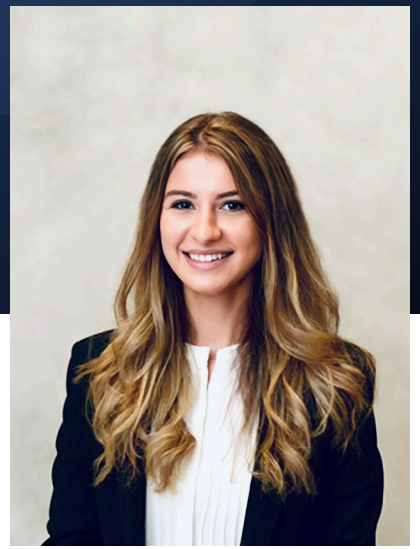
EUGLYCEMIC DIABETIC KETOACIDOSIS IN THE SETTING OF SGLT2 INHIBITOR USE

A presentation for Health Trust Members
May 10, 2022



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Learning Objectives

Pharmacists & Nurses:

- Recall the pathophysiology of diabetic ketoacidosis caused by SGLT2 inhibitors
- Recognize diagnostic criteria and laboratory findings associated with DKA
- Identify current evidence on diabetic ketoacidosis and euglycemic diabetic ketoacidosis based on a patient case

Learning Objectives

Pharmacy Technicians:

- Define DKA and EuDKA
- Identify medications used in treatment of DKA
- Recognize storage requirements for medications used in the treatment of DKA

BACKGROUND

Diabetic Ketoacidosis

Acute, major, life-threatening disease characterized by:

Hyperglycemia

- Blood glucose (BG) >250mg/dL

Metabolic acidosis

- pH <7.3

Ketonemia

- Ketones >5mEq/L
  → Urinary ketone dipstick (2+)
  → Blood beta-hydroxybutyrate level >3 mM

Source: Umpierrez GE, et al. *Diabetes Care.* 2018;41(9):1839-1841.

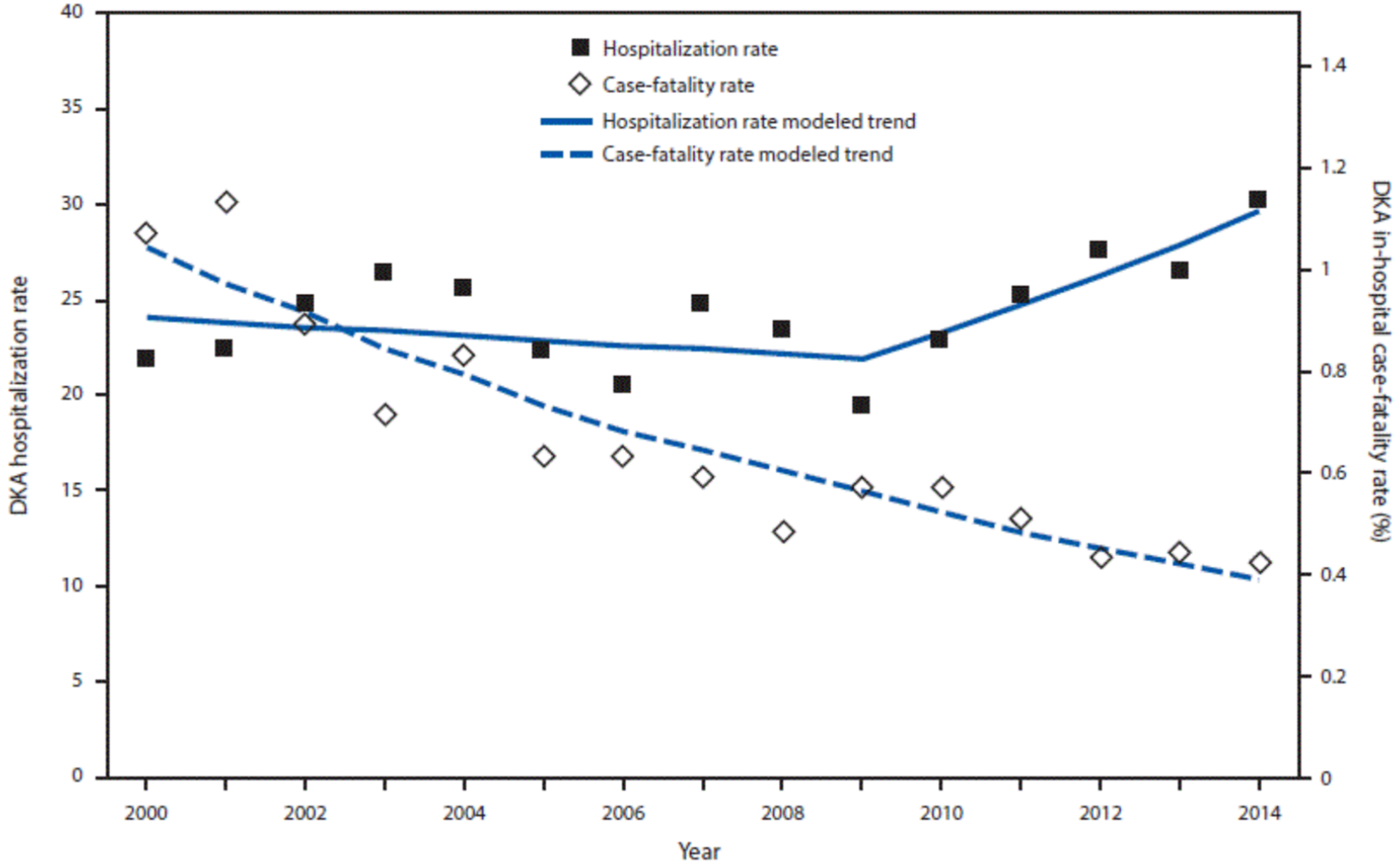
Diabetic Ketoacidosis

Epidemiology

- DKA is a complication of Diabetes Mellitus (DM) which affects approximately 30 million people in the U.S.
- Accounts for 14% of Diabetes related hospital admissions
- Almost 50% of Diabetes related admissions in young persons are related to DKA
- Most common in Type I Diabetes Mellitus (T1DM), but can also be seen in Type II Diabetes Mellitus (T2DM)
- In adults with DKA, mortality rate is <1%
- In elderly and patients with concomitant life-threatening illness, mortality is >5%

Source: Umpierrez GE, et al. *Diabetes Care.* 2018;41(9):1839-1841.

FIGURE. Age-adjusted diabetic ketoacidosis hospitalization rate per 1,000 persons with diabetes and in-hospital fatality rate — United States, 2000–2014*



Abbreviation: DKA = diabetic ketoacidosis.

Source: Bennoit SR, et al. *MMWR Wkly Rep.* 2018;67:362-365.

