Management of Diabetes Ketoacidosis and Hyperglycemic Hyperosmolar Syndrome

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Outline

Definitions

Pathophysiology

Diagnosis

Management

Definitions

- **Diabetic Ketoacidosis (DKA)**
  - Diagnosis of DM based on ALIVE criteria
  - Metabolic acidosis
  - Ketonemia
- **Hyperglycemia Hyperosmolar Syndrome (HHS)**
  - Severe hyperglycemia
  - Hyperosmolality
  - Minimal to absent ketosis

Niessen SJM, et al. *Vet J*. 2022.

Definitions

- **Mixed DKA/HHS**
  - Severe hyperglycemia + Hyperosmolality
  - Evidence of ketosis

Pathophysiology

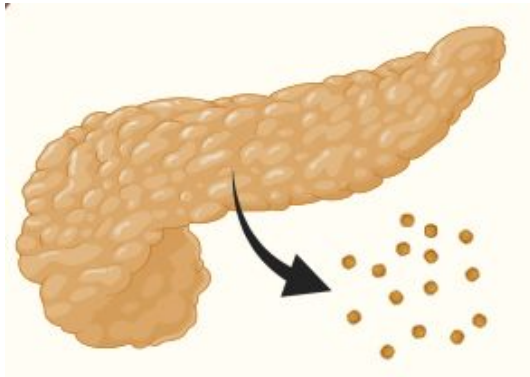
- Persistent deficiency or absence of insulin activity in the body

