HYPOGLYCEMIA

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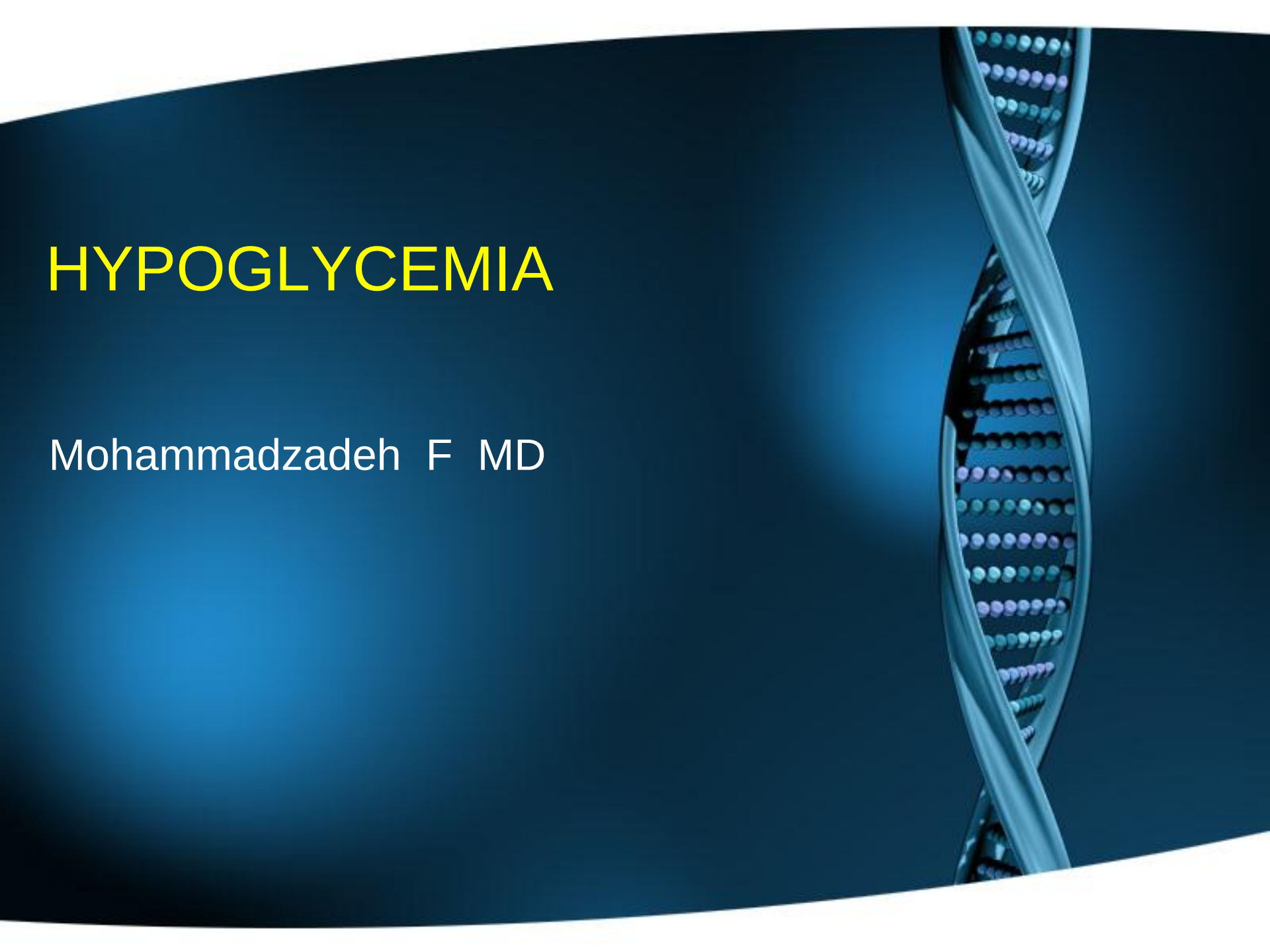