Diabetic Ketoacidosis

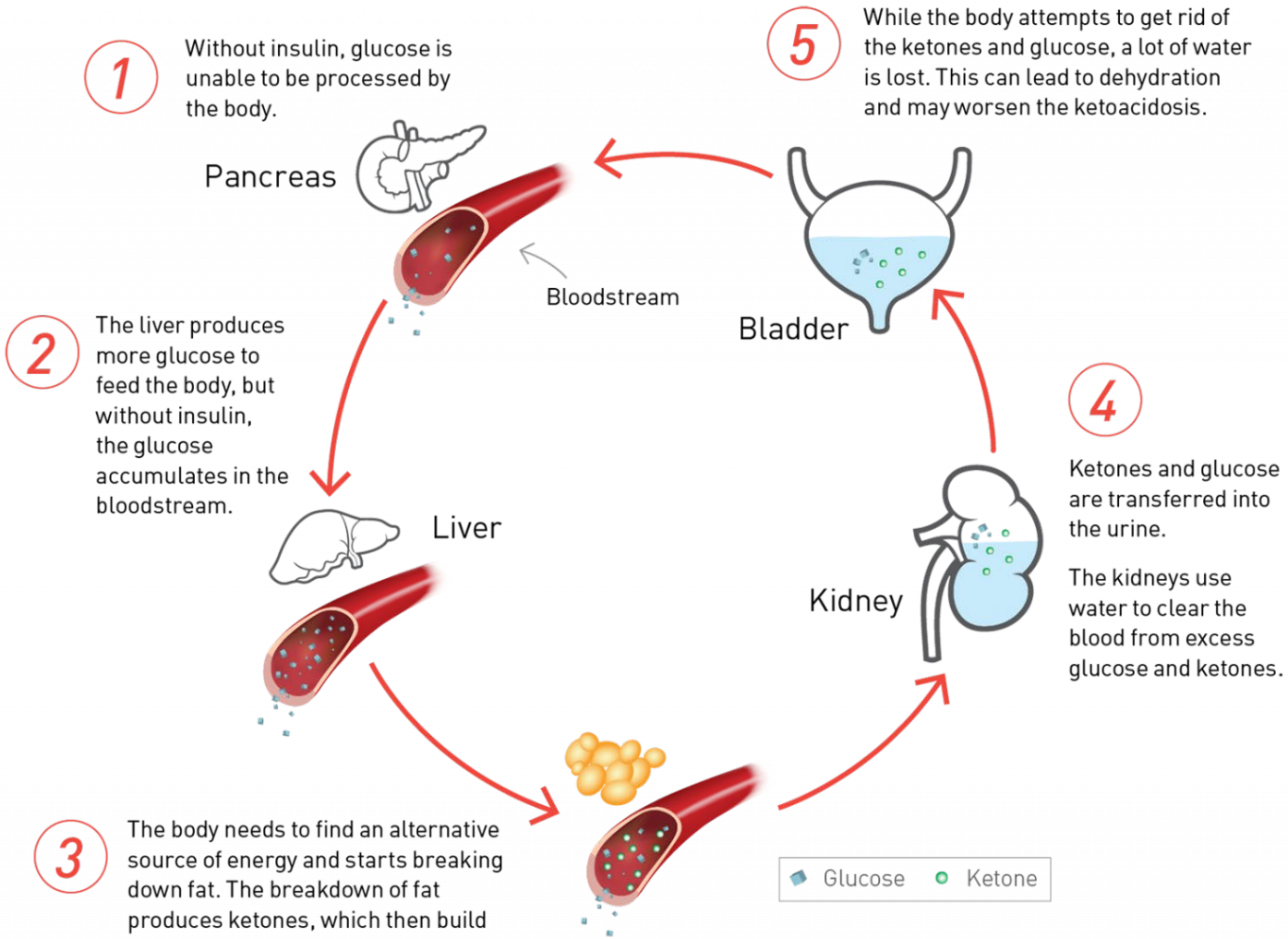
Etiology

- Common precipitating factors:
  - Acute illness or infection
  - Catabolic stress or trauma
  - Non-compliance
  - New-onset Diabetes
  - Medications
    - ❑ Corticosteroids
    - ❑ Thiazides
    - ❑ Sympathomimetic agents
    - ❑ Atypical antipsychotics
    - ❑ SGLT2 inhibitors

Source: Umpierrez GE, et al. *Diabetes Care.* 2018;41(9):1839-1841

Diabetic Ketoacidosis

Pathophysiology



Source: Nipro. *Diabetes Ketoacidosis.* 2018;41(9):1839-1841

Diabetic Ketoacidosis

Diagnosis

Signs and symptoms:

- Polyuria, polydipsia, polyphagia
- Nausea, vomiting, lethargy
- Fruity odor

Laboratory Values:

	DKA		
	Mild (plasma glucose >250 mg/dl)	Moderate (plasma glucose >250 mg/dl)	Severe (plasma glucose >250 mg/dl)
Arterial pH	7.25–7.30	7.00 to <7.24	<7.00
Serum bicarbonate (mEq/l)	15–18	10 to <15	<10
Urine ketone*	Positive	Positive	Positive
Serum ketone*	Positive	Positive	Positive
Effective serum osmolality†	Variable	Variable	Variable
Anion gap‡	>10	>12	>12
Mental status	Alert	Alert/drowsy	Stupor/coma

Source: Kitbachi AE, et al. *Diabetes Care.* 2009;32(7):1335-1344.

Euglycemic Diabetic Ketoacidosis

Patients on SGLT2 inhibitors present with:

Normoglycemia

- BG<250mg/dL

Metabolic acidosis

- pH <7.3

Ketonemia

- Ketones >5mEq/L

Source: Jazi M, et al. *Can Fam Physician.* 2016;62(9):722-724.

Euglycemic Diabetic Ketoacidosis

Epidemiology

- 2.6% to 3.2% of DKA cases are euglycemic

The FDA Adverse Event Reporting System (FAERS) identified 20 cases of DKA in patients on SGLT2 inhibitors from March 2013 to June 2014