Absolute or relative insulin insufficiency

Increase in counterregulatory hormones

Pathophysiology

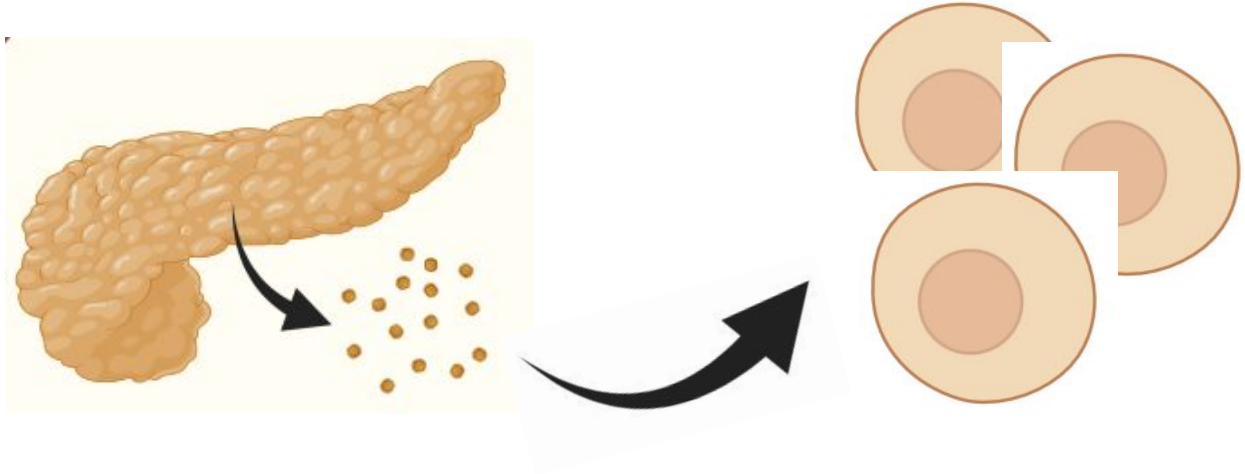
Normal condition



Insulin secreted from pancreas

Pathophysiology

Normal condition

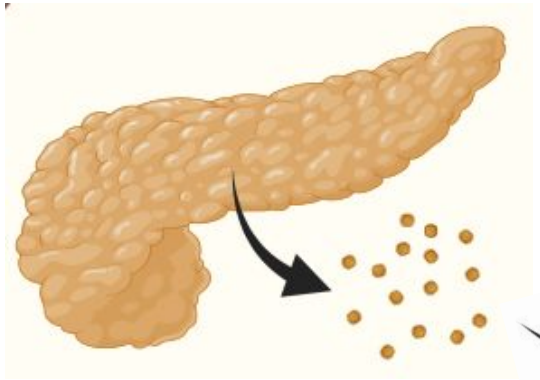


Insulin secreted from pancreas

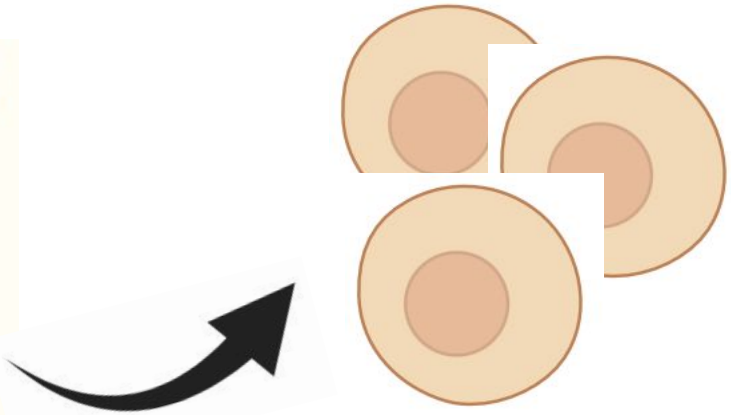
Glucose transported into the cells

Pathophysiology

Normal condition



Insulin secreted from pancreas



Glucose transported into the cells

Glycolysis

↓

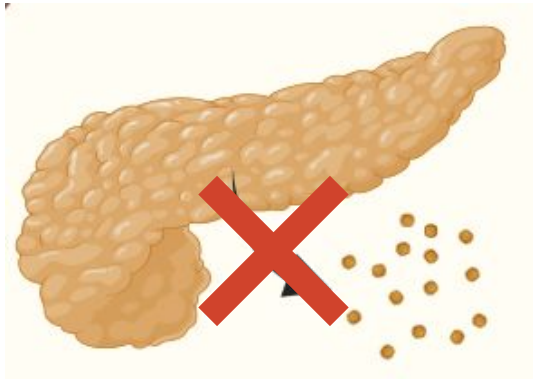
TCA cycle

↓

Oxidative phosphorylation

Pathophysiology

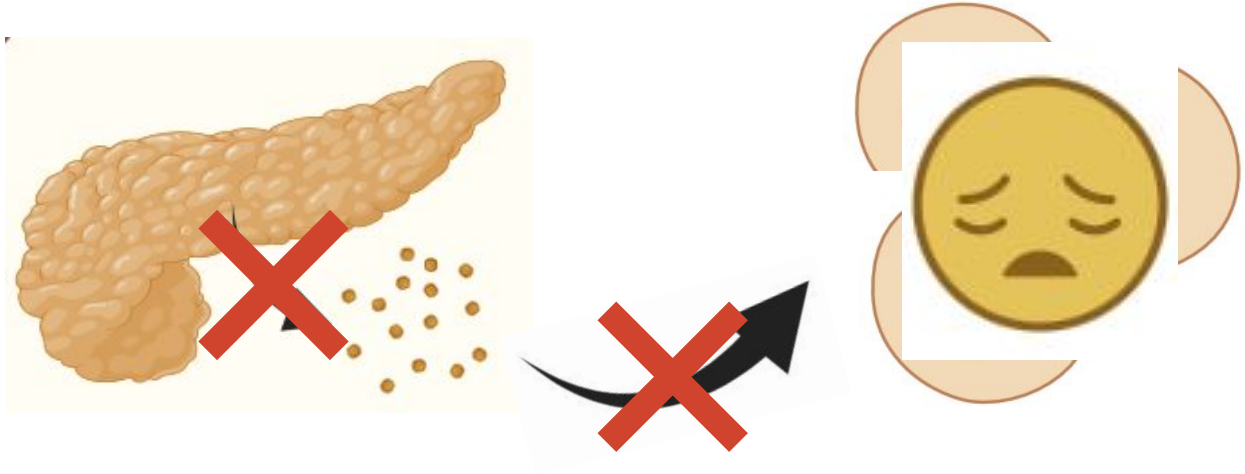
Diabetes mellitus



Insulin secreted from pancreas

Pathophysiology

Diabetes mellitus

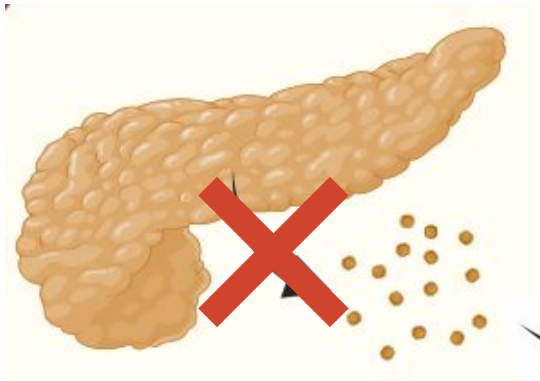


Insulin secreted from pancreas

Cell starvation

Pathophysiology

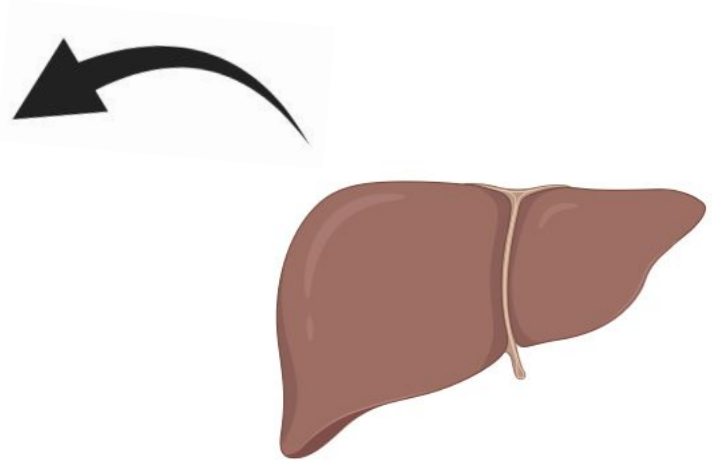
Diabetes mellitus



Insulin secreted from pancreas

Cell starvation

Ketone bodies



Hepatic ketogenesis

Ketone Bodies

- Acetoacetate
- β-hydroxybutyrate
- Acetone

Both ketone bodies and [H^+] ions produced during hepatic ketogenesis can cause metabolic acidosis.

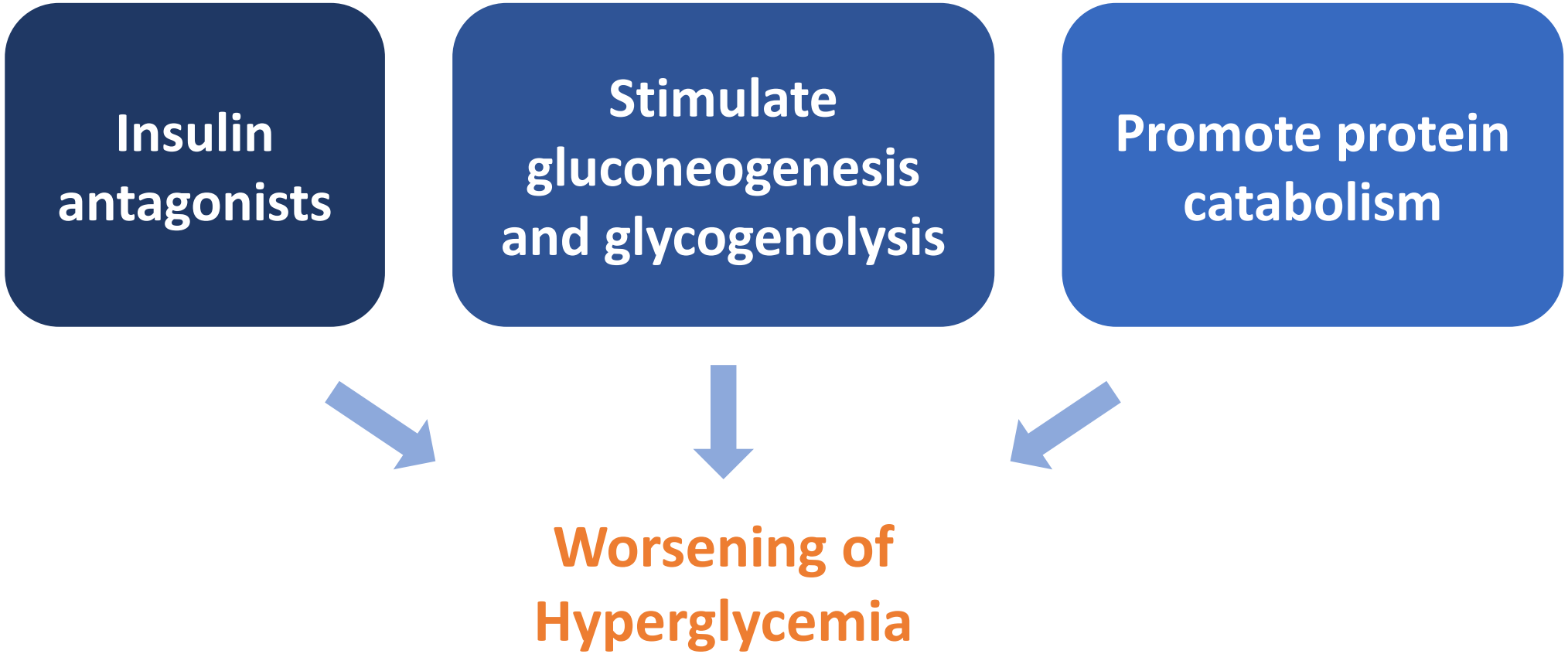
Counterregulatory Hormones

- Typically increases in response to stress and illness
  - Glucagon
  - Catecholamines
  - Cortisol
  - Growth hormone

Counterregulatory Hormones

- Insulin antagonists
- Stimulate gluconeogenesis and glycogenolysis
- Promote protein catabolism

Counterregulatory Hormones



Concurrent Diseases

- Pancreatitis
- Urinary tract infection
- Neoplasia
- Hyperadrenocorticism

- Pancreatitis
- Chronic enteropathies
- Infection
- Neoplasia

Pathophysiology of HHS

- Similar to DKA
- Small amounts of circulating insulin are present

  → inhibiting ketogenesis

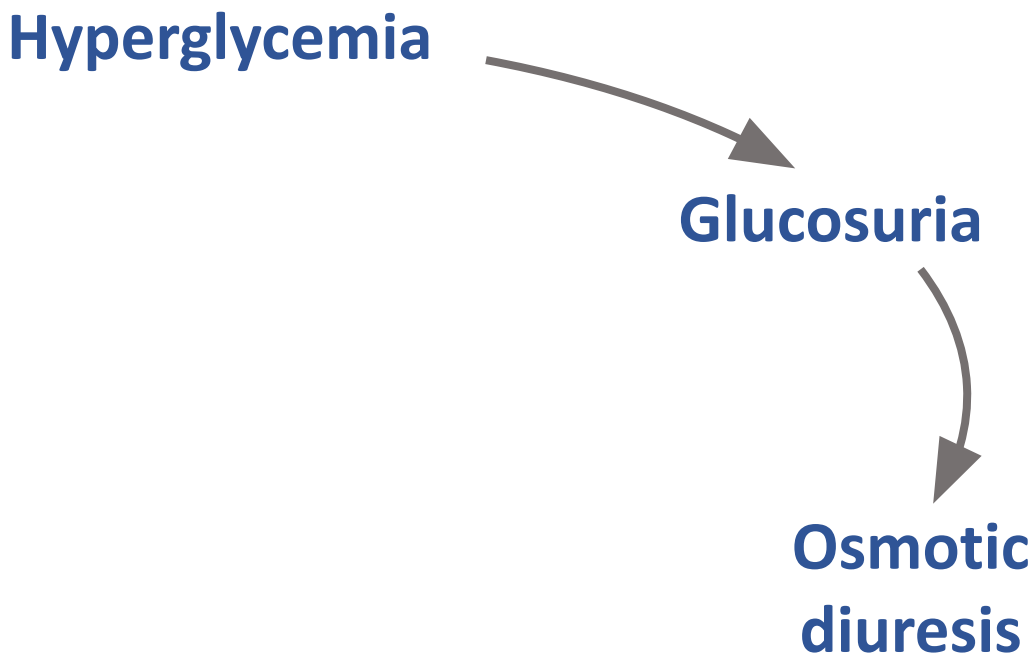
  → minimal to absent ketone body formation

