Assess DKA severity based on the criteria described in the background section
- Consider precipitating causes and treat them appropriately
    - Associated illnesses
        - Infections
        - Acute illnesses with a systemic inflammatory response
    - Noncompliance with insulin regimen
- Assessment and treatment of potential complications
    - Acute kidney injury (may occur in up to 50% of adults)
    - Pulmonary edema
    - Acute pancreatitis
    - Rhabdomyolysis
    - Gastrointestinal bleeding
    - VTE
- Involve the diabetes specialist team at the earliest possible stage
    - Establish usual medication for patients with known diabetes
    - In those using an insulin pump, the pump should be stopped, removed, and stored safely
- Request intensivist consult for patients with moderate or severe DKA or HHS or mild DKA with associated risk factors as below:
    - Young people aged 18–25 years (higher risk for cerebral edema)
    - Elderly >75 years
    - Pregnant
    - Heart or kidney failure on hemodialysis (HD)
    - Other serious co-morbidities
- Supplemental oxygen by NC as needed to keep 90-96%
    - If needed, request ABGs and additional workup to establish the cause
- Place Foley catheter if anuria by 60 minutes

- Place NG tube if patient obtunded or persistent vomiting
- VTE prophylaxis

The DKA pathway of care

Aims

- Restoration of circulatory volume
  - Target SBP >90 mmHg and urine output >0.5 mL/kg/hr
- Clearance of ketones and improvement of acidosis
  - Achieve a rate of fall of ketones of at least 0.5 mmol/L/hr
  - Achieve a rise of bicarbonate by 3.0 mmol/L/hr
- Correction of hyperglycemia
  - Blood glucose should fall by approximately 50 mg/dL/hr
  - Avoid hypoglycemia
- Correction of electrolyte imbalance
  - Maintain serum potassium between 4.0 and 5.5 mmol/L

Management

0 to 60 minutes - immediate management upon diagnosis

- Initiate IVF with crystalloids - LR
  - 500 mL of LR IV bolus over 10-15 min (repeat as needed until SBP >90 mmHg) followed by 1000 mL over one hour
    - Caution in patients at risk for cardiac compromise – consider early hemodynamic monitoring and use of vasopressors accordingly
- Potassium replacement
  - 30 mEq per liter of IV fluid if K <3.5 mmol/L with reassessment if additional K needs to be given
  - 20 mEq per liter if K <5.5 mmol/L
  - No replacement if K >5.5 mmol/L
- Initiate insulin administration only after fluid therapy has been initiated and K levels are ≥3.5 mmol/L
  - A fixed-rate intravenous insulin infusion (FRIII)
    - At 0.1 units/kg/hr ideal body weight (IBW) for moderate or severe DKA or HHS
    - At 0.05 units/kg/hr ideal body weight (IBW) for HHS
  - 0.1 units/kg of rapid-acting insulin analog as SQ bolus for mild DKA

- Mixed DKA/HHS is managed as DKA
- EDKA is treated the same way as DKA but because the glucose is <250 mg/dL:
  - Glucose (D10%) IV infusion is initiated at 125 mL/hr simultaneously with the FRIII at 0.1 units/kg/hr
  - If glucose falls despite D10% IV infusion, the FRIII rate will be reduced to 0.05 units/kg/hr to avoid hypoglycemia
  - Optional based on individual cases, start FRIII at 0.05 units/hr IBW or at 0.1 units/hr IBW

60 minutes to 12 hours

- Monitoring
  - Capillary glucose hourly
  - Venous blood gas for pH and bicarbonate at 60 minutes, every 2 hours for the first 6 hours, and at 12 hours
  - Blood ketone levels at 6 hours and 12 hours

    - Serum potassium 2 hours after starting insulin administration and every 4 hours thereafter until the resolution of DKA

- Continue FRII
    - If the blood glucose level is not falling by at least 50 mg/dL increase the FRIII rate by 1.0 units/hr increments **FROM THE PRIOR RATE** hourly until glucose falls at this rate
- IVF replacement
    - LR 1000 mL over 2 hours with potassium replacement
        - 60 mEq/L if K<3.5 mmol/L
        - 40 mEq/L if K 3.5 – 5.5 mmol/L
        - No replacement if K >5.5 mmol/L
    - Then, LR 1000 mL over 2 hours with potassium replacement as above
    - Then, LR 1000 mL over 4 hours with potassium replacement as above
    - Then, LR 1000 mL over 6 hours with potassium replacement as above
    - When BG <250 mg/dL start D10% at 125 mL/hr, OR D5%/0.45%NS at 200-250 mL/hr, OR D5W/0.9% NS at 200-250 mL/hr, and reduce FRIII by 50% from the prior rate, or by 0.05 units/kg/hr, whichever results in a greater decrease.
- Assess the resolution of ketoacidosis
    - If bicarbonate is not rising by at least 3.0 mmol/L/hr or ketones are not falling by at least 0.5 mmol/L/hr, increase the insulin infusion rate by 1 unit/hr increments hourly until the targets are achieved

