COMPLICATIONS OF DIABETES

Dr. Mahmoudi V.
Emergency Physician MD

Hyperosmolar Hyperglycemic State

- Patients are old, decreased renal clearance of glucose produced by the decline of renal function with age, decreased insulin action results in glycogenolysis, gluconeogenesis, and decreased peripheral uptake of glucose
- The hyperglycemia pulls fluid from the intracellular into the extracellular space, transiently maintaining adequate perfusion, but this fluid is lost in a profound osmotic diuresis, resulting hypotension, decreased renal perfusion, and a subsequent drop in the GFR
- Hypotonic diuresis produces profound dehydration, leading to hyperglycemia, hypernatremia, and associated hypertonicity. Often, the patient is unable to take in adequate fluids because of stroke, Alzheimer disease, or other diseases, greatly exacerbating the dehydration

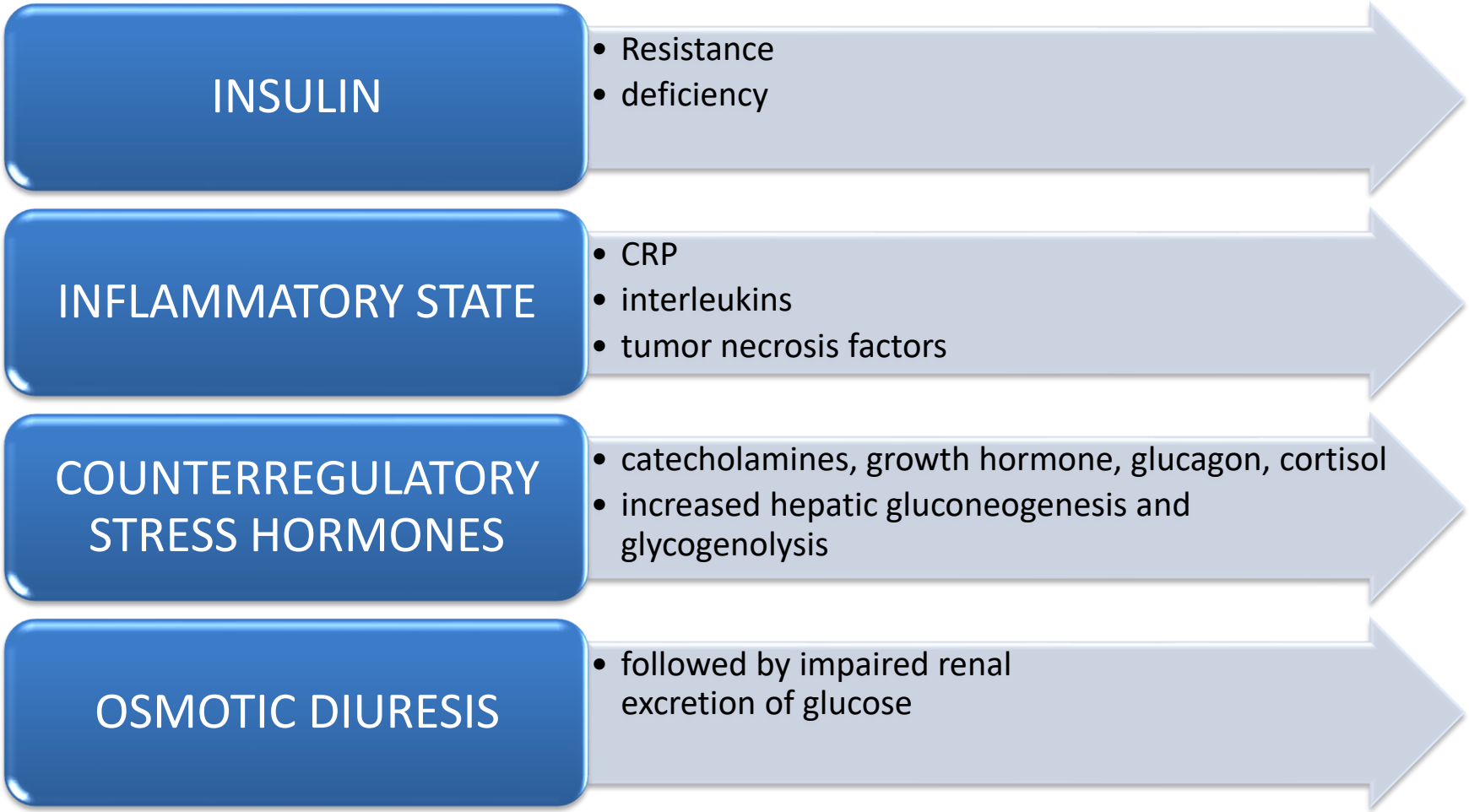
Hyperosmolar Hyperglycemic State

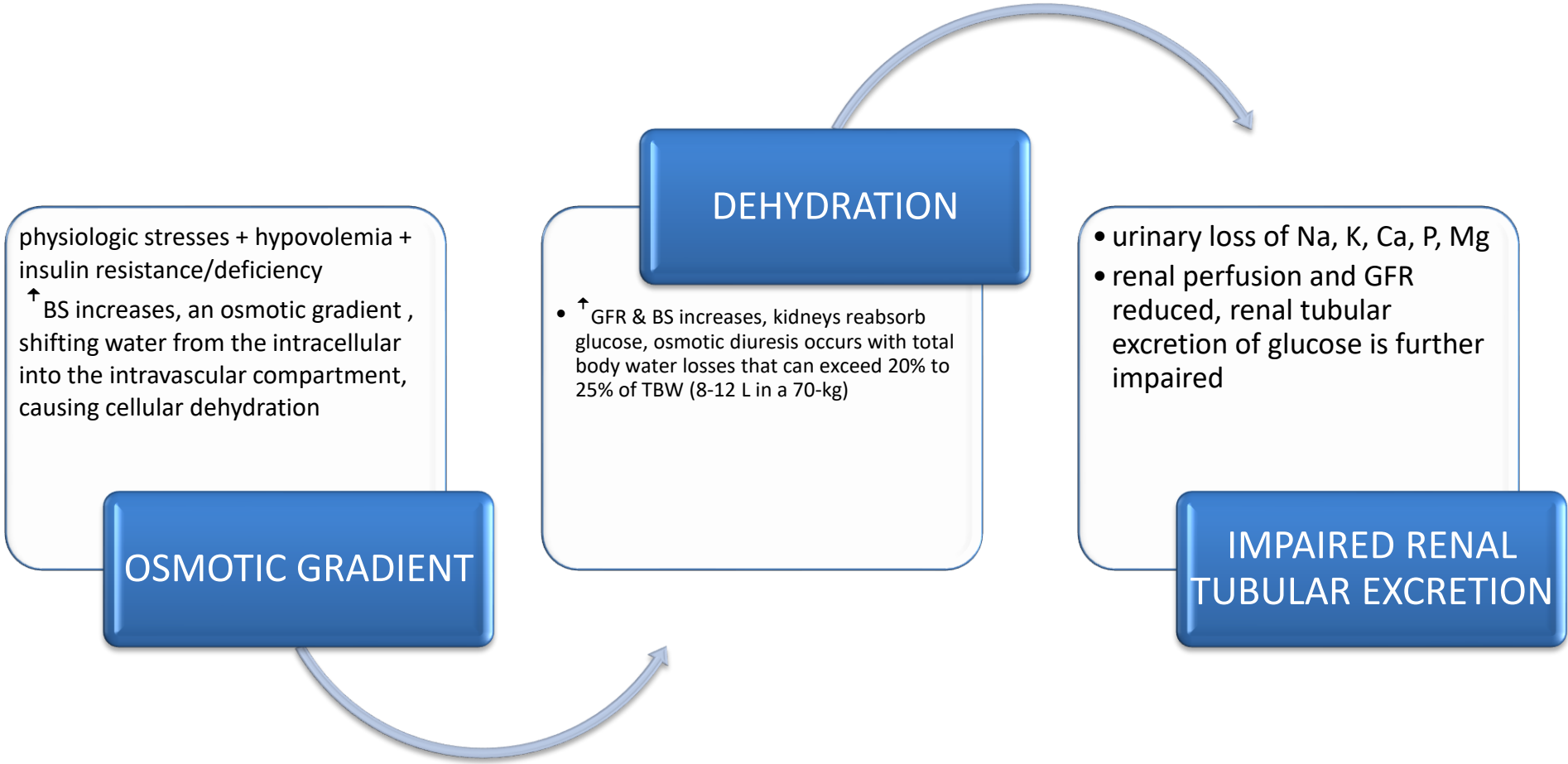