Pathophysiology of HHS

Hyperglycemia

Pathophysiology of HHS

Pathophysiology of HHS



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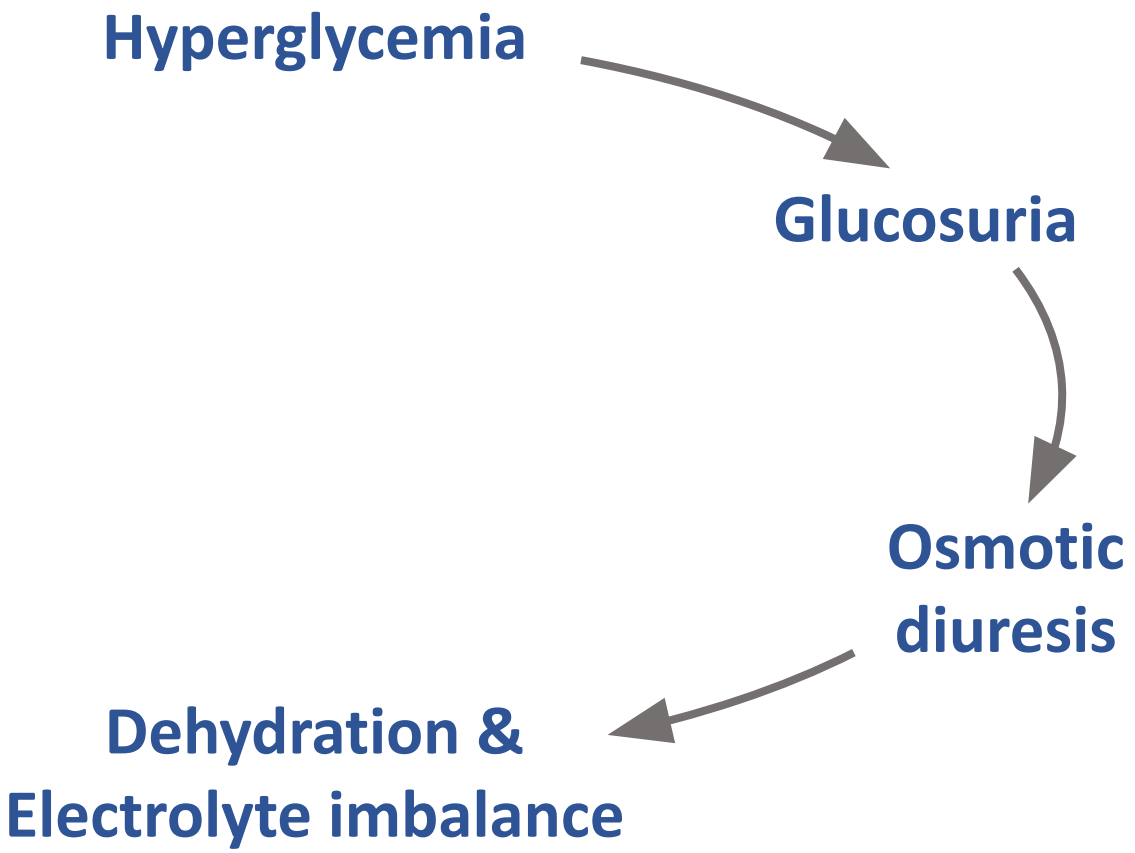

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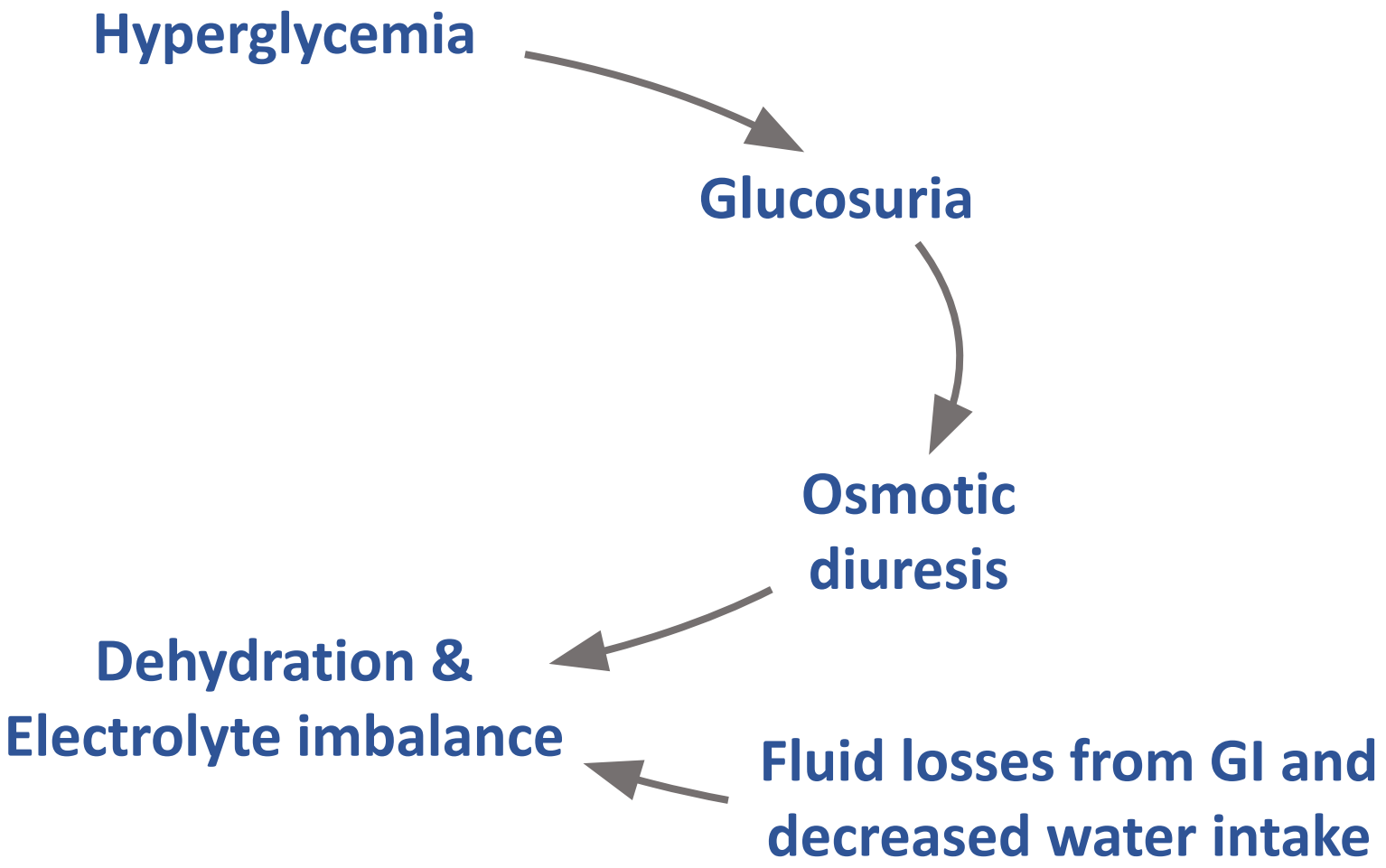