12 to 24 hours - by 24 hours DKA should have resolved

- Continue IV fluids and potassium replacement if the patient is not eating and drinking
- Continue FRII if ketonemia and acidosis have not resolved
    - Monitoring anion gap is not further recommended because of the common development of hyperchloremic metabolic acidosis during IV fluid resuscitation
- Re-assess for complications of treatment e.g. fluid overload, GCS score (if this drops then urgent CT brain will be recommended
- Continue to treat any precipitating factors as necessary
- Transfer to subcutaneous insulin if the patient is eating and drinking normally under endocrinology direction
    - To prevent the recurrence of hyperglycemia or ketoacidosis during the transition period to subcutaneous insulin, it is important to allow an overlap of 1–2 h between the administration of subcutaneous insulin and the discontinuation of intravenous insulin.

Bicarbonate use

Routine bicarbonate administration is not recommended.

- It does not improve cardiac or neurologic outcomes nor the rate of recovery of hyperglycemia and ketoacidosis
- It has potential detrimental effects:
    - Increased risk of hypokalemia
    - Decreased tissue oxygen uptake
    - Cerebral edema and development of paradoxical central nervous system acidosis
- However, severe metabolic acidosis can produce excessive vasodilation and hemodynamic instability. Therefore,
    - Bicarbonate will be given only if pH <7.0
        - 100 mmol of sodium bicarbonate (8.4% solution) in 400 mL of sterile water (an isotonic solution) every 2 h to achieve a pH >7.0.

Phosphate

Routine phosphate administration is not indicated.

- In DKA there is a shift of phosphate from intracellular to extracellular fluid with an excess urinary phosphate loss leading to hypophosphatemia, however:
    - Several prospective randomized studies have failed to show any beneficial effect of phosphate replacement on the clinical outcome of DKA
    - Excessively rapid phosphate replacement may precipitate hypocalcemia
- Alternatively, severe hypophosphatemia can produce muscle weakness and potential respiratory or cardiac compromise, therefore,
    - Phosphate will be given only if the level <1.0 mg/dL
        - 20–30 mmol of potassium phosphate can be added to replacement fluids

ESRD on HD

Hyperglycemia and ketosis can occur without much hypovolemia due to the inability to develop an osmotic diuresis

Therefore, there may be no need for fluid replacement

- For those who are deemed hypovolemic, aliquots of 250 mL (NS or D10%) may be given with frequent clinical assessments

The risk of hypoglycemia is increased due to the inability of the kidneys to clear insulin and decreased renal gluconeogenesis

- A mixed picture of DKA and HHS may also occur because of the high serum tonicity

Mobilization

Mobilization will begin as soon as the patient's condition is considered stable following Flagler protocol. All patients will have Physical Therapy, Occupational Therapy evaluation, and regular skin assessments.

Education

Patients admitted to the hospital with DKA-HHS should receive educational and psychological support before discharge and be followed up by a diabetes specialist team

Example Comment for DKA:

Start drip at 0.1 units/kg/hr IBW

Do not change the rate except for the following:

- If BG increases in any 1-hour period, increase by 1 units/hr from the prior rate
- If BG decreases <50 mg/dL in any 1-hour period, increase by 1 units/hr from the prior rate
- If BG drops >100 mg/dL in any 1-hour period, decrease the rate by 50% from the prior rate
- If BG drops >200 mg/dL in any 1-hour period CONTACT PROVIDER
- If BG <70 mg/dL HOLD insulin, confirm BG, give dextrose per hypoglycemic protocol, check BG every 15 minutes until BG >70 mg/dL, CONTACT PROVIDER, resume insulin per provider

Once BG < 250 mg/dL, start dextrose-containing fluids (5-10%) should be added to the NS saline infusion, and the insulin infusion rate should be reduced to 0.05 units/kg/hr or 50% or prior rate, whichever is the larger rate decrease.