- The reason for the absence of ketoacidosis in HHS is unknown
- FFA levels are lower than in DKA, thus limiting the substrates needed to form ketones. The most likely reason for the blunted counterregulatory hormone release and lack of ketosis seems to be the continued secretion of tiny amounts of insulin that block ketogenesis
- HHS is a syndrome of severe dehydration that results from a sustained hyperglycemic diuresis in which the patient is unable to drink sufficient fluids to offset the urinary losses

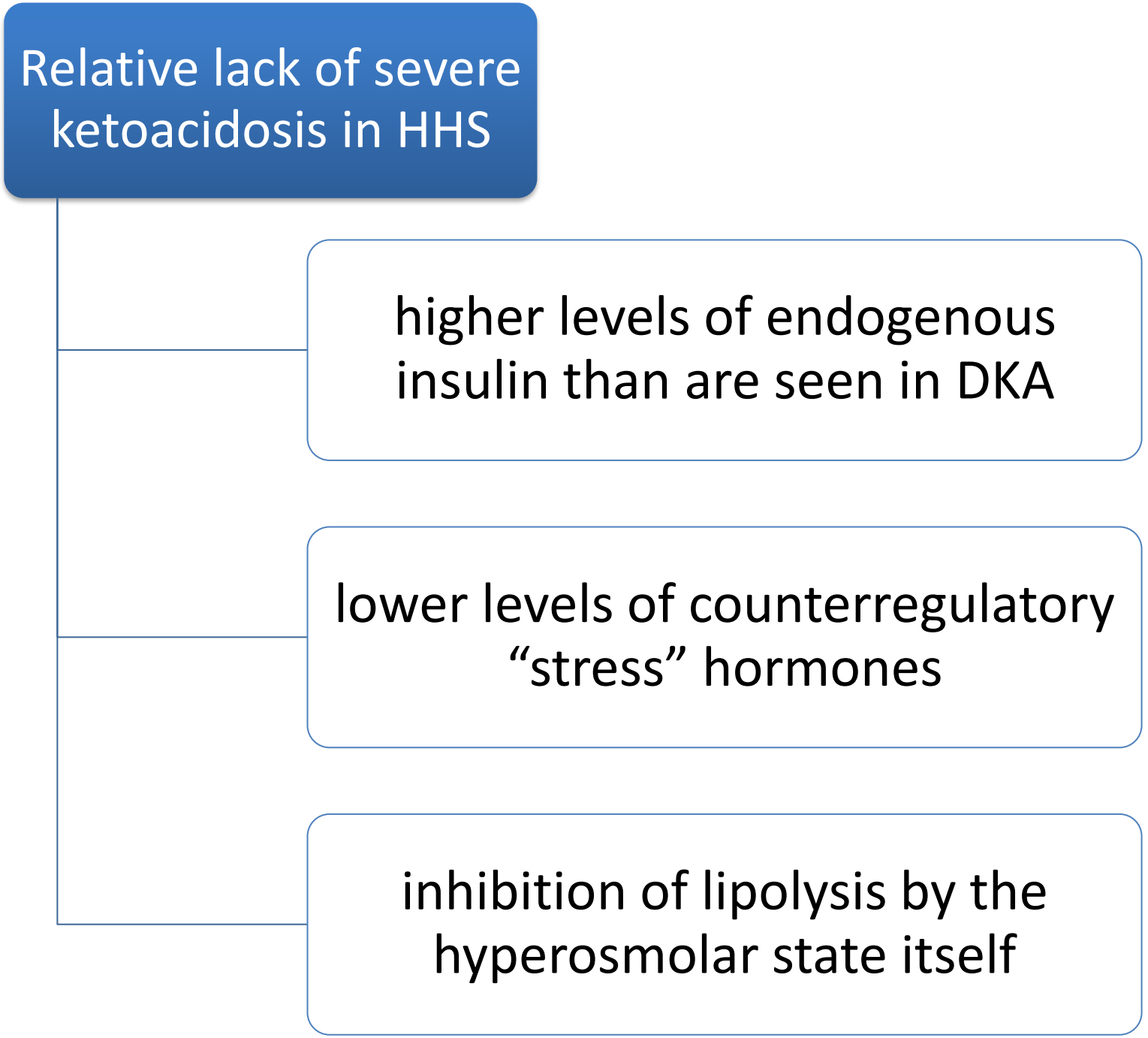
Hyperosmolar Hyperglycemic State

- Progressive hyperglycemia and hyperosmolarity typically found in a debilitated patient with poorly controlled or undiagnosed type 2 diabetes mellitus, limited access to water, and commonly, a precipitating illness
- Although most cases of HHS occur in the elderly, the incidence of HHS in children is increasing, with the common risk factors being obesity and African American race