Definition

- ***Hypoglycemia : a plasma glucose 45 to 50 mg/dL***

  glucose thresholds for hypoglycemia-induced symptoms and physiologic responses vary widely, depending on the clinical setting

⇒***Whipple's triad:***

⇒ (1) symptoms consistent with hypoglycemia

(2) a low plasma glucose concentration

(3) relief of symptoms by ↑ BS

Regulation of Glucose Homeostasis

- Despite wide variation of food intake & activity plasma glucose are maintained within a narrow range, usually between 60 - 150 mg/dL
- **Between meals or during fasting**, plasma glucose levels are maintained primarily by the *glycogenolysis* and by *gluconeogenesis*
- In most persons, **hepatic glycogen stores** are sufficient to maintain plasma glucose levels for **8 to 12 hr**

TABLE 324-2 Physiologic Responses to Decreasing Plasma Glucose Concentrations

Response	Glycemic Threshold, mmol/L (mg/dL)	Physiologic Effects	Role in the Prevention or Correction of Hypoglycemia (Glucose Counterregulation)
↓ Insulin	4.4–4.7 (80–85)	↑ R_a (↓R_d)	Primary glucose regulatory factor/first defense against hypoglycemia
↑ Glucagon	3.6–3.9 (65–70)	↑ R_a	Primary glucose counterregulatory factor
↑ Epinephrine	3.6–3.9 (65–70)	↑ R_a, ↓ R_d	Involved, critical when glucagon is deficient
↑ Cortisol and growth hormone	3.6–3.9 (65–70)	↑ R_a, ↓ R_d	Involved, not critical
Symptoms	2.8–3.1 (50–55)	↑ Exogenous glucose	Prompt behavioral defense (food ingestion)
↓ Cognition	< 2.8 (< 50)	—	(Compromises behavioral defense)

Note: R_a, rate of glucose appearance, glucose production by the liver and kidneys; R_d, rate of glucose disappearance, glucose utilization by insulin-sensitive tissues such as skeletal muscle. (R_d includes glucose utilization by the central nervous system,

…continued

- The glucose thresholds at which various counterregulatory hormone responses occur are dynamic and can be influenced by recent metabolic events
- A person with poorly controlled diabetes can have symptoms of hypoglycemia at higher than normal glucose levels
- Recurrent hypoglycemia, shifts thresholds for symptoms and counterregulatory responses to lower glucose levels

Common Symptoms of Acute Hypoglycemia

Neuroglycopenic	Neurogenic (Autonomic)
Behavioral change	Palpitation
Speech difficulty	Tremor
Incoordination	Anxiety
Confusion	Sweating
Seizure	Hunger
Loss of consciousness	Paresthesia

TABLE 324-1 Causes of Hypoglycemia

- Drugs
  - Especially insulin, sulfonylureas, ethanol
  - Sometimes pentamidine, quinine
  - Rarely salicylates, sulfonamides, and others
- Critical illnesses
  - Hepatic, renal, or cardiac failure
  - Sepsis
  - Starvation and inanition
- Endocrine deficiencies
  - Cortisol, growth hormone
  - Glucagon and epinephrine (type 1 diabetes)
- Non-β-cell tumors
  - Fibrosarcoma, mesothelioma, rhabdomyosarcoma, liposarcoma, other sarcomas
  - Hepatoma, adrenocortical tumors, carcinoid
  - Leukemia, lymphoma, melanoma, teratoma
- Endogenous hyperinsulinism
  - Insulinoma
  - Other β cell disorders
  - Secretagogue (sulfonylurea)
  - Autoimmune (autoantibodies to insulin, insulin receptor, β cell?)
  - Ectopic insulin secretion
- Disorders of infancy or childhood
  - Transient intolerance of fasting
  - Infants of diabetic mothers (hyperinsulinism)
  - Congenital hyperinsulinism
  - Inherited enzyme defects
- Postprandial
  - Reactive (after gastric surgery)
  - Ethanol-induced
  - Autonomic symptoms without true hypoglycemia
- Factitious
  - Insulin, sulfonylureas