In Euglycemic DKA patients start insulin drip at 0.05-0.1 units/kg/hr IBW and start dextrose-containing fluids simultaneously.

Example Comment in HHS:

Start drip at 0.05 units/kg/hr IBW

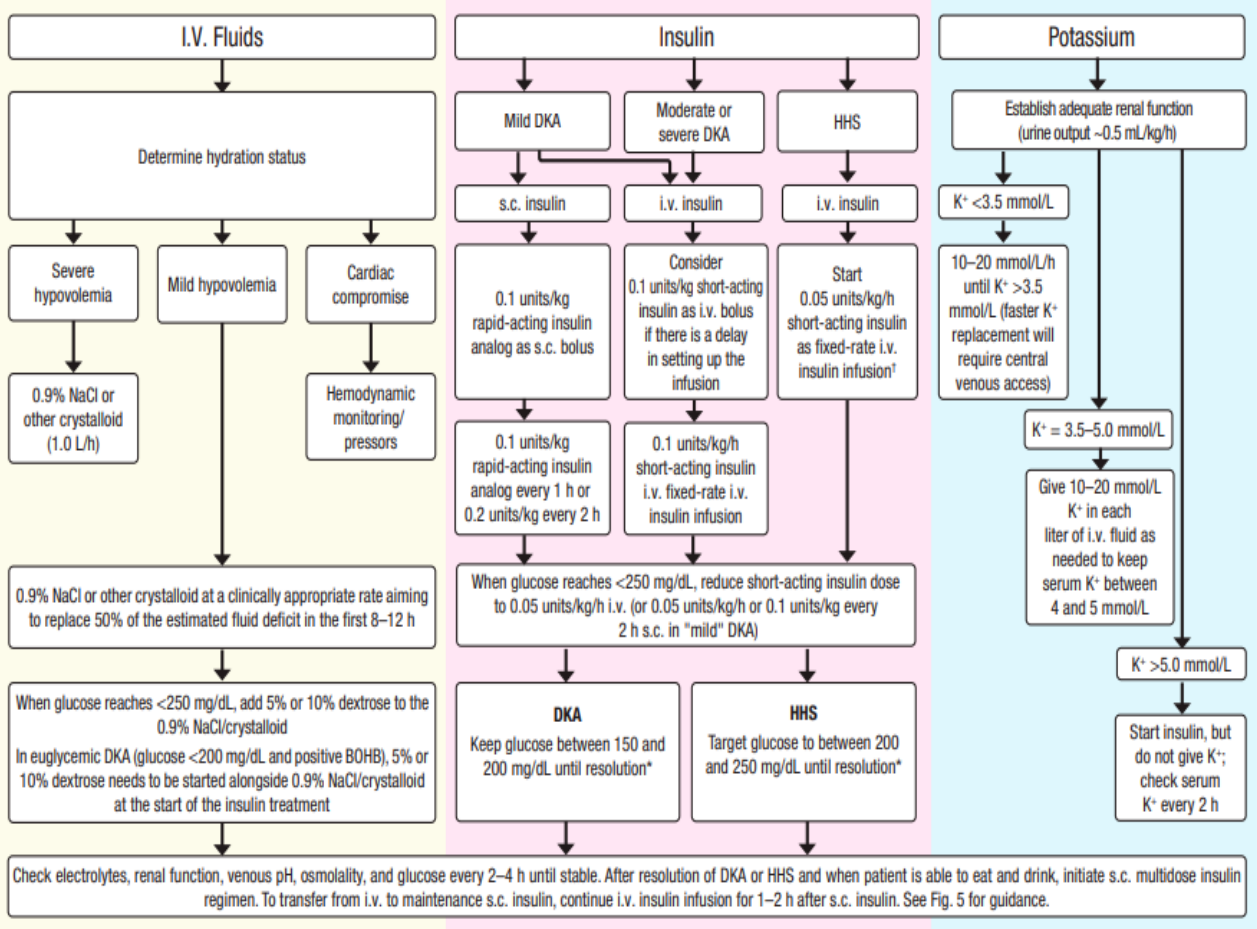
Do not change the rate except for the following:

- If BG increases in any 1-hour period increase by 1 unit/hr from the prior rate
- If BG decreases <50 mg/dL in any 1-hour period, increase by 1 units/hr from the prior rate
- If BG drops >100 mg/dL in any 1-hour period decrease the rate by 50% from the prior rate or if BG decreases <50 mg/dL
- If BG drops >200 mg/dL in any 1-hour period CONTACT PROVIDER
- If BG < 70 mg/dL HOLD insulin, confirm BG, give dextrose per hypoglycemic protocol, check

