PHARMACY VISION 20/20

CSHP SEMINAR 20 • OCTOBER 21-25

Disneyland RESORT

DKA MANAGEMENT: VISION OBSCURED BY SGLT2 INHIBITORS

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DISCLOSURE

- I have no potential conflict of interest to disclose.

LEARNING OBJECTIVES

Pharmacist Objectives:

- Appraise available modes of monitoring and treatment of Diabetic Ketoacidosis (DKA)
- Recognize underlying precipitating causes of DKA and euglycemic DKA secondary to SGLT2 administration
- Identify the risk factors for developing complications in DKA

Pharmacy technician objectives:

- Identify the formulations of insulin for the treatment of DKA
- Recognize the proper solution to administer sodium bicarbonate
- Select the type of intravenous fluids use in the treatment of DKA

PRE-TEST QUESTIONS

1. Which therapeutic interventions should be considered in the setting of DKA? Select all that apply.

A. Insulin B. Potassium C. Intravenous fluid D. Sodium bicarbonate

2. Which clinical parameter allows for intravenous insulin transition to subcutaneous?

A. Serum bicarbonate level 10 mEq/L
B. Venous pH 7.1
C. Calculated anion gap 2- mEq/L
D. Tolerating oral nutrition

3. Which of the following are potential causes of euglycemic DKA? Select all that apply.

A. SGLT-2 inhibitor utilization
B. Poor caloric intake
C. Insulin utilization
D. Dehydration

DIABETIC KETOACIDOSIS (DKA)

- Acute physiological and metabolic complications of diabetes
  - Extends from severe hyperglycemia to euglycemia
  - Mild to severe dehydration
  - Mild to severe electrolyte abnormalities
  - Altered level of consciousness to coma
  - Acidosis to mixed acid base disorders

1. American Diabetes Association. *Diabetes Care*. 2020.

DKA WARNING SIGNS

- **Excessive thirst**
- **Frequent urination**
- Nausea and **vomiting**
- Abdominal pain
- Weakness or fatigue
- Shortness of breath
- **Fruity-scented breath**
- Confusion

2. Kitabchi AE, et al. *Diabetes Care*. 2009.

DKA: Clinical Presentation

- Evolves rapidly, over a 24-hour period
- Patients may present with symptoms such as: nausea, vomiting, and abdominal pain
- Volume depletion is common in DKA and signs include decreased skin turgor, dry oral mucosa, low jugular venous pressure, tachycardia, and, if severe, hypotension
- Patients may present with a fruity odor (due to exhaled acetone) and Kussmaul respirations

2. Kitabchi AE, et al. *Diabetes Care*. 2009.

DKA: PATHOPHYSIOLOGY

- Hyperglycemia is due to a reduction of effective insulin concentrations and elevated concentrations of counterregulatory hormones (catecholamines, cortisol, glucagon, and growth hormone)
  - Polyuria and polydipsia
  - Dehydration
  - Electrolyte abnormalities

2. Kitabchi AE, et al. *Diabetes Care*. 2009.

DKA: PATHOPHYSIOLOGY

- Ketosis can lead to an anion gap acidosis
- Ketosis is due to insulin deficiency and increased counterregulatory hormones
  - Hormone imbalance enhance presence of free fatty acids into the circulation due to lipolysis
  - Hepatic fatty acid oxidation in the liver is unrestrained
    - Elevated ketone bodies (3 beta-hydroxybutyrate and acetoacetate)

2. Kitabchi AE, et al. *Diabetes Care*. 2009.

Precipitating Factors

- Inadequate insulin therapy
- Infection
- New onset of diabetes
- Acute major illness: myocardial infarction, stroke, sepsis, and pancreatitis
- Concomitant drug therapy (including SGLT2 inhibitors)
- Severe burn or trauma
- Renal failure
- Alcohol intoxication or chronic abuse

2. Kitabchi AE, et al. *Diabetes Care*. 2009.

DKA Treatment

- Treatment based on a careful clinical and laboratory assessment is necessary
- Utilize a validated insulin infusion protocol for the critically ill setting or an individualized insulin therapy for non-critically ill
- Goals of Treatment
  - Manage the precipitating factors
  - Resolution of DKA
  - Prevent complications