PATHOPHYSIOLOGY




physiologic stresses + hypovolemia + insulin resistance/deficiency
↑BS increases, an osmotic gradient , shifting water from the intracellular into the intravascular compartment, causing cellular dehydration
OSMOTIC GRADIENT
DEHYDRATION
• ↑GFR & BS increases, kidneys reabsorb glucose, osmotic diuresis occurs with total body water losses that can exceed 20% to 25% of TBW (8-12 L in a 70-kg)
• urinary loss of Na, K, Ca, P, Mg
• renal perfusion and GFR reduced, renal tubular excretion of glucose is further impaired
IMPAIRED RENAL TUBULAR EXCRETION


Relative lack of severe ketoacidosis in HHS
higher levels of endogenous insulin than are seen in DKA
lower levels of counterregulatory “stress” hormones
inhibition of lipolysis by the hyperosmolar state itself

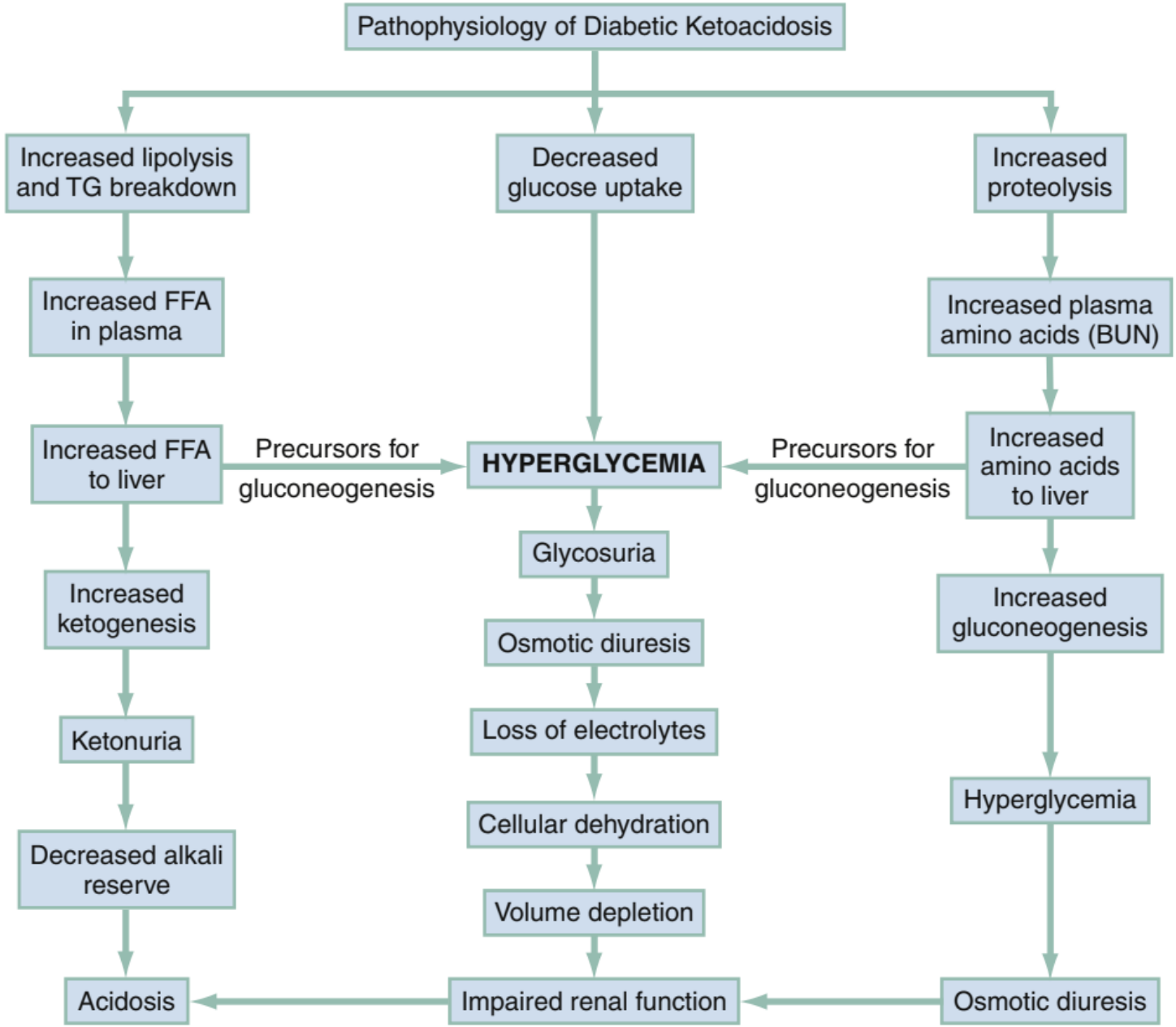
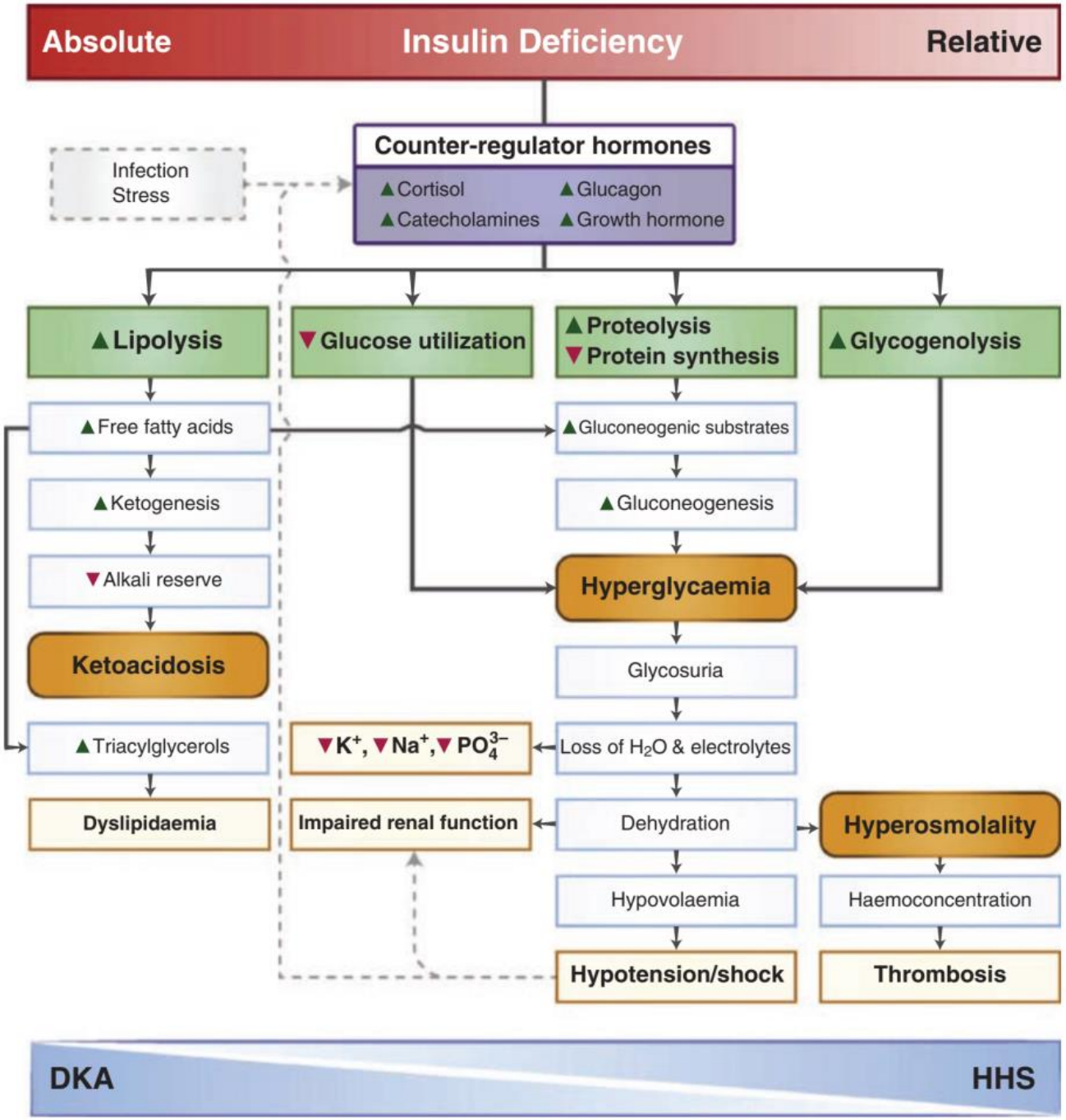