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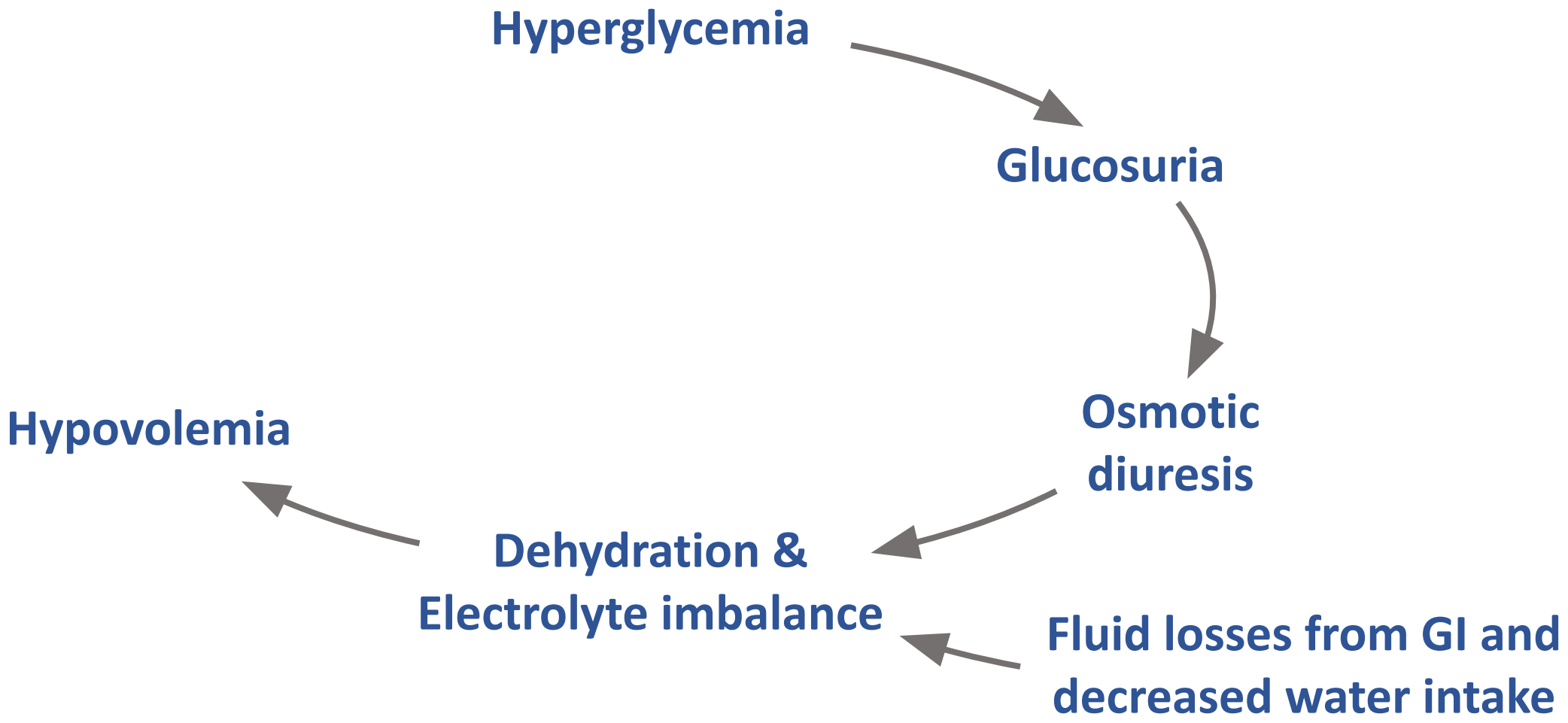

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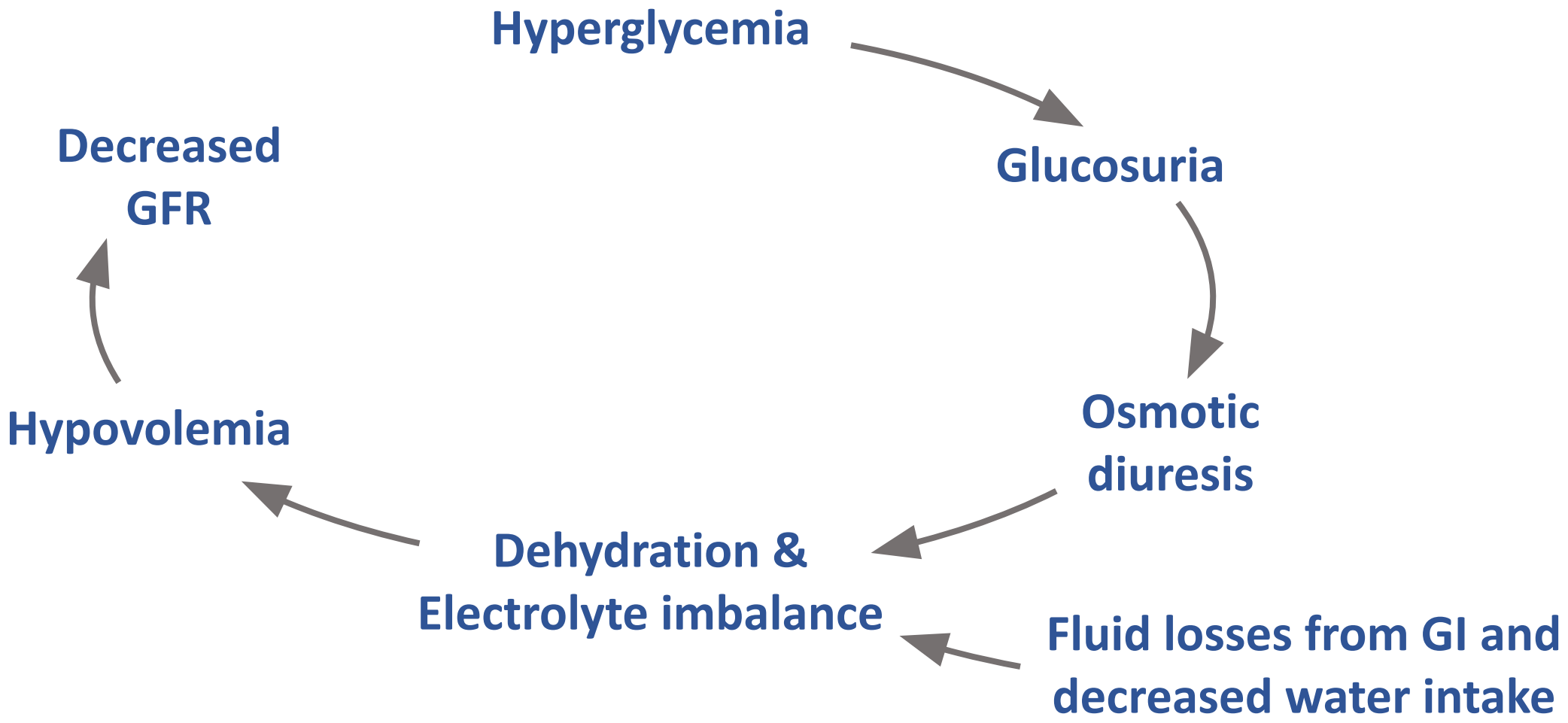