REFERENCES:

1. Umpierrez GE, et al. Hyperglycemic Crises in Adults with Diabetes: A Consensus Report. *Diabetes Care* 2024; 47:1257–1275.
2. The Management of Diabetic Ketoacidosis in Adults. Joint British Diabetes Societies for inpatient care (JBDS-IP). Available to download from the ABCD website at https://abcd.care/joint-british-diabetes-societies-jbds-inpatient-care-group, the Diabetes UK website at www.diabetes.org.uk/joint-british-diabetes-society and the chemotherapy board website at www.ukchemotherapyboard.org.
3. Dhatariya KK. The management of diabetic ketoacidosis in adults: Position statement “An updated guideline from the Joint British Diabetes Society for Inpatient Care”. *Diabetic Medicine 2022*;39: e14788.

Graphics below taken from reference 1



Management of DKA

A to K & D

- A Airway
- B Breathing
- C Circulation
- D Diabetes
- E Electrolytes and pH
- F Fluid replacement
- G Hourly Glucose
- H HbA1C
- I Fixed rate Insulin
- J Clinical Judgement
- K Hourly Ketones

and

- D Diabetes team referral

Diagnostic criteria

All of these must be present to make the diagnosis

D-Blood glucose≥11 mmol/L or history of diabetes*
(glucose will be <11mmol/L in euglycaemic ketoacidosis)
K-Blood ketones ≥3 mmol/L or urine ketones ≥2+
A-pH<7.3 or bicarbonate <15 mmol/L

Consider ITU referral if any of the following:

1. Young or elderly or pregnant **2.** Heart or liver or kidney failure
3. Severe DKA judged by: blood ketones >6mmol/L or bicarbonate <5mmol/L or pH <7.1 or potassium <3.5 mmol/L or GCS <12 or persistent hypoxia or persistent brady/ tachycardia or anion gap >16

Time since diagnosis of DKA

0 min to 60 min

Restore circulatory volume
- Give 500ml of 0.9% sodium chloride stat doses until systolic BP>90 mmHg
- Then give 1000ml 0.9% sodium chloride over 1 hr

Start insulin therapy
- Start fixed rate insulin infusion at 0.1ml/kg/hr
- Continue patient's long-acting insulin

Senior review
Registrar or consultant to review patient

60 min to 6 hrs

Continue fluid replacement
- 1 litre of 0.9% sodium chloride with potassium*, over 2 hr
- Then,1 litre of 0.9% sodium chloride with potassium*,over 2 hr
- Then,1 litre of 0.9% sodium chloride with potassium*,over 4 hr

*** Potassium replacement**
- <3.5- senior review
- 3.5-5.5- 40 mmol/l
- >5.5- no replacement

6 hrs to 12 hrs

Continue fluid replacement
- 1 litre of 0.9% sodium chloride with potassium*, over 4 hr
- Then,1 litre of 0.9% sodium chloride with potassium*,over 6 hr
- **Senior review if DKA persists beyond 12 hours**

Monitor for hypoglycaemia
- Start 500ml 10% glucose at 125ml/hr and reduce insulin infusion rate by 50% (0.05ml/kg/hr) **when glucose≤14 mmol/L**

Monitoring

- Hourly glucose and **hourly ketones**
- Bicarbonate & potassium at 1 hr & 2 hr after diagnosis & 2 hourly thereafter

Check infusion rate if:
- Ketones not reducing by 0.5mmol/hr
- Bicarbonate not increasing by 3mmol/hr
- Glucose not reducing by 3mmol/hr
- **If glucose ≤4 mmol/L, follow hypoglycaemia guidelines and ensure fixed rate insulin infusion is running at 0.05ml/kg/hr if DKA still persists**

DKA Resolution and further management
- DKA is resolved when ketones<0.6 mmol/L and ph>7.3 or bicarbonate>15 mmol/L
- If DKA is resolved, switch to variable rate insulin infusion and seek diabetes specialist review for further management

* Rule out **Euglycaemic ketoacidosis** and **Hyperglycaemic Hyperosmolar State** (HHS) in high risk acutely unwell patients with diabetes (Eg: Pregnancy, those on SGLT-2 inhibitors (gliflozins)