Fig. 115.1 Syndrome of Diabetic Ketoacidosis. *BUN,* Blood urea nitrogen; *FFA,* free fatty acids; *TG,* total glucose concentration.


Absolute
Insulin Deficiency
Relative
Infection
Stress
Counter-regulator hormones
▲Cortisol
▲Glucagon
▲Catecholamines
▲Growth hormone
▲Lipolysis
▼Glucose utilization
▲Proteolysis
▼Protein synthesis
▲Glycogenolysis
▲Free fatty acids
▲Gluconeogenic substrates
▲Ketogenesis
▲Gluconeogenesis
▼Alkali reserve
Hyperglycaemia
Ketoacidosis
Glycosuria
▲Triacylglycerols
▼K+, ▼Na+, ▼PO43–
Loss of H2O & electrolytes
Dyslipidaemia
Impaired renal function
Dehydration
Hyperosmolality
Hypovolaemia
Haemoconcentration
Hypotension/shock
Thrombosis
DKA
HHS

HISTORY AND COMORBIDITIES

- Typical patient with HHS: elderly, often institutionalized, with baseline cognitive impairment and comorbid medical illnesses, abnormal vital signs, and/or mental status changes that have evolved over days to weeks
- In other cases, HHS is noted in patients with no prior history of DM who present with acute illnesses such as stroke, myocardial infarction, pneumonia, abdominal emergencies, and sepsis
- Patient complaints may include malaise, weakness, anorexia, fatigue, vomiting, and cognitive impairment. Up to 15% of patients may present with seizures, which are typically focal, although generalized seizures may occur

TABLE 227-1 Conditions That May Precipitate Hyperosmolar Hyperglycemic State

- Diabetes
- Infection, especially pneumonia or urinary tract infection
- Myocardial infarction
- Renal insufficiency
- Cerebrovascular events
- Mesenteric ischemia
- GI hemorrhage
- Pulmonary embolism
- Pancreatitis
- Severe burns
- Parenteral or enteral alimentation
- Peritoneal or hemodialysis
- Heat-related illness
- Rhabdomyolysis
- Pregnancy
- Trauma

TABLE 227-2 Some Drugs That May Predispose Individuals to the Development of HHS

- Diuretics
- Statins
- β-Blockers
- Chlorpromazine
- Cimetidine
- Glucocorticoids
- β-Agonists
- Antipsychotics
- Antidepressants
- Phenytoin
- Calcium channel blockers
- Pentamidine
- Immunosuppressive drugs (tacrolimus, cyclosporine)
- Diazoxide
- L-asparaginase
- Protease inhibitors
- Nicotinic acid
- Nucleoside reverse transcriptase inhibitors
- Interferons

- The physical findings in HHS generally include signs of severe volume depletion such as poor skin turgor, dry mucous membranes, sunken eyes, tachycardia, hypotension.

- The degree of lethargy and coma has a linear relationship to serum osmolality. Patients with coma tend to be older and have higher osmolality, more severe hyperglycemia, acidosis, and greater volume contraction.