2. Kitabchi AE, et al. *Diabetes Care*. 2009.

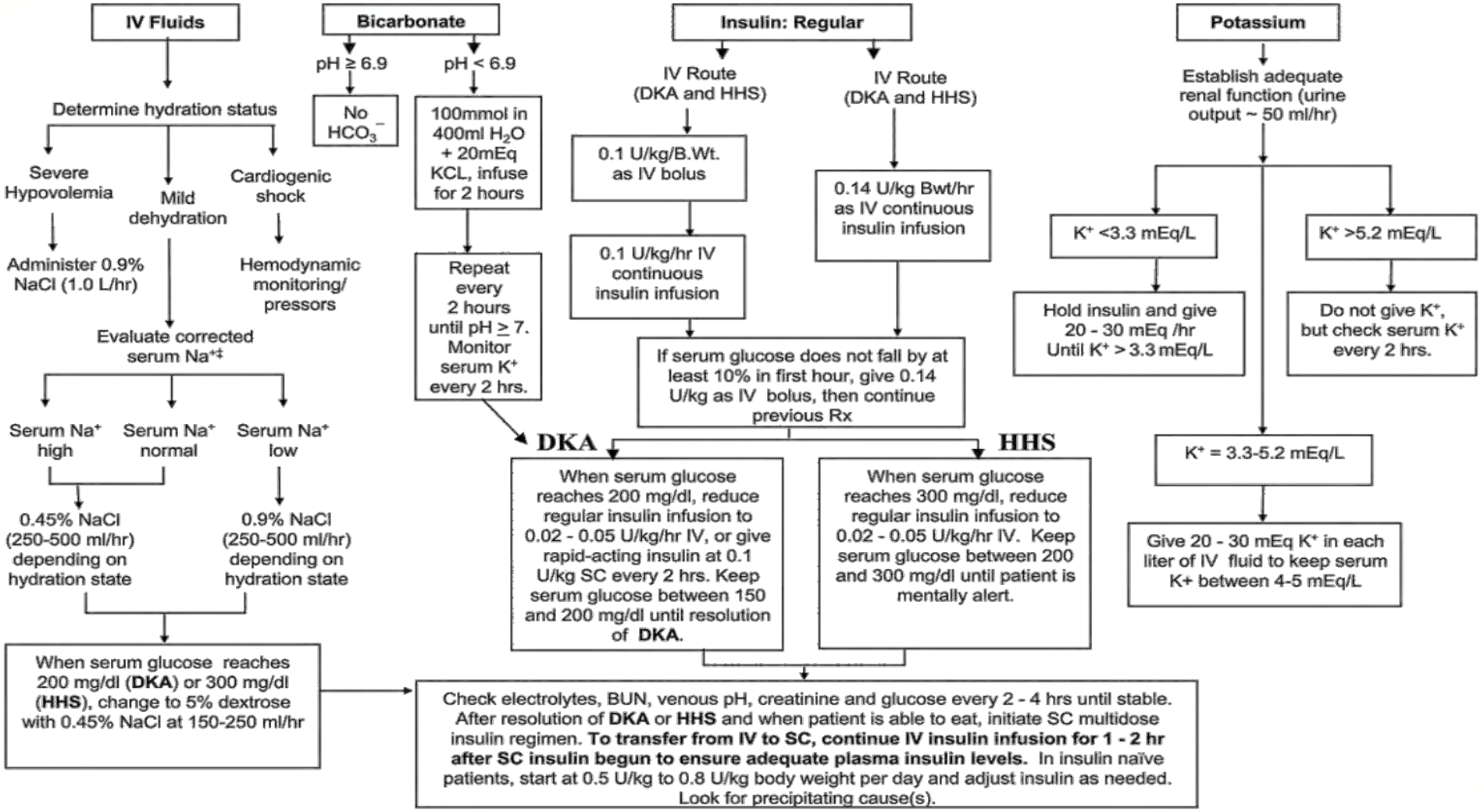
3. American Diabetes Association. *Diabetes Care*. 2009.

DKA Treatment

- Fluid Therapy
- Insulin Therapy
- Potassium Therapy
- Bicarbonate Therapy

2. Kitabchi AE, et al. *Diabetes Care*. 2009.

Complete initial evaluation. Check capillary glucose and serum/urine ketones to confirm hyperglycemia and ketonemia/ketonuria. Obtain blood for metabolic profile. Start IV fluids: 1.0 L of 0.9% NaCl per hour.†



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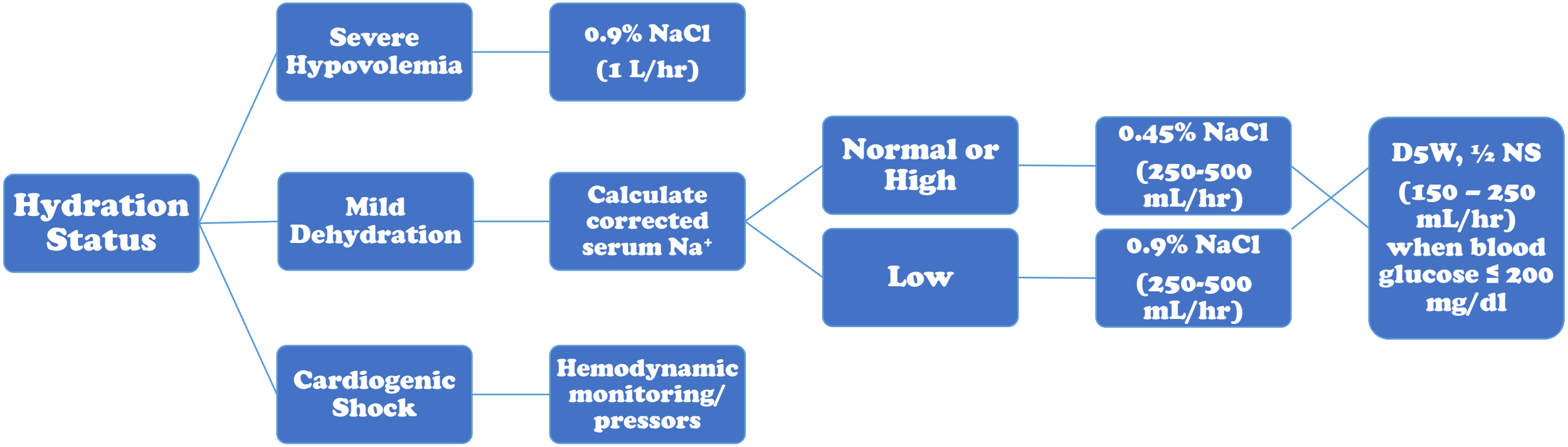
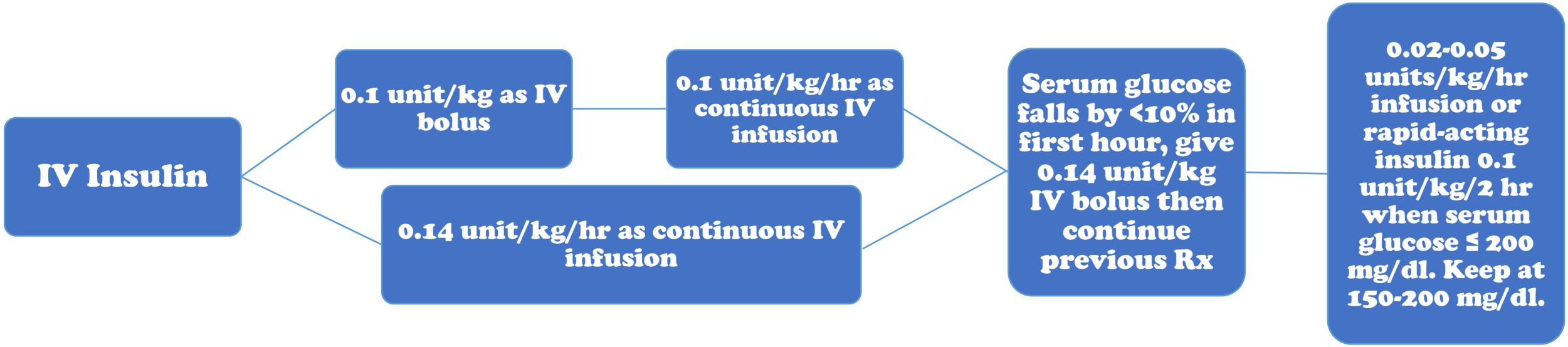
FLUID THERAPY