Median time to onset of symptoms was 2 weeks post initiation of SGLT2 inhibitors

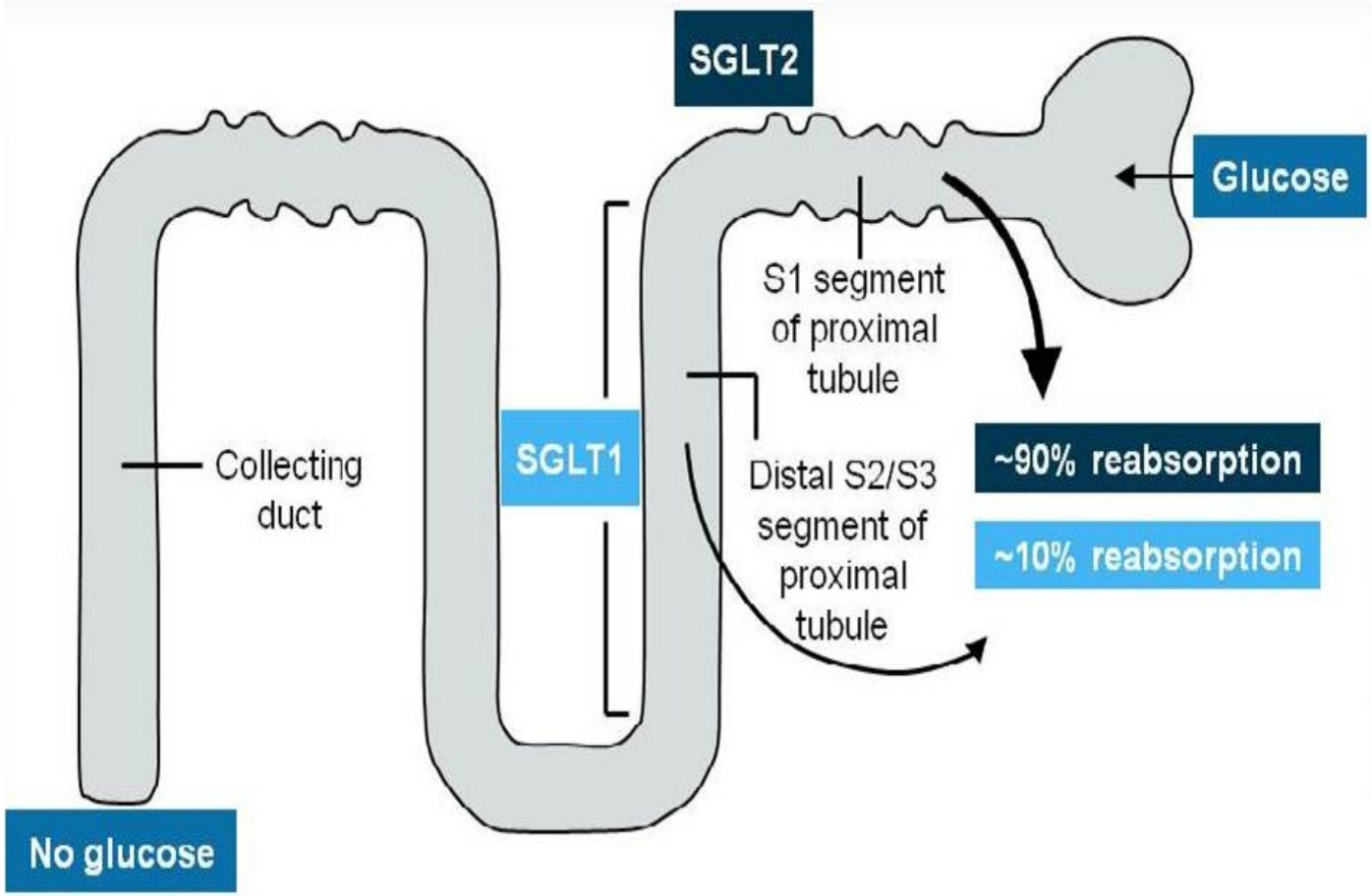
All patients required emergency room visits or hospitalizations

In 2015, the FDA issued a warning that SGLT2 inhibitors may lead to ketoacidosis

Source: FDA.*Drug Safety communication/*2015

Sodium glucose co-transporter 2 inhibitors

- Indicated for T2DM
- Work by reducing renal reabsorption of glucose and increase urinary excretion of glucose
- With improved cardiovascular and kidney outcomes, the use of SGLT2s is growing rapidly



Source: American Diabetes Association.*Diabetes Care* 2022;45(Suppl. 1):S125–S143

Sodium glucose co-transporter 2 inhibitors

	Empagliflozin	Dapagliflozin	Canagliflozin	Ertugliflozin
Dosing	10mg daily Max: 25mg daily	5mg daily Max: 10mg daily	100mg daily Max: 300mg daily	5mg daily Max: 15mg daily
Decrease in HbA1c	0.7-0.9%	0.8-0.9%	0.8-1%	0.7-0.8%
Timing of dose	With or without food	With or without food	Prior to first meal	With or without food
Renal impairment	**T2DM:** eGFR<30mL/min: use is not recommended **HF/CKD:** eGFR<20mL/min: use is not recommended	**T2DM:** eGFR<25mL/min: use is not recommended **HF/CKD:** May continue 10mg daily	eGFR 30 - 60mL/min: 100mg daily eGFR <30mL/min: do not initiate therapy; may continue 100mg daily	eGFR<45mL/min: use is not recommended
Half life	12.4 hours	12.9 hours	10.6 hours	16.6 hours
Common adverse events	Genitourinary tract infections, increased urination, dehydration			

Source: American Diabetes Association.*Diabetes Care* 2022;45(Suppl. 1):S125–S143

SGLT2 inhibitors new indications

- The Kidney Disease Improving Global Outcomes (KDIGO) guideline recommends initiating an SGLT2 inhibitor (canagliflozin, empagliflozin and dapagliflozin) in patients who have CKD with an estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73 m^2 or higher and albuminuria with or without diabetes
- An SGLT2 inhibitor may be continued for kidney protection if the eGFR below 30 mL/min/1.73 m^2.
- Empagliflozin and dapagliflozin are now recommended for treatment of chronic heart failure with reduced ejection fraction (HFrEF)

Source: McDonagh TA, et al. *Eur Heart J. 2021*

SGLT2 inhibitors and risk for DKA

SGLT2 INHIBITORS AND RISK FOR DKA: MULTICENTER COHORT STUDY	
Objective	To assess whether SGLT2 inhibitors, compared with DPP-4 inhibitors, are at increased risk for DKA in patients with T2DM
Design	• Population based cohort study between 2013 and 2018 • Electronic healthcare bases from 7 Canadian provinces and the United Kingdom • 208,757 new users of SGLT2 inhibitors were matched to 208,757 recipients of DPP-4 inhibitors
Inclusion criteria	• Patient newly initiated on SGLT2 inhibitor or DPP-4 inhibitor between January 1, 2013 - June 30, 2018
Exclusion criteria	• Patients <18 years old • Patients with <365 days of health coverage prior to cohort entry • Patients with hospitalization for DKA in the year prior to entry
Primary endpoint	Incidence of DKA

Source: Douros A, et al. *Ann Intern Med.* 2020;173(6):417-425.

SGLT2 inhibitors and risk for DKA

SGLT2 INHIBITORS AND RISK FOR DKA: MULTICENTER COHORT STUDY

Results

- 521 patients were diagnosed with DKA during 370 454 person-years of follow up
  - incidence rate per 1000 person-years, 1.40 [95% CI, 1.29 to 1.53]
- Compared to DPP-4 inhibitors, SGLT-2 inhibitors had increased risk of DKA
  - incidence rate, 2.03 versus 0.75; HR, 2.85 [CI, 1.99 to 4.08]
- Molecule specific HRs:
  - Dapagliflozin 1.86 [CI, 1.11 to 3.10]
  - Empagliflozin 2.52 [CI, 1.23 to 5.14]
  - Canagliflozin 3.58 [CI, 2.13 to 6.03]
- Prior receipt of insulin appeared to decrease the risk