PHYSICAL EXAMINATION

SEVERE VOLUME DEPLETION

- poor skin turgor, dry mucous membranes, sunken eyes, tachycardia, hypotension

CONFUSION

- The degree of lethargy and coma has a linear relationship to serum osmolality

Patients with coma tend to be older and have higher osmolality, more severe hyperglycemia, acidosis, and greater volume contraction

DDx

- **DIAGNOSIS**
  - severe hyperglycemia usually BS>600 milligrams/dL (>33.3 mmol/L)
  - elevated calculated plasma osmolality of >315 mOsm/kg (>315 mmol/kg)
  - serum bicarbonate >15 mEq/L (>15 mmol/L)
  - arterial pH >7.3
  - serum ketones negative to mildly positive

    Metabolic acidosis or ketonemia associated with HHS is likely to be due to tissue hypoperfusion, starvation ketosis, and azotemia

LAB TEST

CBC diff
Metabolic profile
Na, K, Mg, P
Urinalysis
Serum and urine osmolality
Lactate
β-hydroxybutyrate
Blood and urine culturesC
Cardiac markers
Creatine phosphokinase
Arterial or venous blood gas
Thyroid function studies
Procalcitonin
Coagulation profiles

TABLE 115.6 Features Distinguishing Diabetic Ketoacidosis Versus Hyperglycemic Hyperosmolar State

DKA	HHS
• Typically type 1 diabetic patients • Metabolic acidosis present • Blood sugars typically >250 mg/dL, though occasionally can be lower (euglycemic DKA) • May have infection, trauma, myocardial ischemia as underlying triggers, or may be due to inadequate insulin administration • Associated with significant fluid deficits • Insulin and fluids required to correct • Occurs across the age spectrum (toddler to geriatric)	• Typically type 2 diabetic patients • Usually do not have metabolic acidosis as a result of glucose abnormality • Sugars typically markedly high (>500 mg/dL) • Infection most common underlying cause, but may have other etiologies (dehydration, ischemic event, etc.) • Associated with significant fluid deficits • While insulin and fluids may be given, treatment is directed at an underlying cause • Typically seen in geriatric population

TABLE 227-3 Diagnostic Criteria for DKA and Hyperosmolar Hyperglycemic State (HHS)

	DKA	HHS
Plasma glucose	>250 milligrams/dL (>13.8 mmol/L)	>600 milligrams/dL (>33.3 mmol/L)
Serum bicarbonate	≤18 mEq/L (<18 mmol/L)	>15 mEq/L (>15 mmol/L)
Urine acetoacetate*	+	– or small
Serum beta hydroxybutyrate	+	– or small
Serum ketones†	+	– or small
Serum osmolality‡	Variable	>320 mOsm/kg (>320 mmol/kg)
Anion gap#	>12 mEq/L (>12 mmol/L)	<12 mEq/L (<12 mmol/L)
Arterial/venous pH	<7.30	>7.30

*Nitroprusside method.

†Gas chromatography method or nitroprusside method.

‡Osmolality calculation: 2(measured $[Na^+]$ + glucose (milligrams/dL or mmol/L)/18.

#Anion gap calculation: $[Na^+] - [Cl^-] + [HCO_3^-]$.

LABORATORY TESTING & IMAGING

- Alkalosis due to a profound water deficit may occur
- AG metabolic acidosis is often attributable to sepsis, poor tissue perfusion, starvation ketosis, or renal impairment

- **Sodium** Serum sodium level varies and is not a reliable indicator of the degree of volume contraction
- Hyperglycemia has a dilutional effect on measured serum sodium:
  - –Na+ decreases by approximately 1.6 mEq/L (1.6 mmol/L) for every 100 milligrams/dL (5.6 mmol/L) increase in serum glucose >100 milligrams/dL (5.6 mmol/L). For glucose > 400 milligrams/dL (22.2 mmol/L), a correction factor of 2.4 is more accurate

- Chest radiographs and ECGs are generally recommended

- Diagnostic studies, such as CT, lumbar puncture, toxicologic studies, and echocardiography, should be patient specific

Formula for glucose 100-400 milligrams/dL (>5.55-22mmol/L)

$$\text{Corrected } [Na^+] = \text{Measured } [Na^+] + \frac{1.6 \times (\text{glucose in mg/dL} - 100)}{100}$$

Formula for glucose in mmol/L

$$\text{Corrected } [Na^+] = \text{Measured } [Na^+] + \frac{1.6 \times (\text{glucose in mmol/L} - 5.6)}{5.6}$$

OSMOLALITY

- Serum osmolality correlates positively with severity of disease as well as mental status changes and coma. In the United States, many authors suggest using calculated **effective** serum osmolality, which excludes osmotically inactive urea

- Recent guidelines from the United Kingdom suggest that including urea when calculating serum osmolality may more accurately reflect severity of dehydration and help protect against overzealous correction of osmolality, which can predispose patients to cerebral edema and osmotic demyelination syndrome

$$\textit{Osmolality}\ 2[Na^+] + \frac{\text{glucose}}{18} + \text{BUN}/2.8$$

$$\textit{Effective Osmolality}\ 2[Na^+] + \frac{\text{glucose}}{18}$$

- Normal serum osmolality: 275 to 295 mOsm/kg
- Values >300 mOsm/kg: significant hyperosmolality
- Values >320 mOsm/kg: alterations in cognitive function
- Serum osmolality correction should not exceed 3.0 Osm/kg/h.

- **Potassium**

  K losses range from 4 to 6 mEq/kg, but initial serum measurementsmmay be normal or even high in the presence of acidosis, and as intravascular
  volume is replaced and acidosis is reversed, [K+] deficiency becomes more apparent
- Hypomagnesemia is common
- Hypophosphatemia (CNS abnormalities, cardiac dysfunction, and rhabdomyolysis) is uncommon and usually symptoms appear with serum phosphate levels below 1.0 milligram/dL, Routine replacement is usually unnecessary (unless severe)
- Prerenal azotemia is common, with plasma BUN/creatinine ratios often exceeding 30:1, indicating severity of dehydration and the catabolic state

TREATMENT

- Correction of hypovolemia (the key to effective recovery)
- Correction of electrolyte abnormalities
- Gradual correction of hyperglycemia
- Consider medical illnesses such as cardiac, renal, and pulmonary disease
- Avoid overzealous resuscitation