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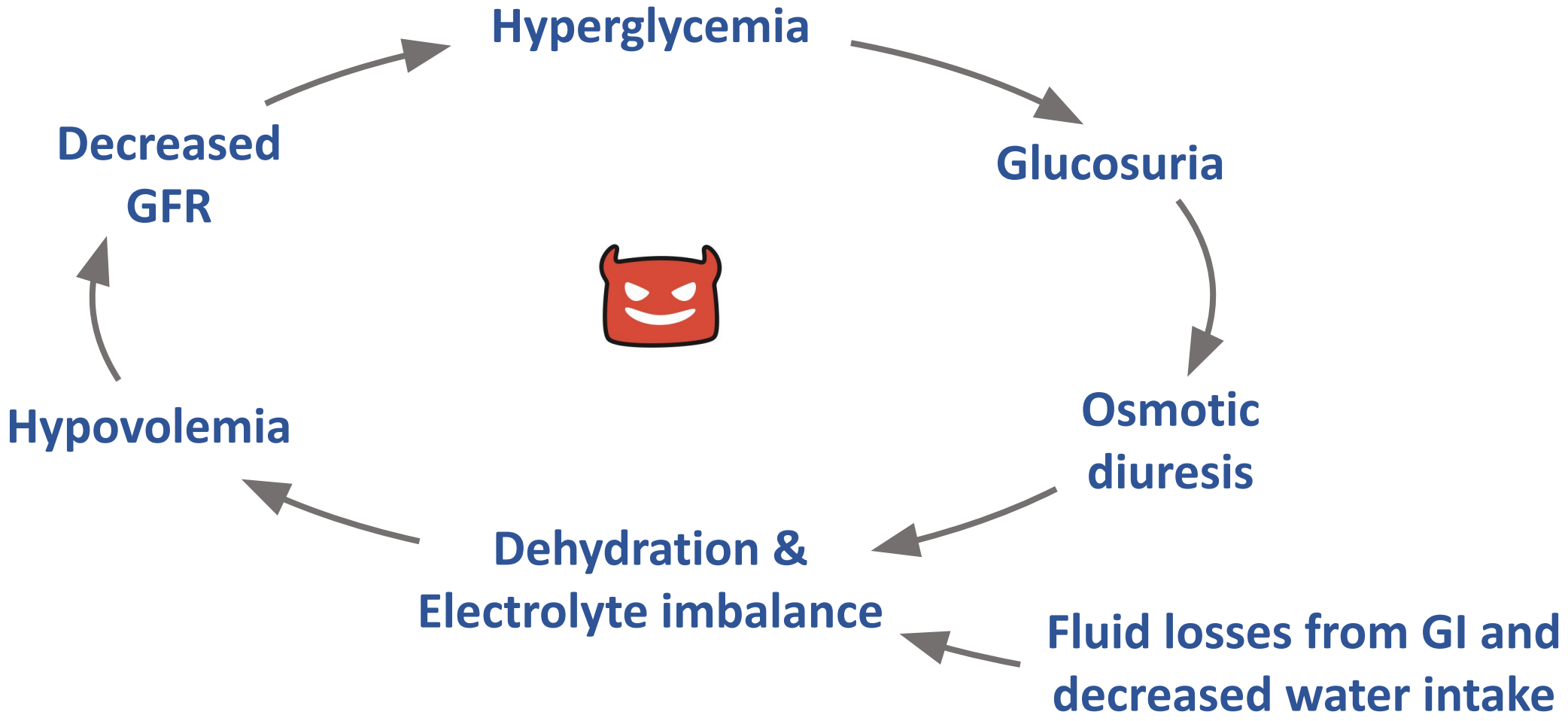


Diagnosis of DKA

- History
- Physical exam
- Laboratory work
  - Confirmed DM (ALIVE criteria)
  - Metabolic acidosis (venous or arterial pH <7.35 + decreased [HCO_3^-])
  - Ketonemia

ALIVE Criteria

- **Dogs**
  - Random (fasted or unfasted) **blood glucose ≥ 11.1 mmol/L (200 mg/dL)**
    + clinical signs of hyperglycemia or hyperglycemic crisis

Niessen SJM, et al. *Vet J.* 2022.

ALIVE Criteria

- **Dogs**
  - Random (fasted or unfasted) **blood glucose ≥ 11.1 mmol/L (200 mg/dL)** + clinical signs of hyperglycemia or hyperglycemic crisis
- **Cats**
  - Random (fasted or unfasted) **blood glucose ≥ 15 mmol/L (270 mg/dL)** + clinical signs of hyperglycemia or hyperglycemic crisis + at least one of the following criteria:

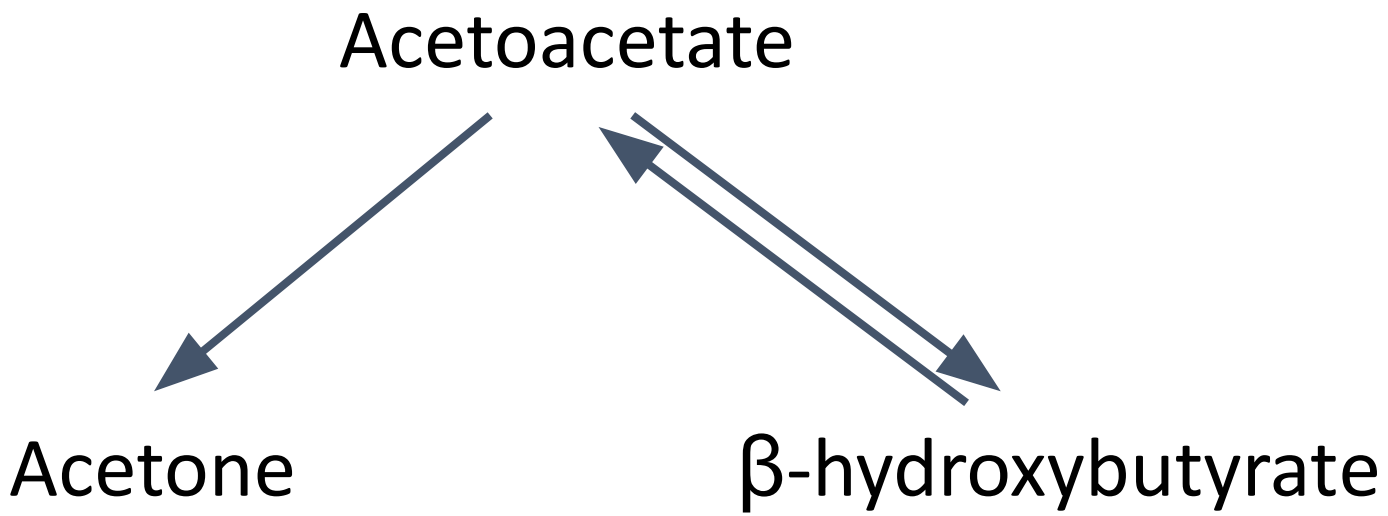
Niessen SJM, et al. *Vet J*. 2022.

ALIVE Criteria

- **Dogs**
  - Random (fasted or unfasted) **blood glucose ≥ 11.1 mmol/L (200 mg/dL)** + clinical signs of hyperglycemia or hyperglycemic crisis
- **Cats**
  - Random (fasted or unfasted) **blood glucose ≥ 15 mmol/L (270 mg/dL)** + clinical signs of hyperglycemia or hyperglycemic crisis + at least one of the following criteria:
    - Increased glycated proteins
    - Glucosuria on > 1 occasion (naturally voided sample acquired at home at least 2 days after any stressful events)

Niessen SJM, et al. *Vet J*. 2022.