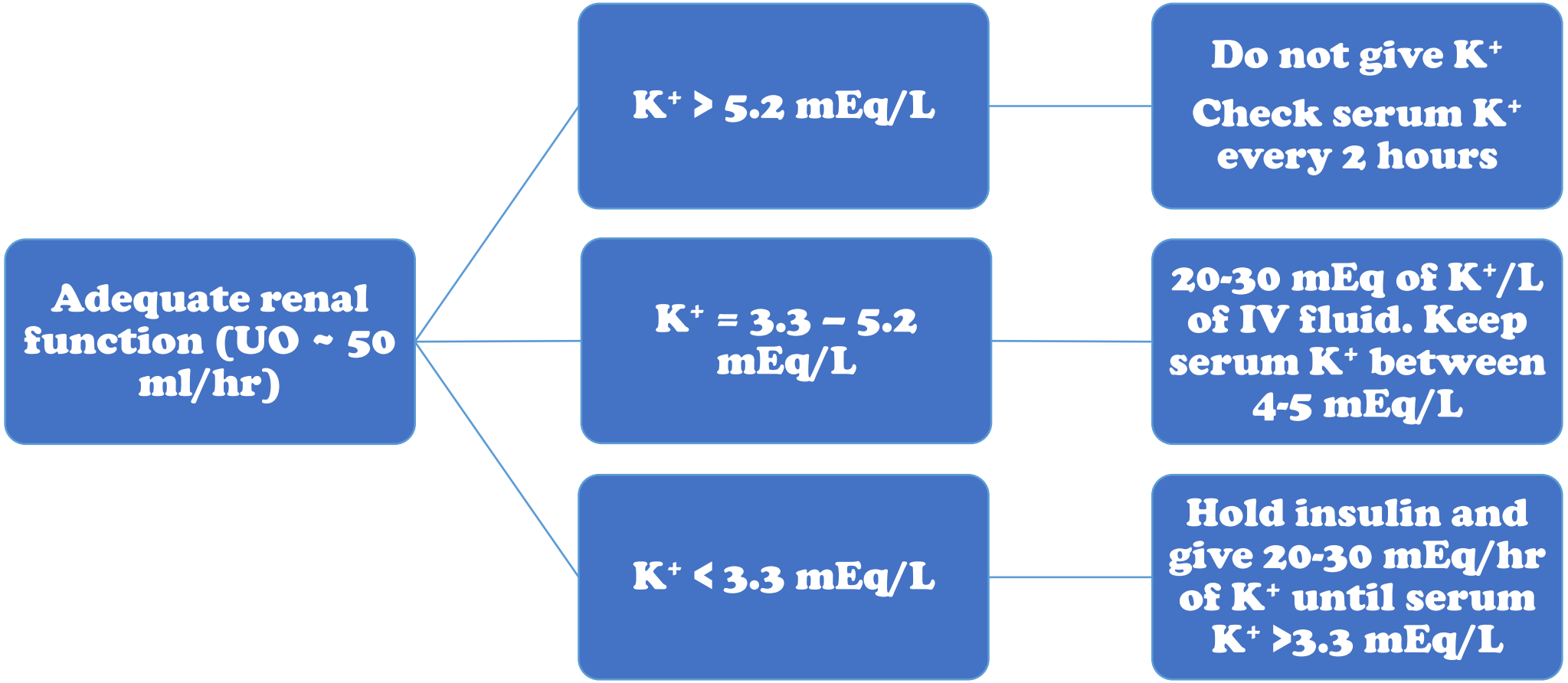
2. Kitabchi AE, et al. *Diabetes Care*. 2009.