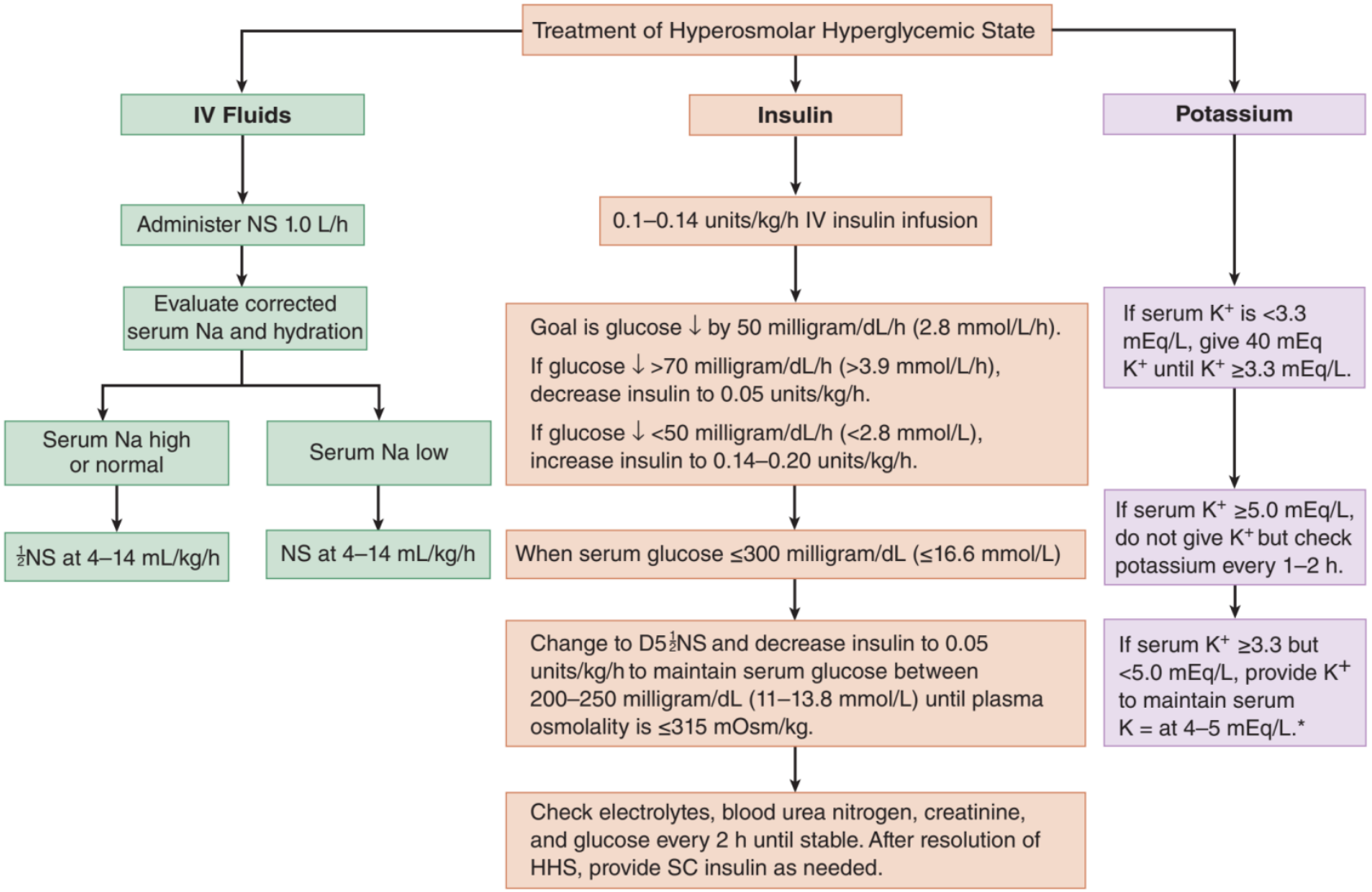


FIGURE 227-2. Protocol for the management of severely ill adult patients with hyperosmolar hyperglycemic state (HHS). *Concentrations of K^+ ≥20 mEq/L should be administered via central line. D5$^1/_2$NS = 5% dextrose in half-normal saline; NS = normal saline.

FLUID RESUSCITATION

- Begin normal saline infusion before insulin therapy is started The average fluid deficit is 20-25% of TBW (8-12 L)
- Half of the fluid deficits should be replaced over the initial 12 hrs and the balance over the next 24 hours when possible administration should be individualized for each patient based on the level of renal and cardiac impairment
- Begin fluid resuscitation with 0.9% normal saline at a rate of 15-20 mL/kg/h during the first hour, followed by rates from 4-14 mL/kg/h
- Limit the rate of volume repletion during the first 4 hours to <50 mL/kg
- Once hypotension, tachycardia, serum hyponatremia, and urinary output improve, 0.45% NaCl can be used to replace the remaining free water deficit

ELECTROLYTES

- In general, replace potassium at a rate of 10 to 20 mEq/h. For lifethreatening hypokalemia, infusion rates of up to 40 mEq/h may be needed, and under these circumstances, central venous access is warranted
- Monitor serum potassium levels every hour until a steady state has been achieved
- Sodium deficits are replenished fairly rapidly, considering the amount of normal saline given during IV fluid replacement
- Replace magnesium deficits with 1-2 g of Mg given over 1 hour
- Phosphate should only be replaced if the phosphate level is <1.0 milligram/dL (<1.0 mmol/L)
- Sodium bicarbonate has been included in American Diabetes Association guidelines if serum pH is <7.0; however, more recent data suggest no benefit and potential harms in the pediatric population

INSULIN

- Begin insulin after initial fluid resuscitation has been completed. If insulin is started too early, intravascular volume may be further depleted by shifting osmotically active glucose and fluids out of the intravascular space.
- Therapy should begin at 0.1 unit/kg/h
- The goal is to maintain a steady rate of decline of 50-75 milligrams/dL/h (2.8–4.1 mmol/L/h)
- With adequate hydration, the insulin infusion may be adjusted every hour until a steady glucose decline is achieved
- Once the patient is mentally alert and able to eat and prior to discontinuing parenteral insulin, administration of longacting SC insulin has demonstrated efficacy in preventing rebound hyperglycemia

DISEASE COMPLICATIONS

- Despite cerebral edema representing >50% of fatalities in children with hyperglycemic emergencies, cerebral edema is an uncommon complication in adults with HHS
- The current recommendation is to limit the rate of volume repletion during the first 4 hours to <50 mL/kg of normal saline, measure serum
  osmolality frequently, and monitor the patient's mental status during treatment
- Although there are no evidence-based treatments for cerebral edema, osmotic agents remain the most practical option
- Venous and arterial thromboses are a common complication in HHS, and unless contraindicated, all patients should receive prophylactic anticoagulation