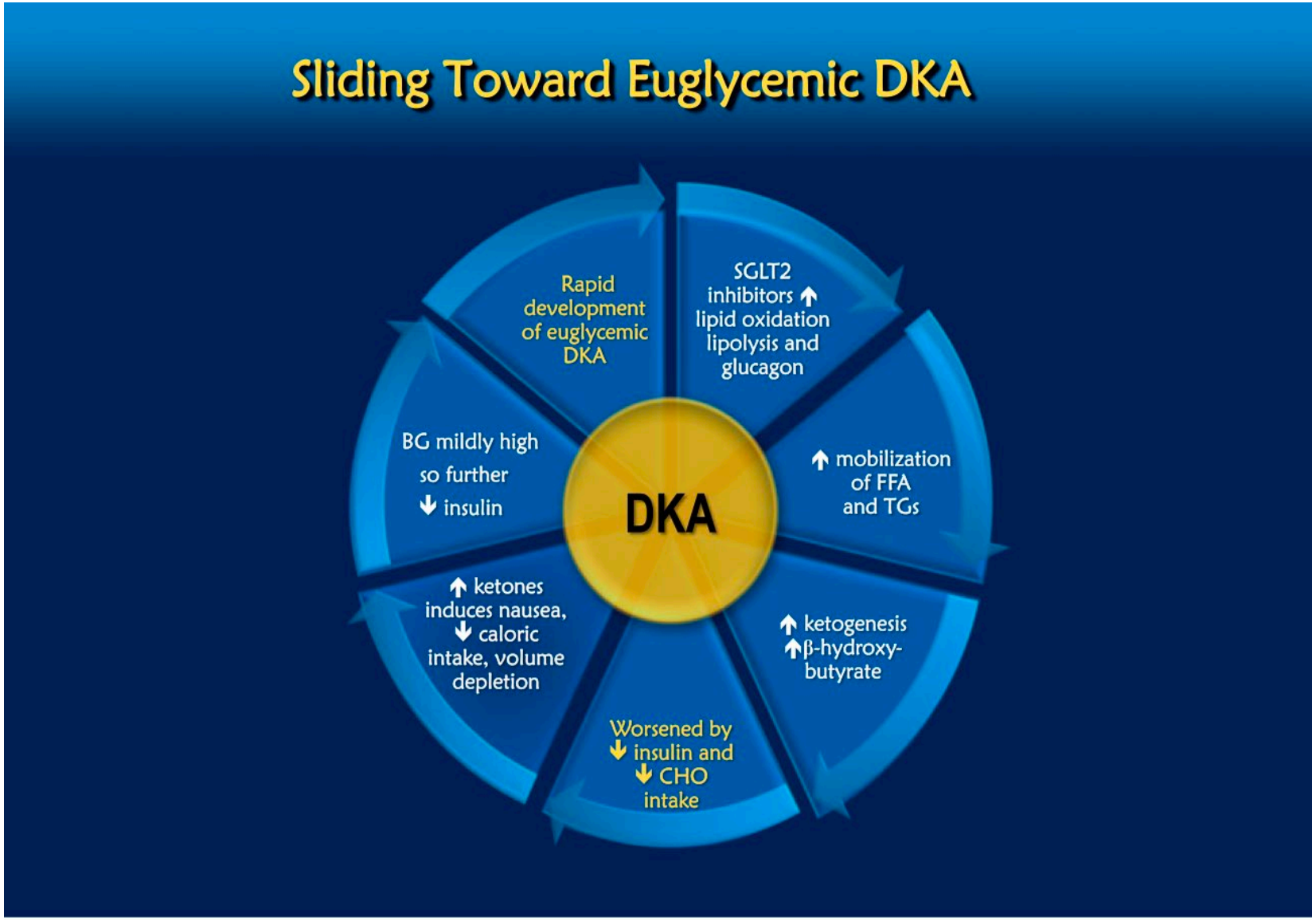
Conclusion

SGLT-2 inhibitors were associated with an almost 3 fold increased risk for DKA

Source: Douros A, et al. *Ann Intern Med.* 2020;173(6):417-425.

Euglycemic Diabetic Ketoacidosis

Pathophysiology

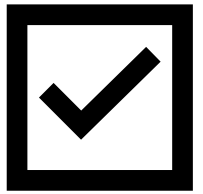


Source: Buse J, et al. *Diabetes Care.* 2020; 43:487-493.

Knowledge Check – Pharmacy Technician

EuDKA is defined as an acute, major, life-threatening disease characterized by:

a. BG <250
b. pH <7.3
c. Ketones >5 mEq
d. All of the above



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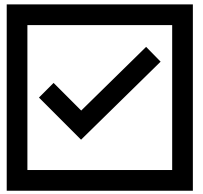
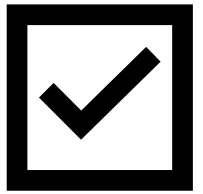


Knowledge Check – Pharmacist/Nurse

Which of the following are true regarding the mechanism of action of SGLT2 inhibitors in EuDKA?

a. A carbohydrate deficit results in decreased serum glucose
b. Increased insulin/glucagon ratio leads to ketoacidosis
c. Decreased gluconeogenesis by the liver and increased glucosuria leads to EuDKA
d. All of the above



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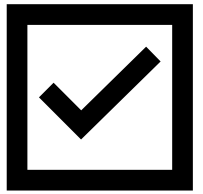
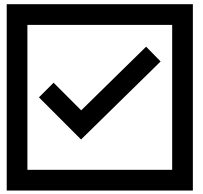


Knowledge Check – Pharmacist/Nurse

A patient presents to do ED with nausea, vomiting, fatigue and loss of appetite. Lab values were obtained and resulted as follows: BG 180, pH 7, K 5. Which of the following are diagnostic criteria associated with Euglycemic DKA? Select ALL that apply.

a. BG 180 mg/dL
b. pH 7
c. K 5
d. A and C



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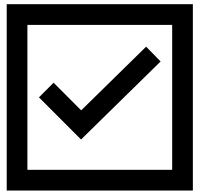


Euglycemic Diabetic Ketoacidosis

Etiology

- Common precipitating factors:
  - Low glucose states: fasting, starvation
  - Chronic liver disease
  - Pregnancy
  - Infection
  - Alcohol use
  - Reduced insulin doses
- COVID-19 may increase risk of EuDKA due to beta-cell destruction from SARS-CoV-2

Source: Umpierrez GE, et al. *Diabetes Care.* 2018;41(9):1839-1841
Vitale RJ et al. *AACE Clin Case Rep*.2020 Dec 28

EuDKA and COVID-19 in patients on SGLT2 inhibitors

- Five cases of EuDKA presenting with glucose levels <300mg/dL were identified between March and May 2020
- None had prior history of DKA or known complications of T2DM
- ↑ incidence of new-onset DM and DKA has been seen during the pandemic
- Direct toxic effect of the SARS-CoV-2 virus on pancreatic islets
- ↑ expression of angiotensin-converting enzyme 2 receptors in pancreatic islets
  - ↑ cell death in insulin-producing cells
  - ↓ endogenous insulin production
  - ↑ likelihood of DKA

Source: Vitale RJ et al. *AACE Clin Case Rep*.2020 Dec 28

EuDKA and SGLT2 inhibitors in surgery

- Postoperative ketoacidosis can occur in patients with DM due to:
  - Anesthesia and operative stress
  - Abrupt discontinuation of insulin or inadequate treatment in the perioperative period
  - Post-operative infection
  - Prolonged poor oral intake or severe dehydration
- Can occur with any type of surgery but most commonly associated with bariatric surgery

Source: Amnian A, et al. *Diabetes Care.* 2016;39(4):e50-e53

EuDKA and SGLT2 inhibitors in surgery

FDA Drug Safety Communication

3-19-2020 Update; Revised 3-15-2022

To lessen the risk of developing ketoacidosis after surgery, FDA has approved changes to the prescribing information for SGLT2 inhibitor medicines. Health care professionals should consider stopping canagliflozin, dapagliflozin, and empagliflozin at least three days before, and ertugliflozin at least four days before scheduled surgery.

Source: FDA. *Drug Safety communication/* 2015

EuDKA and SGLT2 inhibitors in surgery

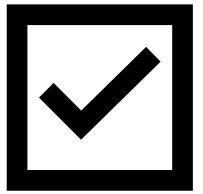
Study	SGLT2 Inhibitor Used	Outcome/Summary
Bobart 2016	Canagliflozin	• Patient presented with EuDKA 2 days after cosmetic surgery • Continued taking canagliflozin with poor oral intake
Dizon 2017	Canagliflozin Dapaglizlozin	• 4/10 patients developed EuDKA in the postoperative period 2 following Roux-en-Y surgery 1 following cholecystectomy 1 following hip-fracture repair
van Niekerk 2018	Canagliflozin	• 52-year-old male with T2DM developed severe anion gap metabolic acidosis postoperative day (POD) 2 discharged on POD 4; euglycemic DKA prolonged his hospital stay by 2 days.