INSULIN THERAPY



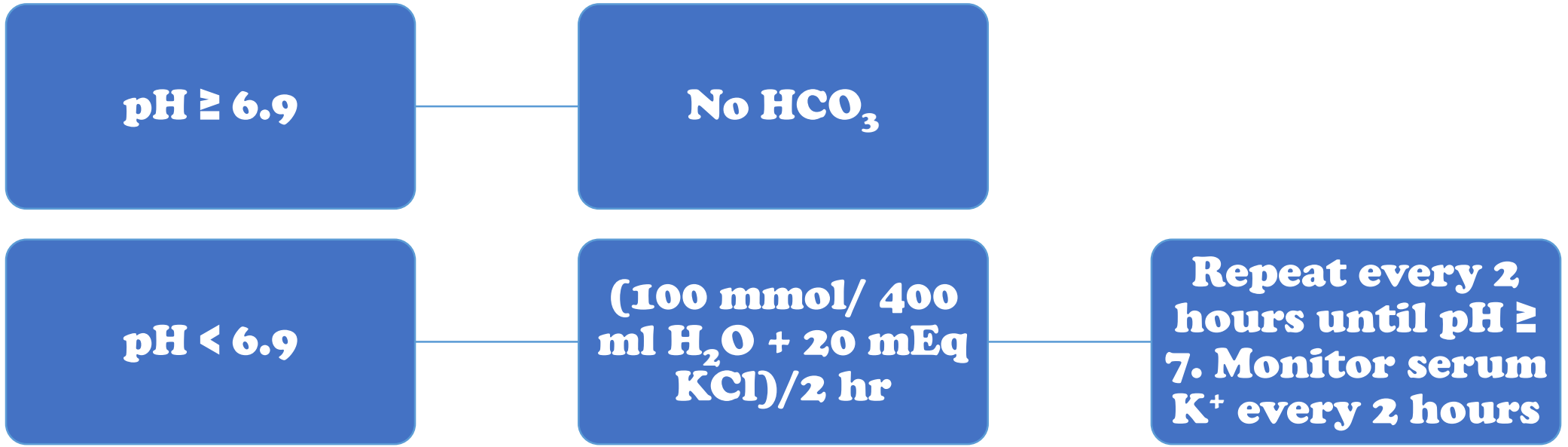
2. Kitabchi AE, et al. *Diabetes Care*. 2009.

POTASSIUM THERAPY



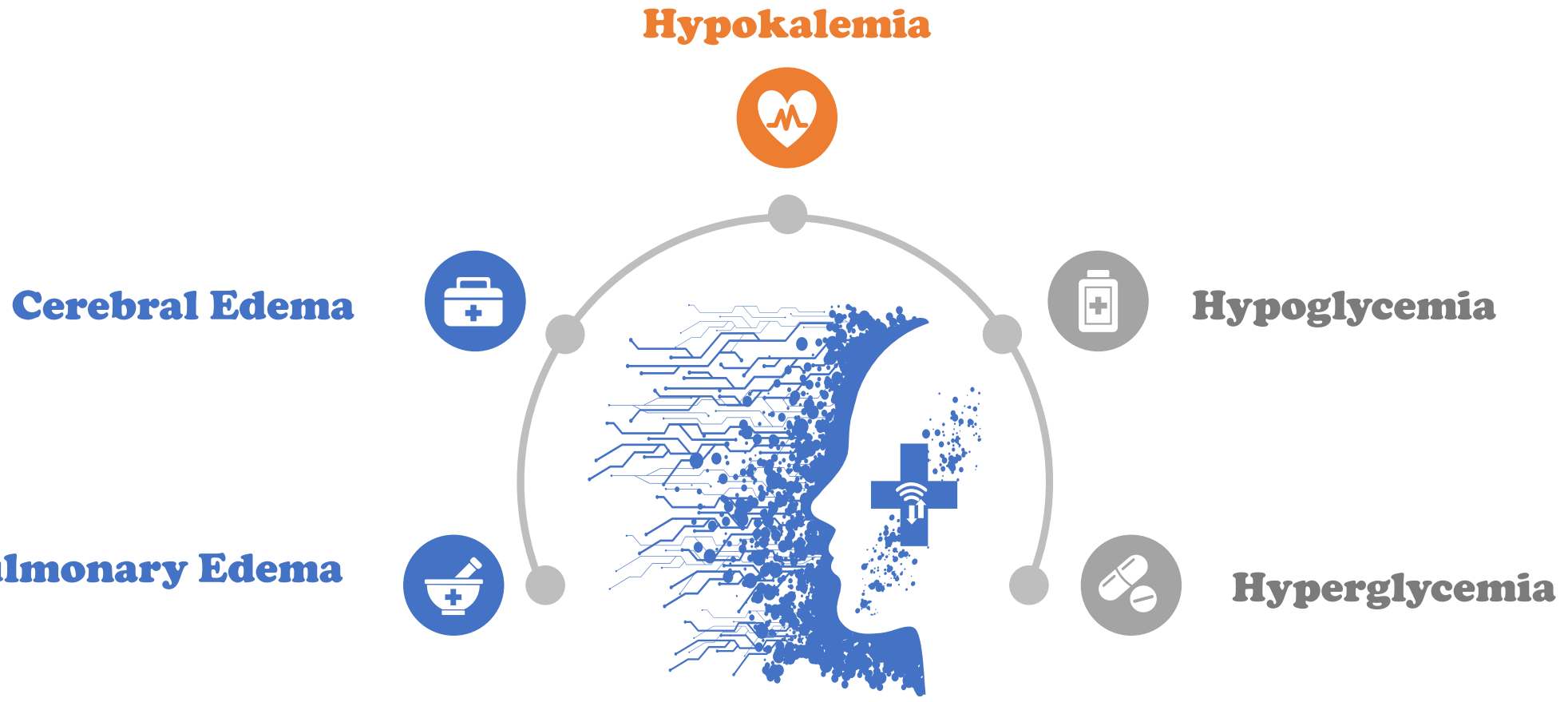
2. Kitabchi AE, et al. *Diabetes Care*. 2009.