Detection of Ketone Bodies



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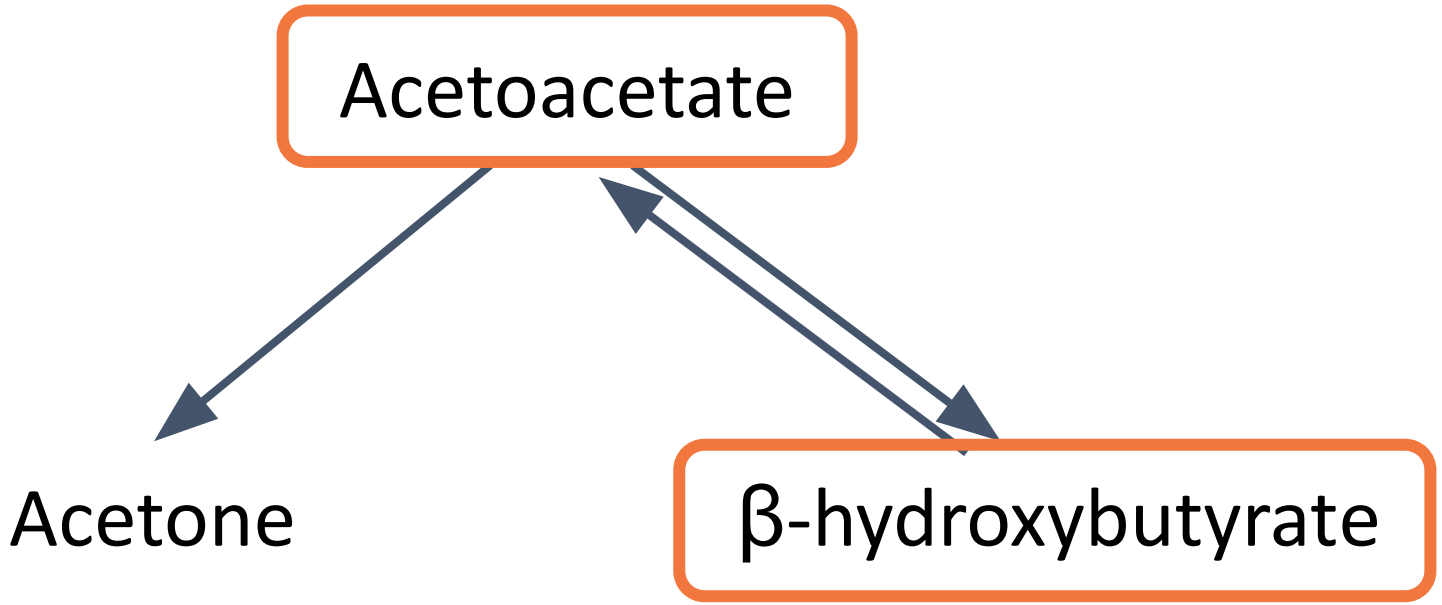

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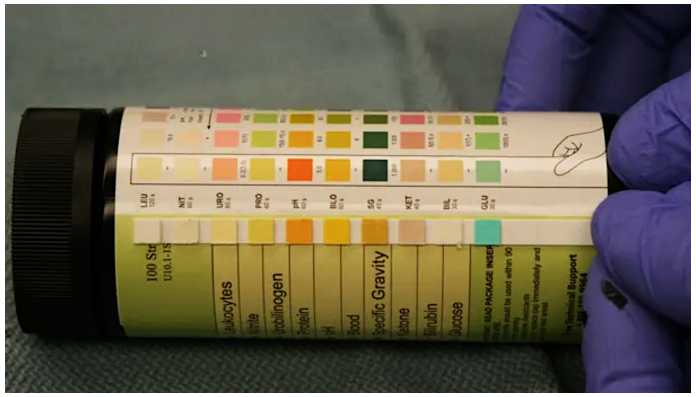


Urine dipsticks

- Mainly detect **acetoacetate**
- Using plasma/serum samples increases sensitivity & specificity

Blood ketone meter

- Mainly detect **β-hydroxybutyrate**
- Considered overall more sensitive than urine dipsticks

Ryan K. Clinician's Brief. 2015.

Blood Ketones

Dog

- Normal: 0.02 – 0.15 mmol/L
- Diagnostic for DKA: >3.8 mmol/L

Cat

- Normal: 0 – 0.1 mmol/L
- Diagnostic for DKA: >2.5 mmol/L

Diagnosis of HHS

- **Severe hyperglycemia**
  - > 600 mg/dL [33.3 mmol/L]
- **Hyperosmolality**
  - Dog: serum osmolality > 325 mOsm/kg
  - Cat: > 350 mOsm/kg
- **Minimal to absent ketosis**

Diagnosis of HHS

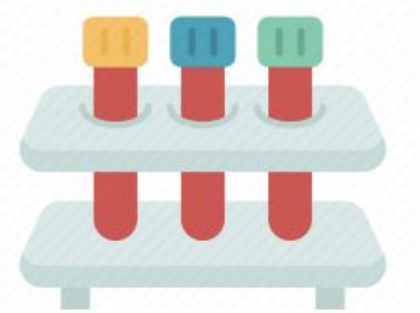
- How to determine serum osmolality
  - Measured
  - Calculated

$$\textbf{Calculated Osmolality (mOsm/kg)}$$

$$= 2\times[Na^{+}(\textbf{mEq/L})] + \left[\frac{\textbf{Blood glucose(mg/dL)}}{18}\right] + \left[\frac{\textbf{BUN(mg/dL)}}{2.8}\right]$$

Other Diagnostic Tests

- Complete blood count
- Serum biochemistry
- Urinalysis
- Urine culture
- Thoracic radiographs
- Abdominal imaging



Management of DKA

Restoring volume deficits and addressing dehydration

Correcting electrolyte and acid-base imbalances

Administering insulin therapy

Treating underlying or concurrent diseases

Fluid Therapy

- Fluid resuscitation for hypovolemia
- Tailored fluid therapy for rehydration, maintenance requirements, and ongoing losses
- Regular reassessment and readjustment is crucial!

Choice of Fluids

Balanced crystalloid solutions (e.g., Lactated Ringer's solution, Normosol-R, Plasma-Lyte 148)

vs

Isotonic saline (i.e., 0.9% NaCl)

Self WH, et al. *JAMA Netw Open*. 2020.
Catahay JA, et al. *Heart Lung*. 2022.

Choice of Fluids

Balanced crystalloid solutions (e.g., Lactated Ringer's solution, Normosol-R, Plasma-Lyte 148)

vs

Isotonic saline (i.e., 0.9% NaCl)

Balanced crystalloid solutions led to faster DKA resolution compared to isotonic saline

Self WH, et al. *JAMA Netw Open*. 2020.
Catahay JA, et al. *Heart Lung*. 2022.

Electrolyte Abnormalities

- Sodium – often hyponatremic
  - Dilutional effect of hyperglycemia
  - Hypovolemia-induced antidiuretic hormone release
  - Glucosuria-induced osmotic diuresis (leads to hypernatremia)
  - GI fluid losses

Electrolyte Abnormalities

- Corrected sodium
  - Estimates the sodium level once hyperglycemia resolves
  - Assesses potential hypotonic fluid losses from osmotic diuresis
    - Elevated corrected sodium level → excessive hypotonic fluid losses

$$\textbf{Corrected Sodium (mEq/L)} = \textbf{Measured Sodium } (mEq/L) + 1.6 \times \left[\frac{\textbf{Measured blood glucose(mg/dL)} - 100}{100}\right]$$

Ing TS, et al. Front Med. 2022.

Electrolyte Abnormalities

- Corrected sodium
  - Levels may fluctuate after initiating treatment
  - Frequent recalculations help detect significant changes
  - If corrected sodium is elevated, when to treat?

Ing TS, et al. Front Med. 2022.