Source: Bobart SA, et al. *Ann Intern Med.* 2016;165(7):530-532.
Dizon, S, et al. Can J Diabetes. 2017;41(5):499-503
Van Niekerk C, et al. BMJ Case Rep. 2018

Knowledge Check – Pharmacist/Nurse

Which of the following SGLT2 inhibitors should be held at least 4 days prior to surgery?

a. Empagliflozin
b. Canagliflozin
c. Ertugliflozin
d. Dapagliflozin



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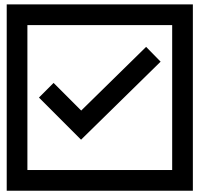


MANAGEMENT OF EUGLYCEMIC DKA

Stepwise approach

1

Stop SGLT2 inhibitor until EuDKA resolves

2

Start Fluid replacement therapy with monitoring of ketones and electrolytes

3

Start continuous insulin infusion

4

Start dextrose administration

Management goals

CORRECT DEHYDRATION

CORRECT ELECTROLYTE IMBALANCES

IDENTIFY COMORBID PRECIPITATING EVENTS

FREQUENT PATIENT MONITORING

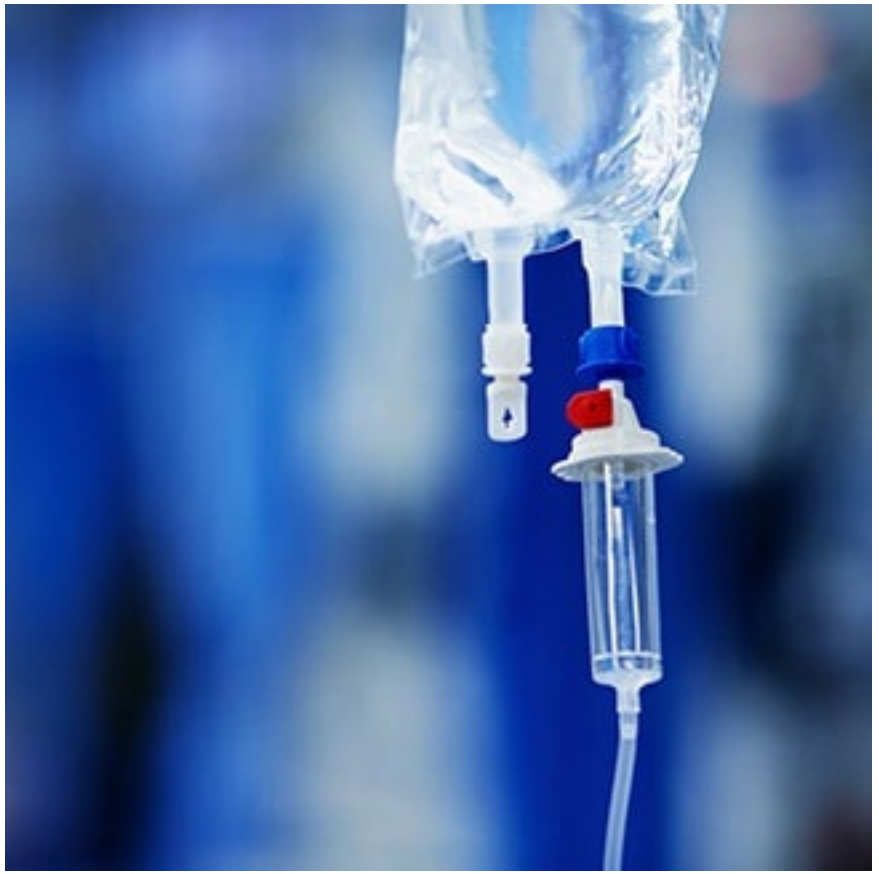
Fluid resuscitation

Fluid loss due to EuDKA can range from 6L-9L

1L/hour to 1.5L/hour of normal saline or Lactated Ringer's (LR) solution during the first 1-2 hours of fluid resuscitation

IV fluids should be continued until anion gap closes and acidosis has resolved

Monitor blood ketones and electrolytes hourly and then every four hours



Source: Kitbachi AE, et al. *Diabetes Care.* 2009;32(7):1335-1344.

Fluid consideration in DKA

Goal:

- Expand intravascular, interstitial, and intracellular volume
- Restore renal perfusion

Fluid choice:

- Isotonic fluid
- Dependent on hemodynamics, state of hydration, serum electrolyte levels and urinary output
  - Normal saline: can lead to hyperchloremia and acidosis
  - Balanced crystalloid: closer to physiological makeup

Source: Kitbachi AE, et al. *Diabetes Care.* 2009;32(7):1335-1344.

Fluid resuscitation

CLINICAL EFFECTS OF BALANCED CRYSTALLOIDS VS SALINE IN ADULTS WITH DKA

Objective	To compare the clinical effects of balanced crystalloids with the clinical effects of saline for the acute treatment of adults with DKA
Design	• Subgroup analysis of adults with DKA in 2 previously reported trials (SALT-ED) and (SMART) at Vanderbilt University Medical Center
Intervention	• Patients were assigned crystalloid type in the ED and ICU based on the fluid of choice each month • In months assigned to balanced crystalloids, clinicians had the option to select either LR or Plasma-Lyte A, and in months assigned to saline, saline was the only option
Inclusion criteria	• Adults 18 years or older • Presented to ED during the 15 month period when both the ED and ICU were participating in the SALT-ED and SMART trials • Had a clinical diagnosis of DKA in the ED and a medical record confirming DKA was present at time of ED evaluation rather than delayed onset in the hospital after admission • Laboratory values in the ED were consistent with DKA, including plasma glucose >250mg/dL, bicarbonate $\leq$18mEq/L and calculated anion gap >10 mEq/L

Source: Self WH, et al. *JAMA Netw Open.* 2020;3(11):e2024596.

Fluid resuscitation

CLINICAL EFFECTS OF BALANCED CRYSTALLOIDS VS SALINE IN ADULTS WITH DKA	
Exclusion criteria	• Transfer from an outside hospital (patients received IV fluids outside the study protocol) • Admission to the cardiac or neurologic ICU (these units had opposite crystalloid schedule compared to the ED) • Presentation to the ED within 24 hours prior to a planned crossover in the trial
Primary Endpoint	• Time between ED presentation and DKA resolution, as defined by the American Diabetes Association criteria
Secondary Endpoint	• Time between initiation and discontinuation of continuous insulin infusion

Source: Self WH, et al. *JAMA Netw Open.* 2020;3(11):e2024596.

Fluid resuscitation

CLINICAL EFFECTS OF BALANCED CRYSTALLOIDS VS SALINE IN ADULTS WITH DKA		
Results	**Sample size**	N= 172 patients
	Primary Endpoint	Time to DKA resolution: • 13.0 hours in the balanced crystalloid group vs 16.9 hours in the saline group • Adjusted hazard ratio [aHR] = 1.68; 95% CI, 1.18-2.38; *P* = .004
	Secondary endpoint	Time to insulin infusion discontinuation: • 9.8 hours in the balanced crystalloid group vs 13.4 hours in the saline group • aHR = 1.45; 95% CI, 1.03-2.03; *P* = .03
Conclusion		• Treatment with balanced crystalloids (LR) was associated with more rapid resolution of DKA and discontinuation of insulin infusion. • Balanced crystalloids may be preferred over saline for adult management of DKA

Source: Self WH, et al. *JAMA Netw Open.* 2020;3(11):e2024596.