DISPOSITION AND FOLLOW-UP

- When considering the patient population predisposed to developing HHS (debilitated patients with multiple comorbidities), intensive care unit monitoring for the initial 24 hours of care is usually the most appropriate course of action
- Patients without significant comorbid conditions who demonstrate a good response to initial therapy may be considered for monitored step-down or non–intensive care unit admission
- In a retrospective study that looked at predictors of recurrent hospitalization for patients with DKA and HHS, age <35 years, history of depression or substance abuse, self-pay or publicly funded insurance, and HbA1c level >10.6% were associated with higher odds of readmission

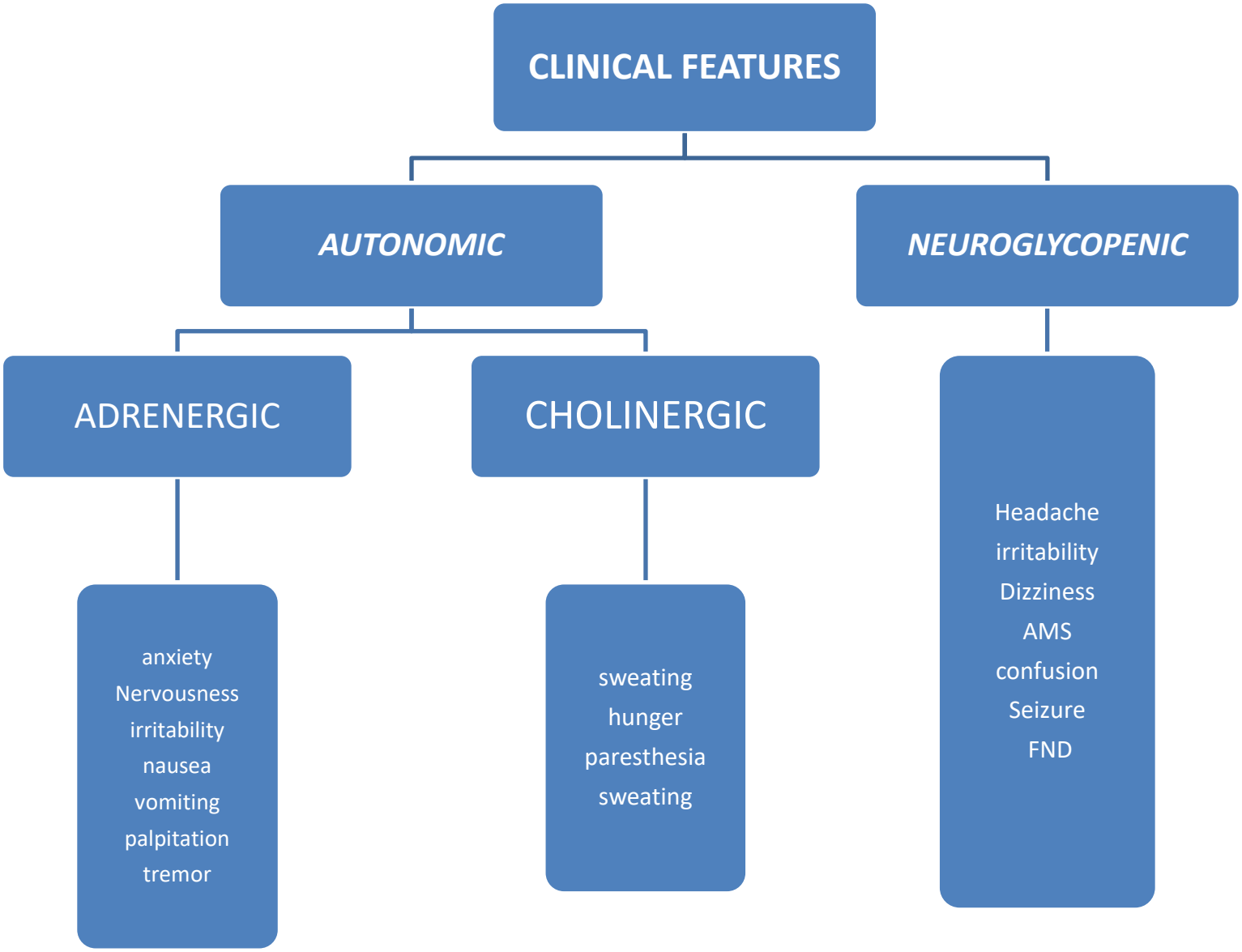
HYPOGLYCEMIA

HYPOGLYCEMIA

- Hypoglycemia (plasma glucose <70 milligrams/dL [<3.9 mmol/L]) is the major adverse effect of tight glycemic control
- Severe hypoglycemia: BS < 40-50 mg/dL and impaired cognitive function
- Modern physiologic regimens of insulin administration (once-daily long-acting insulin with short-acting doses immediately before meals) have significantly reduced the incidence of hypoglycemia
  a. symptoms consistent with the diagnosis
  b. symptoms associated with a low glucose level
  c. symptoms resolve with glucose administration

- The human brain depends on glucose as its primary source of energy, and is unable to synthesize or store glucose (AMS)
- Physiologic response to low blood glucose: suppression of insulin secretion - release of the counterregulatory hormones (e.g., glucagon and epinephrine)
- Renal clearance of insulin decreases with age (enhances the risk of hypoglycemia)
- Hypoglycemia occurs most frequently with insulin and sulfonylureas (rarely metformin)

- Risk factors: age, vascular disease, renal failure, decreased food ingestion, alcohol consumption, drug interactions
- In nondiabetics: adverse effects of drugs (and alcohol), factitious hypoglycemia, tumors (insulinoma or non–islet cell), critical illness (e.g., sepsis or liver failure), hormone deficiencies (adrenal insufficiency or hypopituitarism)



The patient is commonly found pale and diaphoretic, with some levels of altered mental status

TABLE 224-14 Differential Diagnosis of Hypoglycemia

- Stroke
- Transient ischemic attack
- Seizure disorder
- Traumatic head injury
- Brain tumor
- Narcolepsy
- Multiple sclerosis
- Psychosis
- Sympathomimetic drug ingestion
- Hysteria
- Altered sleep patterns and nightmares
- Depression