Electrolyte Abnormalities

- Potassium & Phosphorus – total body depletion is expected
  - Increased renal excretion
  - GI losses
  - Extracellular shift in exchange of [H^+] (mainly potassium)
  - Activation of renin-angiotensin-aldosterone system (RAAS) (mainly potassium)

Electrolyte Abnormalities

- Potassium supplementation
  - CRI based on the published sliding scale
  - Should not exceed 0.5 mEq/kg/hr
- Phosphorus supplementation
  - 0.03 to 0.12 mmol/kg/hr

Electrolyte Abnormalities

- Magnesium – usually low due to urinary loss
- Clinical signs
  - Refractory hypokalemia
  - Hypotension
  - Neurological signs (e.g., seizures), weakness
  - Arrhythmias

Electrolyte Abnormalities

- Diagnosis of Hypomagnesemia
  - Low total serum magnesium + known risk for deficiency
  - Low ionized magnesium (more accurate)
    - Dog 0.43 – 0.6 mmol/L
    - Cat 0.43 – 0.7 mmol/L
- CRI: 0.25–1 mEq/kg/day

Insulin Therapy

- **Timing**
  - Delay insulin therapy until full rehydration is NOT recommended
  - Stabilize and treat marked hypovolemia, severe hypokalemia, or hypophosphatemia before initiating insulin therapy
  - Human: initiate 1 hour after starting fluid therapy
  - Small animals: initiate within 6 hours of starting fluid therapy

Glaser N, et al. *Pediatr Diabetes*. 2022.
DiFazio J, Fletcher DJ. *J Vet Emerg Crit Care (San Antonio)*. 2016.

Insulin Therapy

- **Insulin regimens**
  - Insulin CRI protocol
    - Regular insulin (dog & cat)
    - Lispro insulin (cat)
  - IM/SC Glargine protocol (cat)
  - Regular insulin IM protocol
  - Lispro insulin IM protocol (dog)

Gal A, Odunayo A. *Vet Clin North Am Small Anim Pract*. 2023.
Zeugswetter FK, et al. *J Vet Emerg Crit Care (San Antonio)*. 2021.
Malerba E, et al. *Front Vet Sci*. 2020.
Malerba E, et al. *J Feline Med Surg*. 2019.
Malerba E. Chapter 290. In: *Ettinger's Textbook of Veterinary Internal Medicine. 9th* ed. Elsevier; Year:2024.

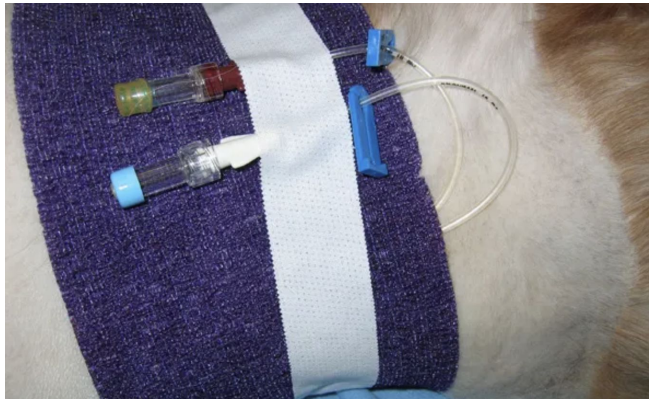
Treatment for Concurrent Diseases & Supportive Care

- Broad-spectrum antibiotics (if indicated)
- GI support (e.g. anti-emetics, prokinetics)
- Nutritional support
- Pain management

Monitoring

- Frequent blood sampling is often required
  - Utilize central or peripheral sampling lines when possible
- Be vigilant for iatrogenic anemia

Lab parameter	Frequency (hrs)
Blood glucose	2 – 4
Venous blood gas	4 – 6
Phosphorus	4 – 6
Corrected sodium	4 – 6



Beal MW. Clinician's Brief. 2005.

Continuous Glucose Monitoring Systems (CGMS)

- Measures interstitial glucose levels
  - Skin thickness and hydration status can influence readings
- Less accurate when BG < 90 mg/dL (5 mmol/L)
- Requires regular calibration
- Verify with blood glucose if clinical signs do not fit with readings

Transition to Long-acting Insulin

Criteria

- ☑ Ketosis and acidemia are resolved
- ☑ Hydration status is adequate
- ☑ Serum electrolytes are normalized
- ☑ Consistent appetite without GI signs

Management of HHS

Prompt but cautious fluid resuscitation

Correct electrolyte imbalances

Normalize serum osmolality

Insulin can wait!

Management of HHS

Blood glucose ↓

Serum osmolality ↓

Sodium ↑

Management of HHS

Blood glucose ↓

Serum osmolality ↓

Sodium ↑

Osmotic diuresis also contributes to elevation of [Na^+]

Management of HHS

Blood glucose ↓ → Serum osmolality ↓ → Sodium ↑

Osmotic diuresis also contributes to elevation of $[Na^+]$

$$\textbf{Corrected Sodium (mEq/L)} = \textbf{Measured Sodium } (mEq/L) + 1.6 \times \left[\frac{\textbf{Measured blood glucose(mg/dL)} - 100}{100}\right]$$

Management of HHS

Safe BG reduction rate: ≤ 50 mg/dL per hour (2.8 mmol/L/hour)

Safe serum osmolality reduction: 3 – 8 mOsm/kg/h

Safe sodium elevation rate: ≤ 10 mmol/L per 24 hours

Management of HHS

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- Fluid resuscitation to treat hypovolemia
  - Isotonic crystalloid

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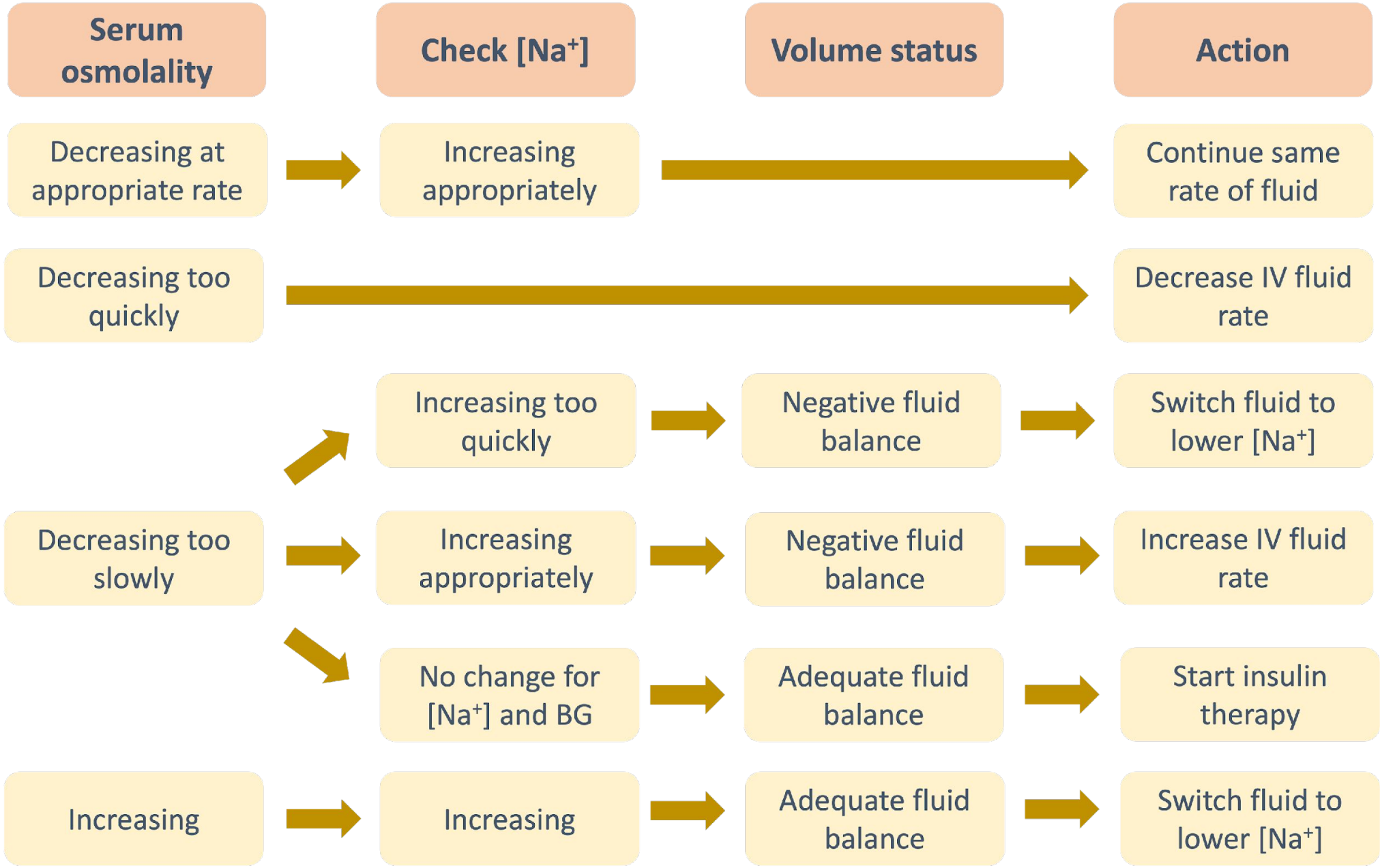
  - Isotonic crystalloid
- Recheck BG, venous blood gas, corrected [Na^+], serum osmolality