Insulin infusion in DKA

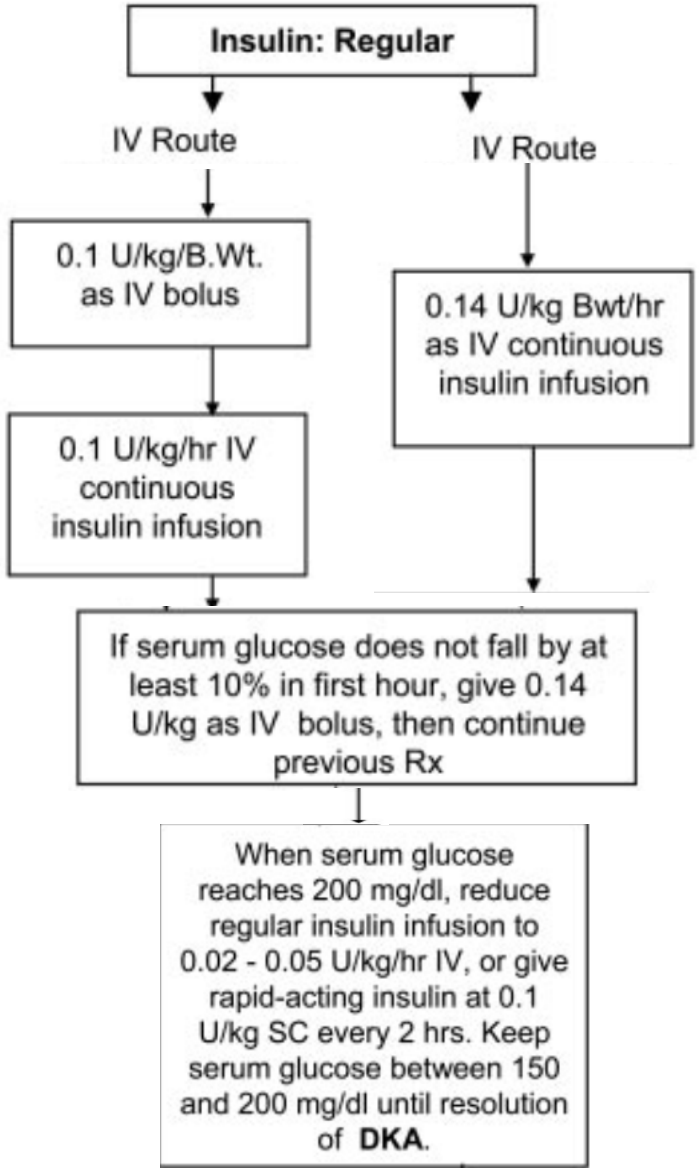
Continuous insulin infusion should be started at a rate of 0.05 unit/kg/hour to 0.1 unit/kg/hour with serum potassium levels >3.3 mEq/L

Once DKA has resolved start patient on subcutaneous (SUBQ) basal-bolus insulin regimen to control BG

Continue insulin infusion at least 1-2 hour after SUBQ insulin is given

Source: Kitbachi AE, et al. *Diabetes Care.* 2009;32(7):1335-1344.

Insulin infusion



*Remember to prime insulin infusion with 20ml volume *

Source: Kitbachi AE, et al. *Diabetes Care.* 2009;32(7):1335-1344.

Transition to SUBQ insulin

- Patients should be treated with regular insulin until:
  - AG ≤ 12 and resolution of ketoacidosis
    - → BG < 200
    - → bicarb ≥ 15 mEq/L
      - or –
    - → venous pH > 7.3

- Overlap insulin infusion and SUBQ insulin for 1 - 2 hours
  - → If patient is NPO continue regular insulin infusion
  - → Start meal associated and sliding scale insulin
    - If insulin naïve patients, start at 0.5units/kg to 0.8units/kg daily and adjust insulin as needed
  - → Encourage patients to eat

Source: Kitbachi AE, et al. *Diabetes Care.* 2009;32(7):1335-1344.

Transition to SUBQ insulin

Long-acting basal insulin

- Determine total daily requirement of basal insulin
- For patients on home subcutaneous insulin → patient's home basal dose
- For patients naive to insulin, a starting dose of **0.25 units/kg** daily of insulin glargine may be used

Insulin products can be stored at room temperature for 28 days

Source: Kitbachi AE, et al. *Diabetes Care.* 2009;32(7):1335-1344.

Insulin infusion vs SUBQ insulin

Evaluation of Outcomes Following Hospital-Wide Implementation of a Subcutaneous Insulin Protocol for DKA	
Objective	To assess outcomes after implementation of a SUBQ insulin protocol for treating DKA
Design	• Retrospective cohort study of implemented SUBQ insulin protocol • Participants included hospitalized patients with DKA at 21 hospitals between January 1, 2010, and December 31, 2019
Inclusion criteria	• Adults 18 years or older with DKA
Exclusion criteria	• Any medical condition that would require ICU admission • Glasgow Coma Scale Score <8
Endpoints	• Mortality within 30 days of hospital admission • Hospital readmission within 30 days of discharge • Admission to ICU • Length of say

Source: Self WH, et al. *JAMA Netw Open.* 2020;3(11):e2024596.

Insulin infusion vs SUBQ insulin

Evaluation of Outcomes Following Hospital-Wide Implementation of a Subcutaneous Insulin Protocol for DKA

Results	N=7989 • ICU admission: - adjusted rate ratio for ICU admission: 0.43 (95% CI, 0.33-0.56) at the intervention sites, a 57% reduction compared with control sites • 30-day hospital readmission: - 0.50 (95% CI, 0.25-0.99) , a 50% reduction • no significant changes in hospital length of stay and rates of death
Conclusion	Use of SUBQ insulin significantly decreased need for ICU and reduced rates of readmission, with no increase in hypoglycemia or mortality

Source: Rao P, et al. *JAMA Netw Open.* 2022;5(4):e226417.