HYPOGLYCEMIA (nondiabetics)

POSTPRANDIAL

alimentary hyperinsulinism, such as that seen in patients who have undergone gastrectomy, gastrojejunostomy, pyloroplasty, or vagotomy

FASTING

Imbalance between glucose production and use

- production: hormone defciencies, enzyme defects, substrate defciencies, severe liver disease, drugs
- overuse: insulinoma, exogenous insulin, sulfonylureas, drugs, septic shock, extrapancreatic tumors, enzyme defciencies

DIAGNOSIS

- Always consider hypoglycemia as a potential cause of altered mental status
- The accuracy of bedside reflectance tests is acceptable although less reliable at extremely low and high glucose levels
- Glucose values of whole blood are approximately 15% less than that of serum or plasma (send a serum sample to the laboratory for confirmation)
- In diabetic patients who develop hypoglycemia while taking the usual dose of sulfonylurea, suspect an underlying cause (drug interactions, decreased drug metabolism, and decreased drug excretion)
- In nondiabetic patients: serum insulin, pro-insulin, and C-peptide, a *fasting test and* endocrinologist consult

SOMOGYI PHENOMENON

- Iatrogenic hypoglycemia
- Excessive insulin dosing results in an unrecognized hypoglycemic episode that usually occurs in the early morning while the patient is sleeping
- The counterregulatory hormone response produces rebound hyperglycemia, evident when the patient awakens
- The patient and physician interpret this hyperglycemia as an indication to increase the insulin dosage, which exacerbates the problem
- The insulin dosage should be lowered or the timing changed

TREATMENT

- In alert patients with mild symptoms, oral carbohydrates
- In other patients, 1-3 ampules of D50W IV while the patient's airway, breathing, and circulation are assessed and maintained
- Augmentation of the blood glucose level by administration of an ampule of D50W may range from 40-350 mg/Dl
- Thiamine if alcohol use disorder is suggested
- In children younger than 8 yrs: D25W or D10W
- The dose is 0.5 to 1 g/kg body weight or 2 to 4 mL/kg when using D25W
- If shortages of D50W, use 250 mL D10W (similar glucose load to an ampule of D50W)
- May be repeated after 15 min if hypoglycemia persists

TREATMENT

- PO or IV administration of rapidly metabolized carbohydrates (glucose or dextrose)
- When blood glucose reaches 70 milligrams/dL and the patient regains consciousness, continue carbohydrates to prevent recurrence of hypoglycemia
- If blood glucose is normalized but the patient is still unconscious or receiving nothing by mouth, provide a continuous IV infusion of dextrose (5% dextrose in water at a rate to maintain the serum glucose >100 milligrams/dL [5.55 mmol/L])
- Check blood glucose every 30 min for the first 2 hrs (looking for rebound hypoglycemia)
- Failure to respond to parenteral glucose administration should prompt consideration of other causes of hypoglycemia, such as sepsis, toxin, insulinoma, hepatic failure, or adrenal insufficiency
- Pure fructose does not cross the blood–brain barrier and does not significantly improve blood glucose levels

- Hypoglycemia resulting from sulfonylureas is much more challenging than insulin-induced hypoglycemia (Hemodialysis and charcoal hemoperfusion, although mentioned in case reports)

- **Octreotide** is a somatostatin analog and is able to suppress insulin secretion immediately and negates the effects of the sulfonylurea
- 50-100 microgram SC; serial SC injections (50 to 100 micrograms every 6-12 hrs, pediatric dosages of 0.1 μg/kg) or constant IV infusion (125 micrograms/h) after a second hypoglycemic episode
- Some suggest that the addition of octreotide (50 micrograms SC) may result in a decrease in frequency of hypoglycemic episodes and an increase in mean plasma glucose

- **Diazoxide** has also been used in the treatment of refractory sulfonylurea-induced hypoglycemia. It acts by directly inhibiting insulin secretion from pancreatic β cells. Diazoxide may cause hypotension and so should be administered as a slow IV infusion (300 milligrams over 30 minutes every 4 hours)

- **Glucagon** is a FDA approved alternative that may be used SC or IM (even IN) in the absence of IV access but slower (7-10 min)
- 1 mg SC injection can cause an approximate 100 milligram/ dL (5.55 mmol/L) increase in serum glucose of hypoglycemic patients
- In patients who are thought to be glycogen-depleted (such as heavy alcohol users or marathon runners after the race), glucagon therapy is not recommended
- Glucagon is not recommended for sulfonylurea-induced hypoglycemia

DISPOSITION AND FOLLOW-UP

ADMITTED

- sulfonylureas
- non–short-acting insulins
- meglitinides

DISCHARGED

- accidental hypoglycemia
- not resulting from oral hypoglycemic agents of long-acting insulin
- reliable follow-up
- discharged from the ED upon completion of an uneventful 4-hour observation period
- All patients should be given a meal before discharge

HYPOGLYCEMIA IN PATIENTS USING INSULIN PUMPS

- Treat hypoglycemia just as in other patients
- Do not discontinue the pump, as diabetic ketoacidosis can rapidly develop
- If recurrent hypoglycemia develops after initial treatment, pump malfunction may be the cause
- consult endocrinology (replacement of the pump with long-acting insulin)

INSULIN PUMP COMPLICATIONS

- If the pump is defective or needs to be removed for a procedure such as MRI, give the patient either a dose of rapid-acting insulin or long-acting insulin, especially if the insulin pump is to be interrupted for over an hour
- If a patient on an insulin pump needs to be NPO, the insulin pump should not be removed and glucose levels should be checked every 30-60 min, If the patient has hypoglycemia reduce the pump basal rate and consultation is recommended
- Search for infections (cellulitis at the infusion site or lipodystrophy)

HYPOGLYCEMIA IN PATIENTS USING INSULIN PUMPS

Ask specific questions about the insulin pump:

- When was the insulin reservoir filled?
- When was the infusion set last changed?
- Is the insertion site of the infusion set periodically changed?
- When was the insulin reservoir last changed?
- Has the pump been submerged in water?
- Have any device alarms been sounding?

Examine the device thoroughly to ensure:

- the pump is on
- the reservoir is not empty
- no alarms are indicated
- the tubing is not kinked
- the infusion site is well attached to the skin