BICARBONATE THERAPY



2. Kitabchi AE, et al. *Diabetes Care*. 2009.

AVOID TREATMENT COMPLICATIONS



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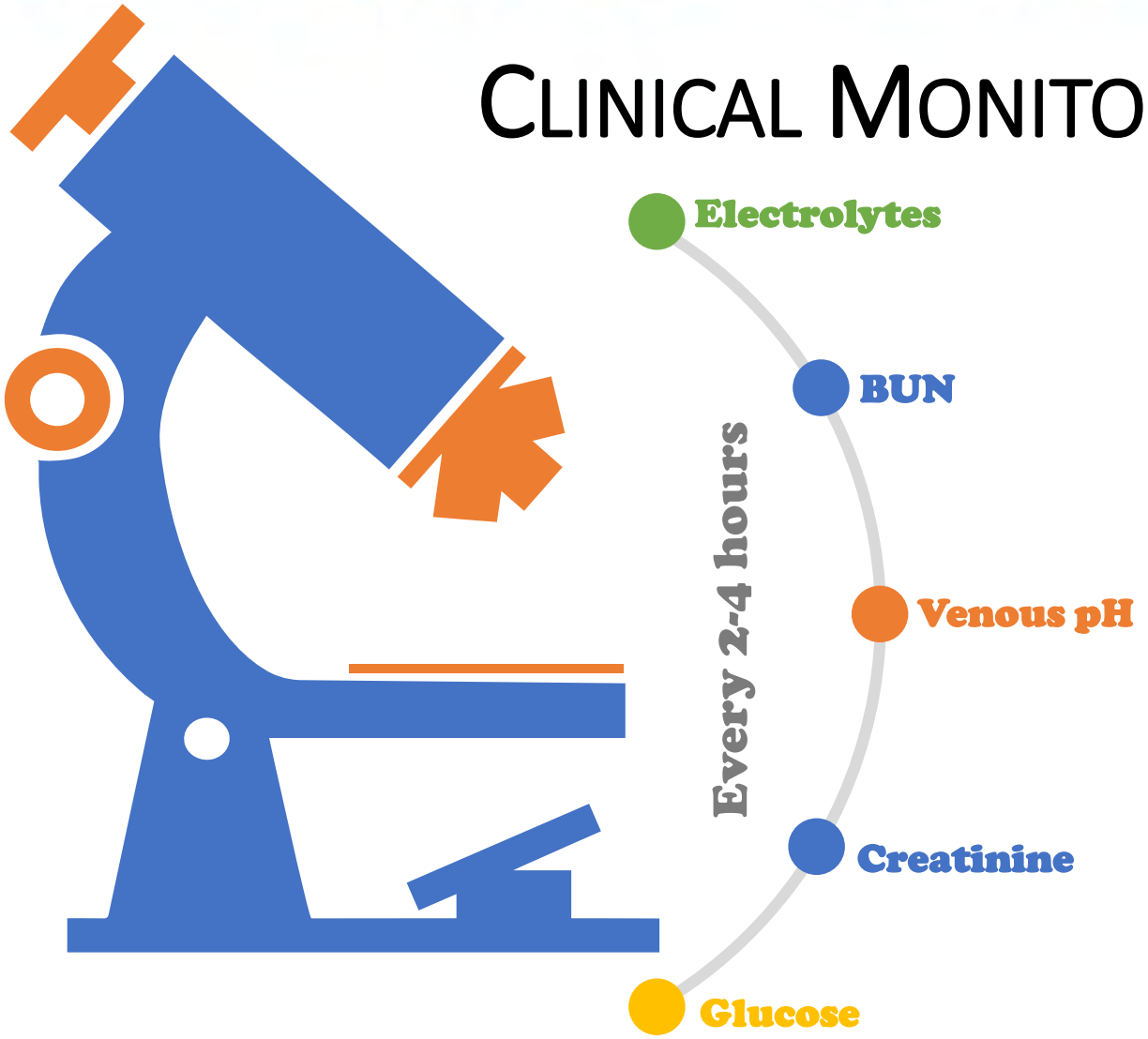
CLINICAL MONITORING



2. Kitabchi AE, et al. *Diabetes Care*. 2009.

DKA Resolution

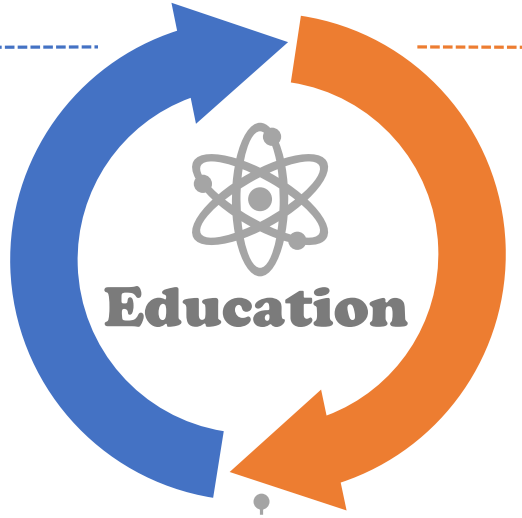
- Resolution of DKA
  - Blood glucose 200 mg/dL with two of the following criteria:
    - Serum bicarbonate level 15 mEq/L
    - Venous pH 7.3
    - Calculated anion gap 12 mEq/L
- Once the patient is tolerating oral nutrition and the precipitating factor is corrected, initiate a subcutaneous insulin regimen
  - Insulin naïve patients: 0.5-0.8 unit/kg/day