Dextrose administration

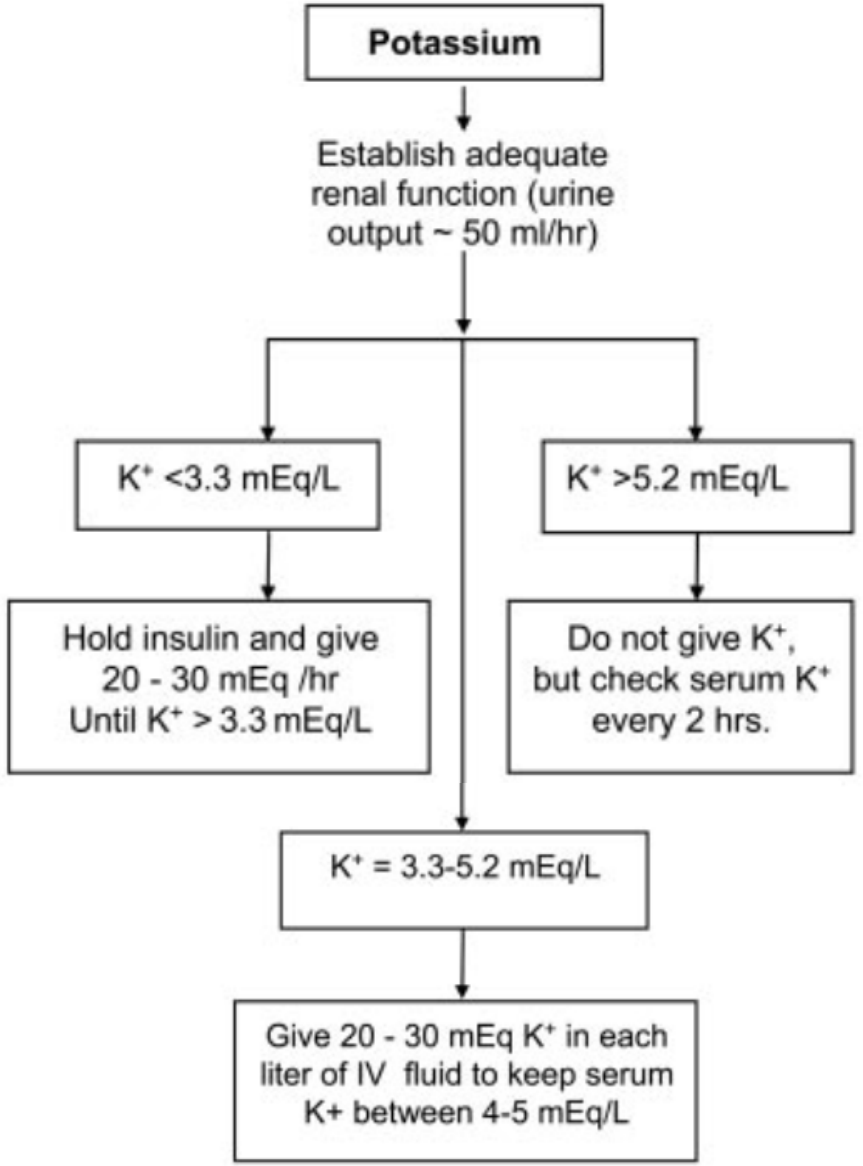
- Dextrose 5% should be added initially to isotonic fluids to avoid hypoglycemia and hasten clearance of ketosis
- Mildly hypovolemic patients: D5 LR ~250ml/hr
- Euvolemic patients: D10W ~125ml/hr
- Dextrose is given to restore normal cellular utilization, resulting in enhanced clearance and reduced ketone bodies
- Addition of D5W prevents hypoglycemia by serving as an exogenous source of glucose in setting of insulin utilization
- Check blood glucose levels hourly

Source: Kitbachi AE, et al. *Diabetes Care.* 2009;32(7):1335-1344.

Electrolyte monitoring

Potassium

Goal: maintain serum potassium between 4 – 5 mEq/L

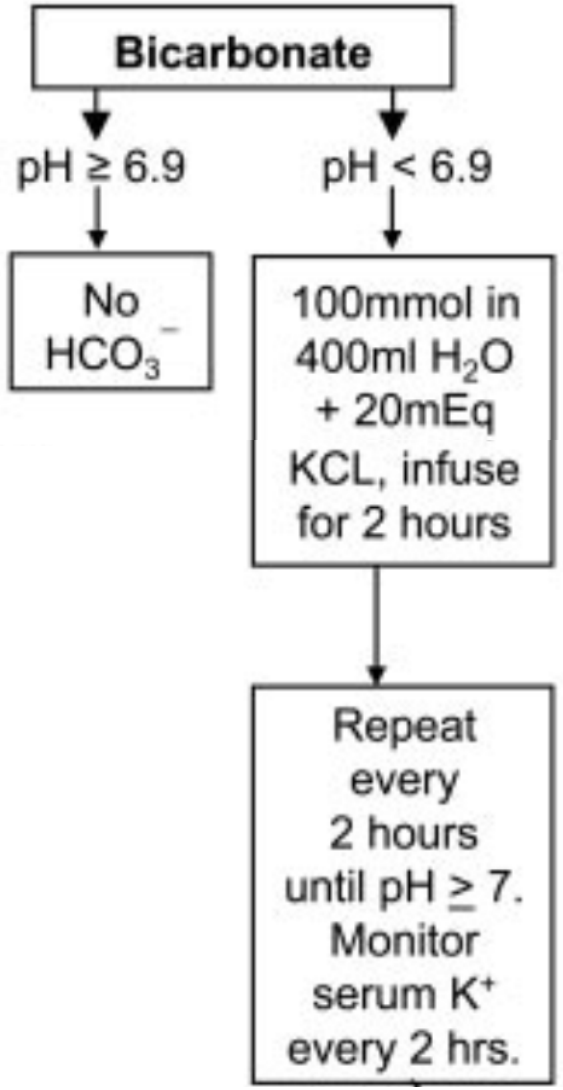


Source: Kitbachi AE, et al. *Diabetes Care.* 2009;32(7):1335-1344.

Electrolyte monitoring

Bicarbonate

Severe metabolic acidosis can lead to impaired myocardial contractility, cerebral vasodilation and coma and GI complications



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Electrolyte monitoring

IV SODIUM BICARBONATE THERAPY IN SEVERELY ACIDOTIC DKA	
Objective	To determine whether the use of IV bicarbonate therapy was associated with improved outcomes in patients with severe DKA seen in the ED
Design	• Retrospective review from 2007-2011 in the ED at a tertiary teaching hospital • Patients were stratified in two groups based on receipt of IV sodium bicarbonate • N=86 ; N=44 IV bicarbonate; N=42 placebo
Inclusion criteria	• Adults diagnosed with DKA with initial pH<7
Primary endpoint	• Time to resolution of acidosis defined as pH>7.2
Secondary endpoint	• Length of stay, continuous infusion insulin use, intravenous fluid, potassium and insulin requirements for the first 24 hours of hospital admission

Source: Duhon B, et al. *Ann Pharmacother.* 2013;47(7-8):970-975.

Electrolyte monitoring

IV SODIUM BICARBONATE THERAPY IN SEVERELY ACIDOTIC DIABETIC KETOACIDOSIS	
Results	• Time to resolution of acidosis: 8 hours vs 8 hours; p = 0.7 • Time to hospital discharge (68 hours vs 61 hours; p = 0.3) between patients who received IV bicarbonate (n = 44) compared with those who did not (n = 42) • Insulin and fluid requirements in the first 24 hours were higher in patients who received IV bicarbonate compared with those who did not (100 units vs 86 units; p = 0.04 and 7.6 L vs 7.2 L; p = 0.01, respectively) • No significant difference in hours of continuous insulin infusion (27 hours vs 26 hours; p = 0.09) or potassium requirements in the first 24 hours of hospital stay (135 mEq vs 120 mEq; p = 0.84).
Conclusion	• Intravenous bicarbonate therapy did not decrease time to resolution of acidosis or time to hospital discharge for patients with DKA with an initial pH less than 7.0.

Source: Duhon B, et al. *Ann Pharmacother.* 2013;47(7-8):970-975.