Management of HHS

- Fluid resuscitation to treat hypovolemia
  - Isotonic crystalloid
- Recheck BG, venous blood gas, corrected [Na^+], serum osmolality
- Correct dehydration over 24-48 hours
  - Isotonic crystalloid with [Na^+] close to patient's [Na^+]
  - Human: 0.9% NaCl as initial fluid

Management of HHS

- Fluid resuscitation to treat hypovolemia
  - Isotonic crystalloid
- Recheck BG, venous blood gas, corrected [Na^+], serum osmolality
- Correct dehydration over 24-48 hours
  - Isotonic crystalloid with [Na^+] close to patient's [Na^+]
  - Human: 0.9% NaCl as initial fluid
- Recheck BG, venous blood gas, corrected [Na^+], serum osmolality every 1-2 hours
  - Supply potassium or phosphorus if indicated


Serum osmolality
Check [Na+]
Volume status
Action
Decreasing at appropriate rate
Increasing appropriately
Continue same rate of fluid
Decreasing too quickly
Decrease IV fluid rate
Increasing too quickly
Negative fluid balance
Switch fluid to lower [Na+]
Decreasing too slowly
Increasing appropriately
Negative fluid balance
Increase IV fluid rate
No change for [Na+] and BG
Adequate fluid balance
Start insulin therapy
Increasing
Increasing
Adequate fluid balance
Switch fluid to lower [Na+]

Mixed DKA/HHS

- Insulin therapy may need to be initiated earlier than typical HHS
  - After fluid resuscitation but but before full correction of the dehydration deficit
- Starting insulin therapy at lower rate
- Closely monitor BG, venous blood gas, phosphorus, corrected [Na^+] and serum osmolality

Take Home Messages

- Pathophysiology of DKA and HHS
- Diagnostic criteria of DKA and HHS
- Utilization of corrected sodium in clinical assessment
- Appropriate insulin therapy strategies
- Intensive patient monitoring plan

Thank you!

Ketone Bodies

- Acetoacetate
- β-hydroxybutyrate
- Acetone

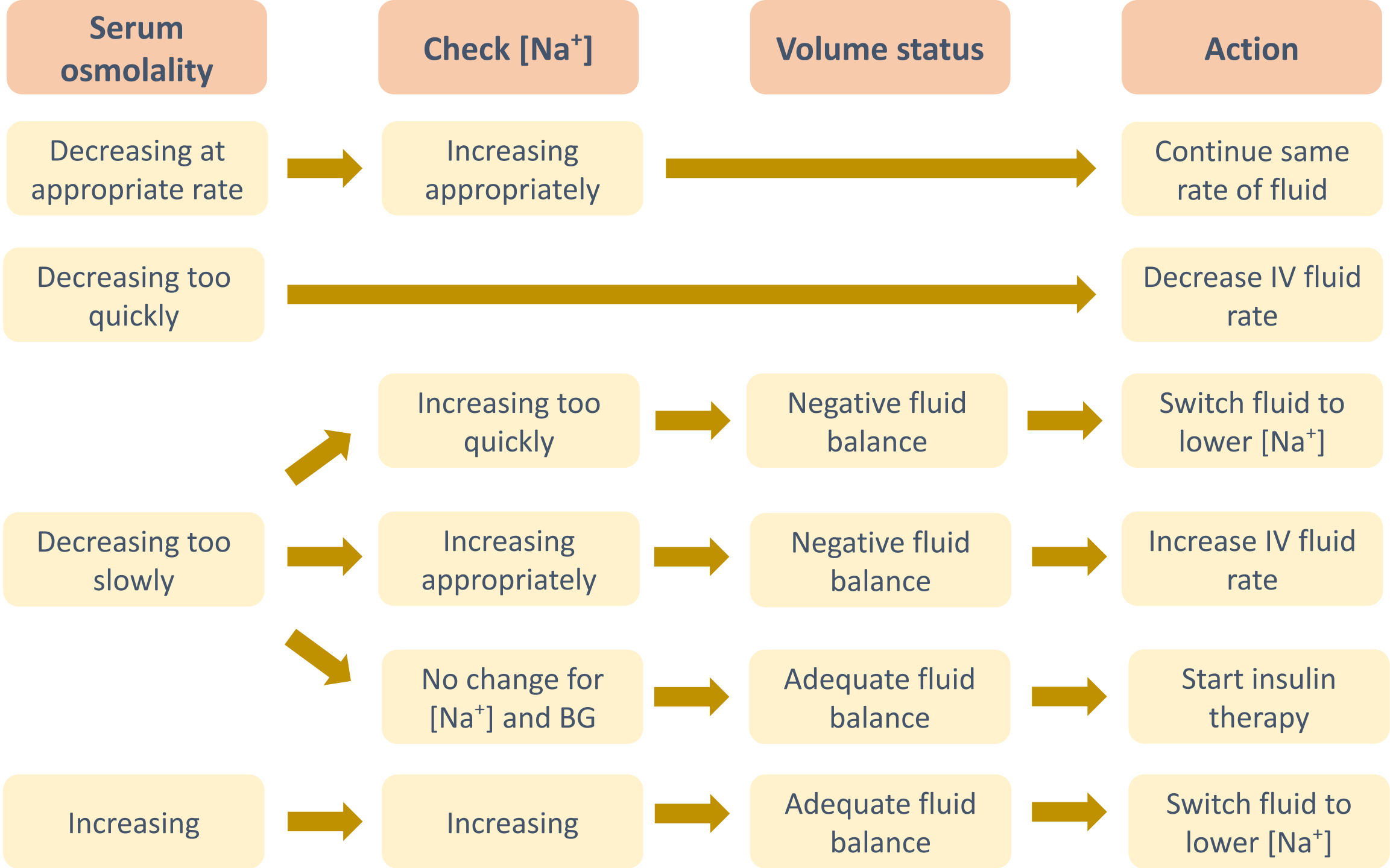
Absolute or relative insulin insufficiency

- Both ketone bodies and [H^+] ions produce during hepatic ketogenesis can cause metabolic acidosis

Electrolyte Abnormalities

- Clinical signs of hypokalemia
  - Muscle weakness
  - Cardiac arrhythmias
  - Hemolysis
  - Plantigrade stance
  - Hypoventilation due to respiratory muscle paralysis

Scudder C., et al. The Veterinary Nurse. 2016.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