2. Kitabchi AE, et al. *Diabetes Care*. 2009.

PREVENTION

Patients

Family and Caregivers



Early healthcare provider contact

Sick Day Management

Self-Monitoring of blood glucose and vitals

2. Kitabchi AE, et al. *Diabetes Care*. 2009

PREVENTION & AWARENESS

Euglycemic Diabetic Ketoacidosis

EUGLYCEMIC DIABETIC KETOACIDOSIS

- Euglycemic Diabetic Ketoacidosis is a form of diabetic ketoacidosis with milder degrees of hyperglycemia (<200 mg/dL)
- Euglycemic DKA may be easily missed solely basing symptoms on classic manifestations of DKA (ie. dehydration induced by hyperglycemia may not be present)
  - Polyuria and polydipsia can be less prominent
- May present with malaise, anorexia, tachycardia, tachypnea, (+/-) fever

4. Barski L, et al. *European Journal of Internal Medicine*. 2019.

5. Peters AL, et al. *Diabetes Care*. 2015.

POTENTIAL CAUSES OF EUGLYCEMIC DKA

- **SGLT-2 inhibitors**
- Decreased caloric intake
- Pregnancy
- Glycogen storage diseases and chronic liver diseases
- Acute pancreatitis
- Heavy alcohol use
- Cocaine intoxication

5. Peters AL, et al. *Diabetes Care*. 2015.

VISION OBSCURED BY SGLT2 INHIBITORS

SGLT2-INHIBITORS: EUGLYCEMIC DKA

- Euglycemic DKA (plasma glucose <250 mg/dL) has been reported in patients with type 2 diabetes taking SGLT2 inhibitors
- FDA issued a Drug Safety Communication in May 2015 warning about the risk of ketoacidosis with SGLT2 inhibitors
- Absence of substantial hyperglycemia delays recognition of the problem by patients and clinicians

5. Peters AL, et al. *Diabetes Care*. 2015.

6. Palmer BF, et al. J Diabetes Complications. 2016.

7. Fralick M, et al. N Engl J Med. 2017.

SGLT-2 INHIBITOR MECHANISM: KETONE PRODUCTION

- SGLT2 inhibitors lower blood glucose levels by increasing urinary glucose excretion
  - Reduces insulin secretion from pancreatic β-cells
    - Decline in circulating insulin levels results can lower antilipolytic activity
  - Increase free fatty acids can be converted to ketone bodies by β-oxidation in the liver
  - Simulate secretion of glucagon which can promote the transportation of fatty acids to the liver leading to the production of ketone bodies

8. Ogawa W et al. J Diabetes Investig. 2016.

SGLT2-INHIBITORS: EUGLYCEMIC DKA RISK

- Decreased caloric intake is frequently associated with the development of DKA
  - Can be due to nausea and vomiting due to illness or ketoacidosis
- Prolonged fasting can cause glycogen depletion which can contribute to normal glucose levels, while still worsening metabolic acidosis
  - Fasting state can accelerate lipolysis and free fatty acid production is accelerated
- Reduction in insulin secretion and administration lower the effectiveness of lipolysis and ketogenesis suppression