Pseudohyponatremia

- Elevated serum blood glucose levels and the production of ketone bodies increase plasma osmolality and create an osmotic gradient between the intracellular and extracellular fluid → water movement from cells to the plasma
- Hyperosmolality stimulates antidiuretic hormone (ADH) secretion →Hyponatremia results from fluid shifts and increased water intake
- Persistently increased plasma glucose levels greater than 180–200 mg/dl overwhelm the proximal tubule's ability to reabsorb filtered glucose from urine, leading to glycosuria and significant osmotic diuresis
- Not a problem in EuDKA

Sodium correction formula = Measured Na + [(1.6 x (glucose – 100)/100)]

Source: Kitbachi AE, et al. *Diabetes Care.* 2009;32(7):1335-1344.

Electrolyte monitoring

Phosphate

- Usually normal at presentation
- Insulin therapy can decrease serum phosphate
- No benefit has been shown in phosphate replacement
- Indicated to avoid potential cardiac and skeletal muscle weakness and respiratory depression
- Phosphate replacement may sometimes be indicated in patients with cardiac dysfunction, anemia, or respiratory depression and in those with serum phosphate concentration < 1.0 mg/dL
- Safe treatment of severe hypophosphatemia = 4.5 mmol/h
    - 20 – 30 mEq KPO_4

Source: Kitbachi AE, et al. *Diabetes Care.* 2009;32(7):1335-1344.

Management of recurrent EuDKA

Causes of recurrent DKA:

- Restarting SGLT2 inhibitor prior to EuDKA resolution
- Insulin infusion stopped too early
- Insufficient meals
- Ongoing systemic inflammation

Treatment:

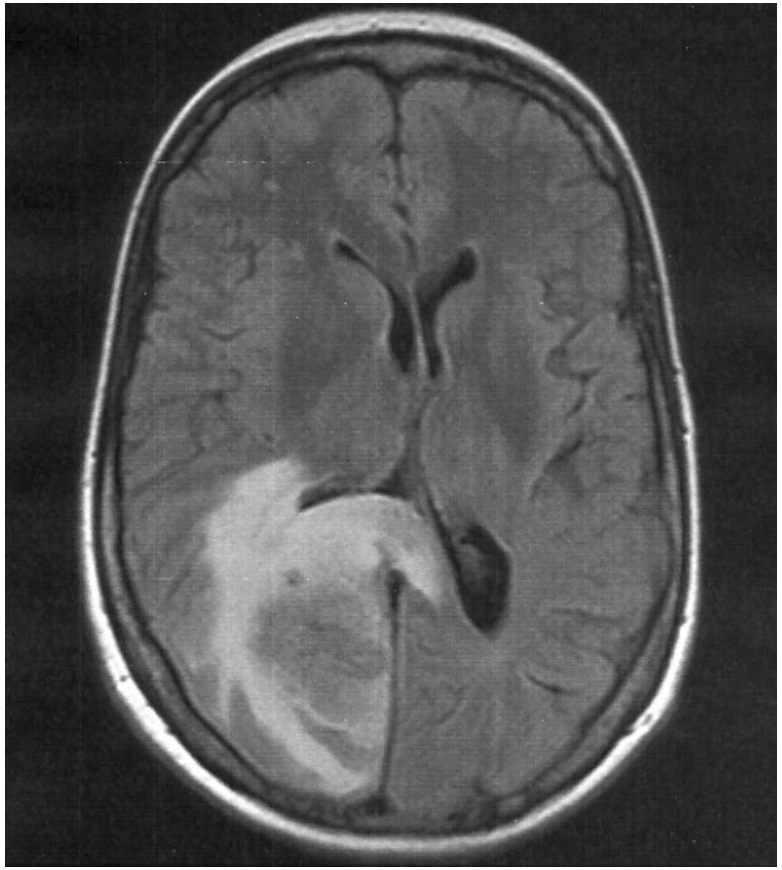
- Discontinue SGLT2 until EuDKA has fully resolved
- Restart insulin infusion
- Address reversible causes of DKA
- Correct electrolyte disturbances

Source: Kitbachi AE, et al. *Diabetes Care.* 2009;32(7):1335-1344.

Complications in DKA

Cerebral Edema

- Extremely rare in adult patients; mortality 20-40%
- Increased cerebral blood flow, disruption of cell membrane ion transport and a rapid shift in extracellular and intracellular fluids results in changes in osmolality
- Avoid excessive hydration
- Target a reduction in serum osmolality by ~20 mOsm/day
- Not a concern in EuDKA



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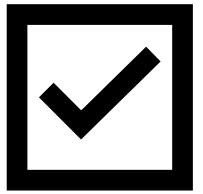
Knowledge Check – Pharmacist/Nurse

Based on current guidelines what is the treatment for EuDKA?

a. Insulin drip at 0.05unit/kg/hour to 0.1unit/kg/hour plus D5W
b. Insulin drip 0.05unit/kg/hour to 0.1unit/kg/hour initially; add D5W only if patient is hypoglycemic
c. 0.05unit/kg/hour to 0.1unit/kg/hour subcutaneous insulin
d. D5W only since BG<250mg/dL



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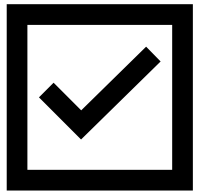
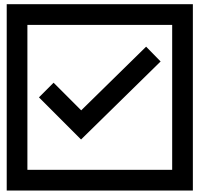


Knowledge Check – Pharmacy Technician

You are the technician transporting patient specific medications to the floor. You notice that for one of your patients you have to stock to following medications: Insulin drip 1unit/ml, atorvastatin 80mg, lisinopril 40mg, empagliflozin 10mg. Which of the following medications are used in DKA treatment?

a. Empagliflozin
b. Atorvastatin
c. Insulin drip
d. A and C



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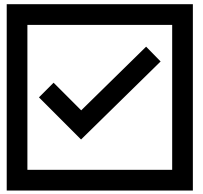
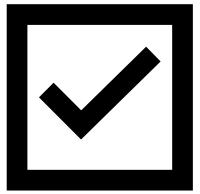


Knowledge Check – Pharmacy Technician

After taken out of the fridge, how many days can insulin be stored at room temperature?

a. 28 days
b. 32 days
c. 24 hours
d. 48 hours



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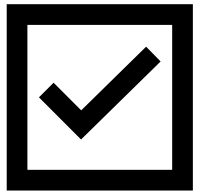

Patient counseling

Recommendations
Maintain appropriate fluid intake
Ensure adequate carbohydrate intake and avoid low-carbohydrate diets
Avoid skipping insulin doses and skipping meals
In situations of acute illness, vomiting, diarrhea, or inability to eat or drink
Discontinue SGLT2i
Contact provider even if blood glucose levels are not elevated
Continue to monitor glucose levels and monitor for presence of urinary ketones
If on insulin therapy, contact provider for dose adjustments; do not stop insulin
Ketoacidosis symptoms are nonspecific (malaise, nausea, anorexia, vomiting) and can occur despite normal or minimally elevated blood glucose level
If ketonuria detected, patient may be advised to administer dose of rapid-acting insulin and consume 30 g carbohydrate
Restart SGLT2i when eating and drinking normally, usually after 24–48 h as directed by medical provider

Source: Palmer B, et al. *CSJASN.* 2021;16(8):1284-1291.

Conclusion

- Ketoacidosis is a rare but serious adverse effects of SGLT2 inhibitors
- Atypical presentation and euglycemic state can be misleading
- SGLT2 inhibitors should be stopped during the peri-operative period and in times of dehydration
- Early diagnosis and treatment can improve morbidity and mortality
- SGLT2 inhibitor treatment should be discontinued as soon as EuDKA is diagnosed

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THANK YOU!

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