6. Palmer BF, et al. J Diabetes Complications. 2016.

7. Fralick M, et al. N Engl J Med. 2017.

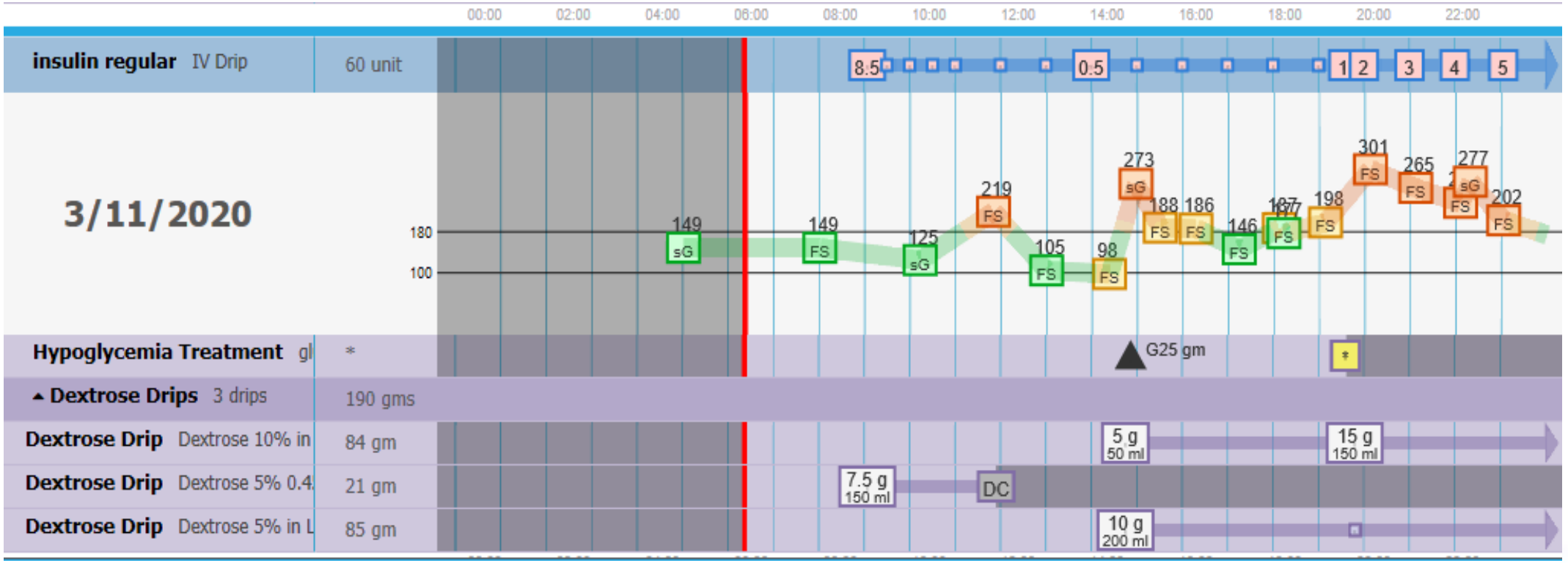
PATIENT CASE: EU DKA

- JS is a 29-year-old male who presented to the ED on 3/11/20 with a chief complaint of ***abdominal pain*** and ***oral intolerance due to nausea and vomiting*** for two days. He reported that his home blood glucose levels have been elevated around the ***400-500 range***, in which he tried to decrease with water and a ***healthier diet***. Upon presentation he endorses shortness of breath, weakness, body aches, dizziness, anorexia, ***polydipsia, polyuria***, nausea, vomiting, chest pain.

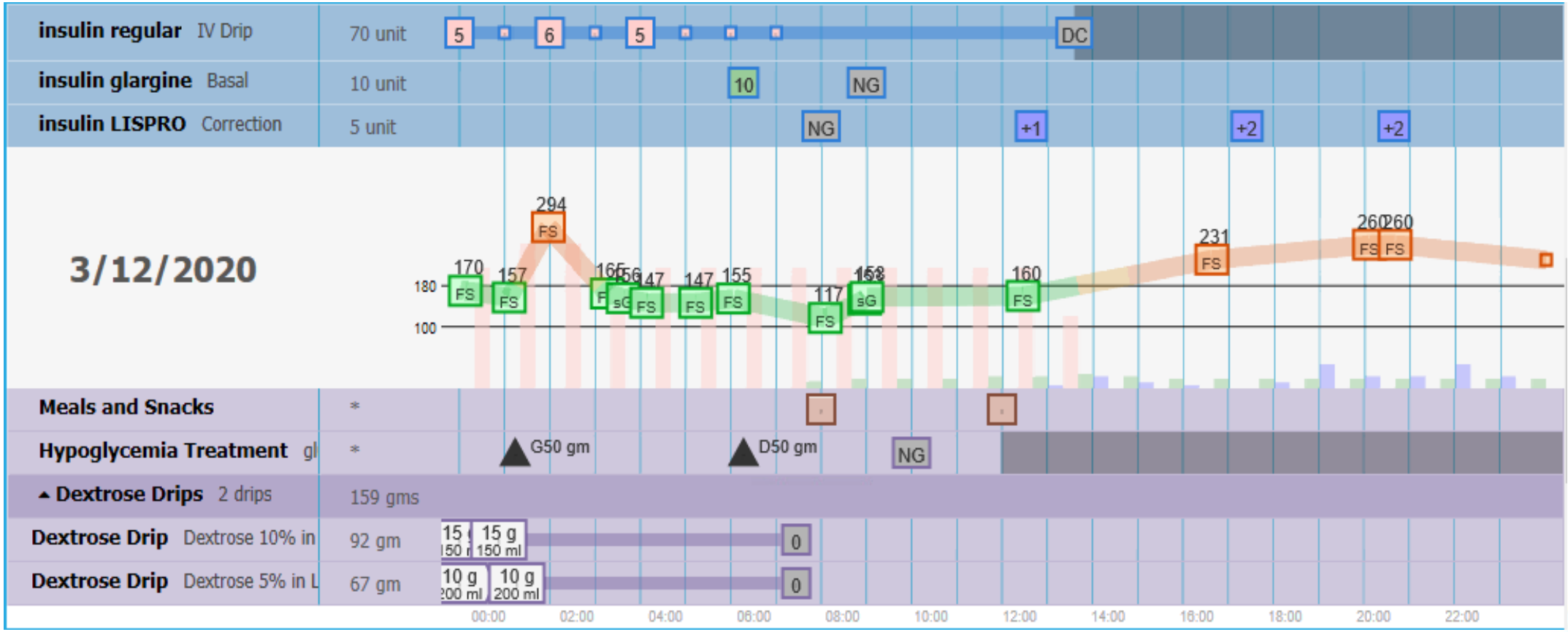
PATIENT CASE: EU DKA

- PMH: Type II Diabetes at the age of 22 with an HgA1c 13.
- Home Medications: Janumet 50/1000 mg PO BID, ***empagliflozin 10 mg po qAM***
- ED Labs: Afebrile, VSS, ***BG 149***, ***bicarb 10, anion gap 22, 3-beta-hydroxybutyrate 7.68***
- ED Medications: Insulin drip, D5 with 0.45% Normal Saline with potassium.
- Admitted to the ICU.

PATIENT CASE: GLYCEMIC CARE



EU DKA Glycemic Care in the ICU



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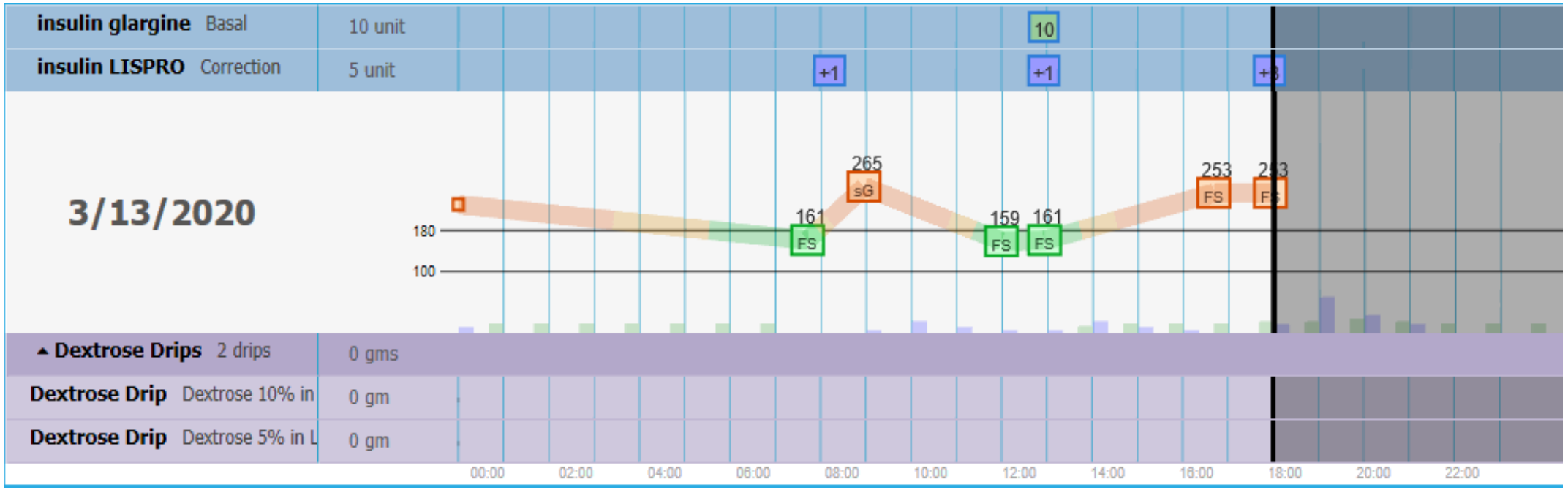

EUGLYCEMIC DKA TREATMENT

- Patients with euglycemic DKA need immediate medical attention and treatment
- Treatment is based on the severity of dehydration, electrolyte abnormalities and acidosis
- Euglycemic DKA can be clinically considered and treatment protocols should allow for higher concentration of intravenous dextrose solution to facilitate insulin infusion
  - Omission of a bolus dose of insulin should be consider

EUGLYCEMIC DKA PREVENTION

- Ensure appropriate utilization of SGLT-2 inhibitors
- Consider holding SGLT-2 inhibitors during acute illness, major surgery, dehydration, poor nutrition, and excessive alcohol intake
  - Hold SGLT2 approximately 3 days prior to major surgery

- 4. Barski L, et al. *European Journal of Internal Medicine*. 2019.

CONCLUSION

- DKA can be a life-threating complication of diabetes and requires a multi-disciplinary approach with proper comprehension of fluid, electrolyte, and acidemia management
- DKA recognition can be obscured in the setting of euglycemia
  - Clarity can be facilitated through conscious attention of precepting factors for euglycemia
    - Awareness of precipitation factors hasten the clinical recognition of euglycemic DKA which will allow practitioners to augment their treatment

POST-TEST QUESTIONS

1. Which therapeutic interventions should be considered in the setting of DKA? Select all that apply.

A. Insulin B. Potassium C. Intravenous fluid D. Sodium bicarbonate

2. Which clinical parameter allows for intravenous insulin transition to subcutaneous?

A. Serum bicarbonate level 10 mEq/L B. Venous pH 7.1

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Reference List

1. American Diabetes Association. Diabetes care in the hospital: Standards of Medical Care in Diabetesd2020. Diabetes Care 2020;43 (Suppl.1):S193-S202.
2. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic Crises in Adult Patients With Diabetes. Diabetes Care 2009;32(7):1335.
3. Moghissi ES, Korytkowski MT, DiNardo M, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Care 2009; 32(6): 1119-1131.
4. Barski L, Eshkoli T, Brandstaetter E, Jotkowitz A. Euglycemic diabetic ketoacidosis. European Journal of Internal Medicine 2019; 63:9-14.

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5. Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium-Glucose Cotransporter 2 Inhibition. Diabetes Care. 2015;38(9):1687-93.

6. Palmer BF, Clegg DJ, Taylor SI, Weir MR. Diabetic ketoacidosis, sodium glucose transporter-2 inhibitors and the kidney. J Diabetes Complications. 2016;30(6):1162.

7. Fralick M, Schneeweiss S, Patorno E. Risk of Diabetic Ketoacidosis after Initiation of an SGLT2 Inhibitor. N Engl J Med. 2017;376(23):2300-2.

8. Ogawa W, Sakaguchi K. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors. J Diabetes Investig. 2016;7(2):135-8.

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