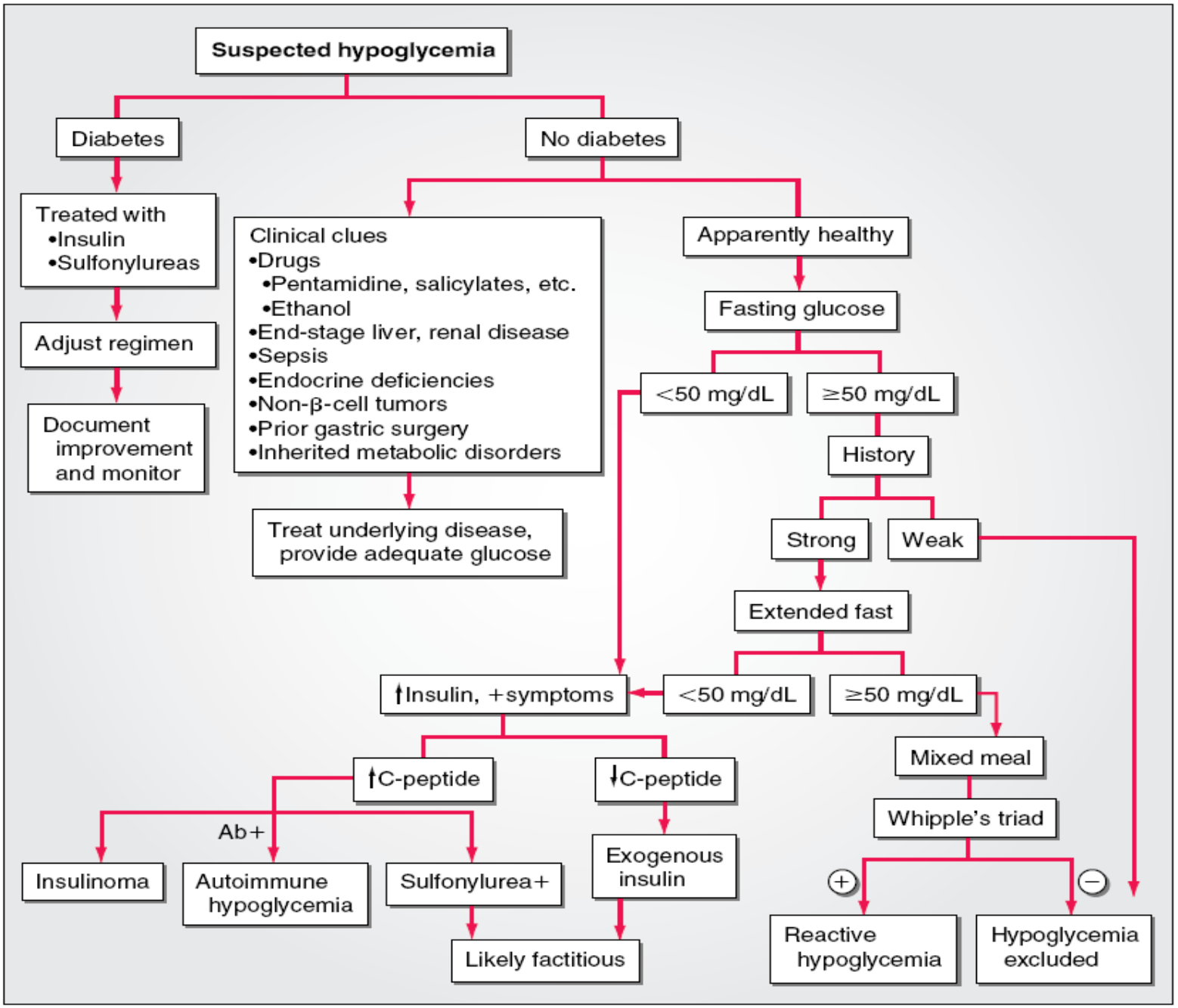
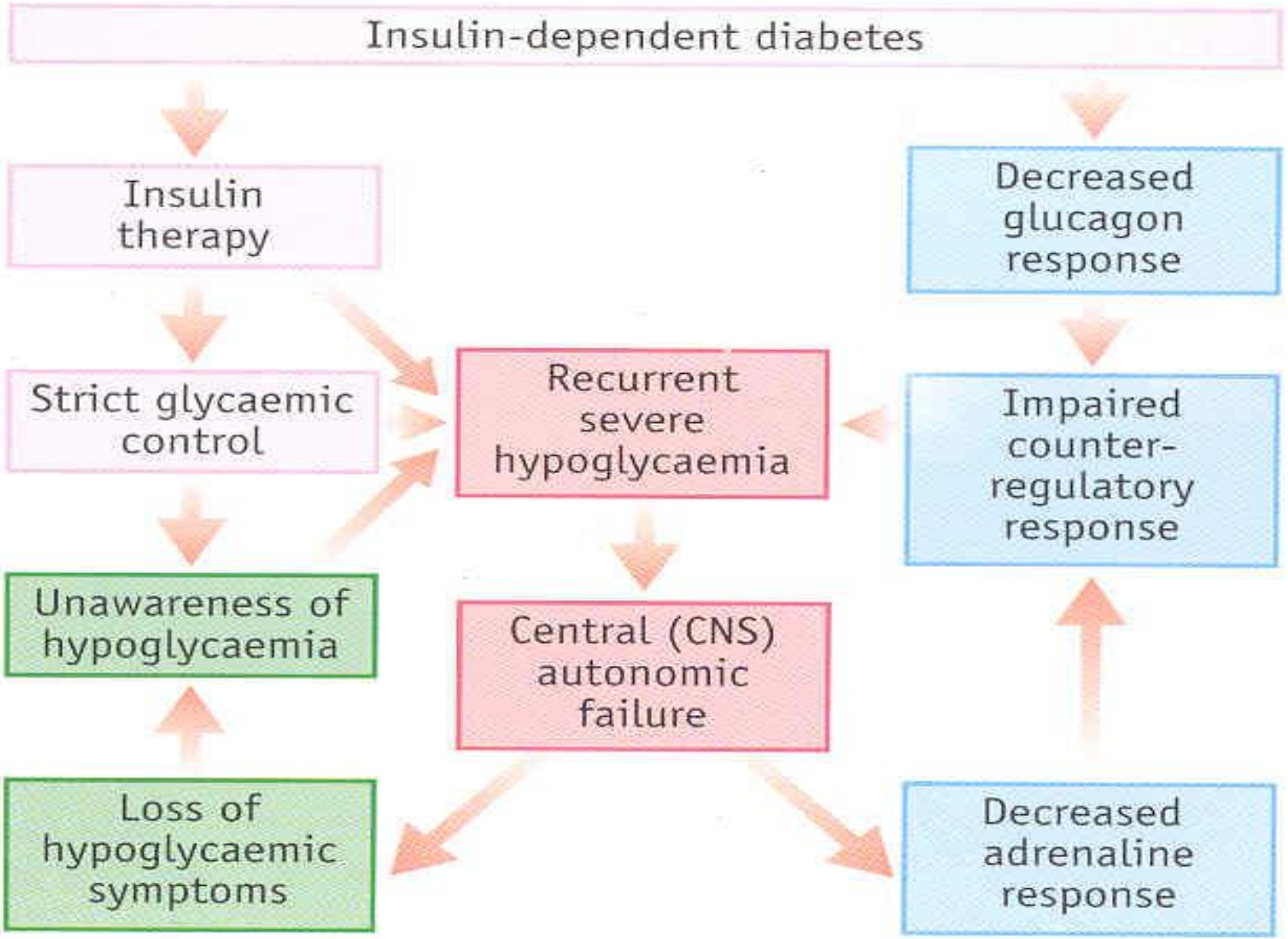


FIGURE 324-3 Diagnostic approach to a patient with suspected hypoglycemia based on a history of symptoms, a low plasma glucose concentration, or both.

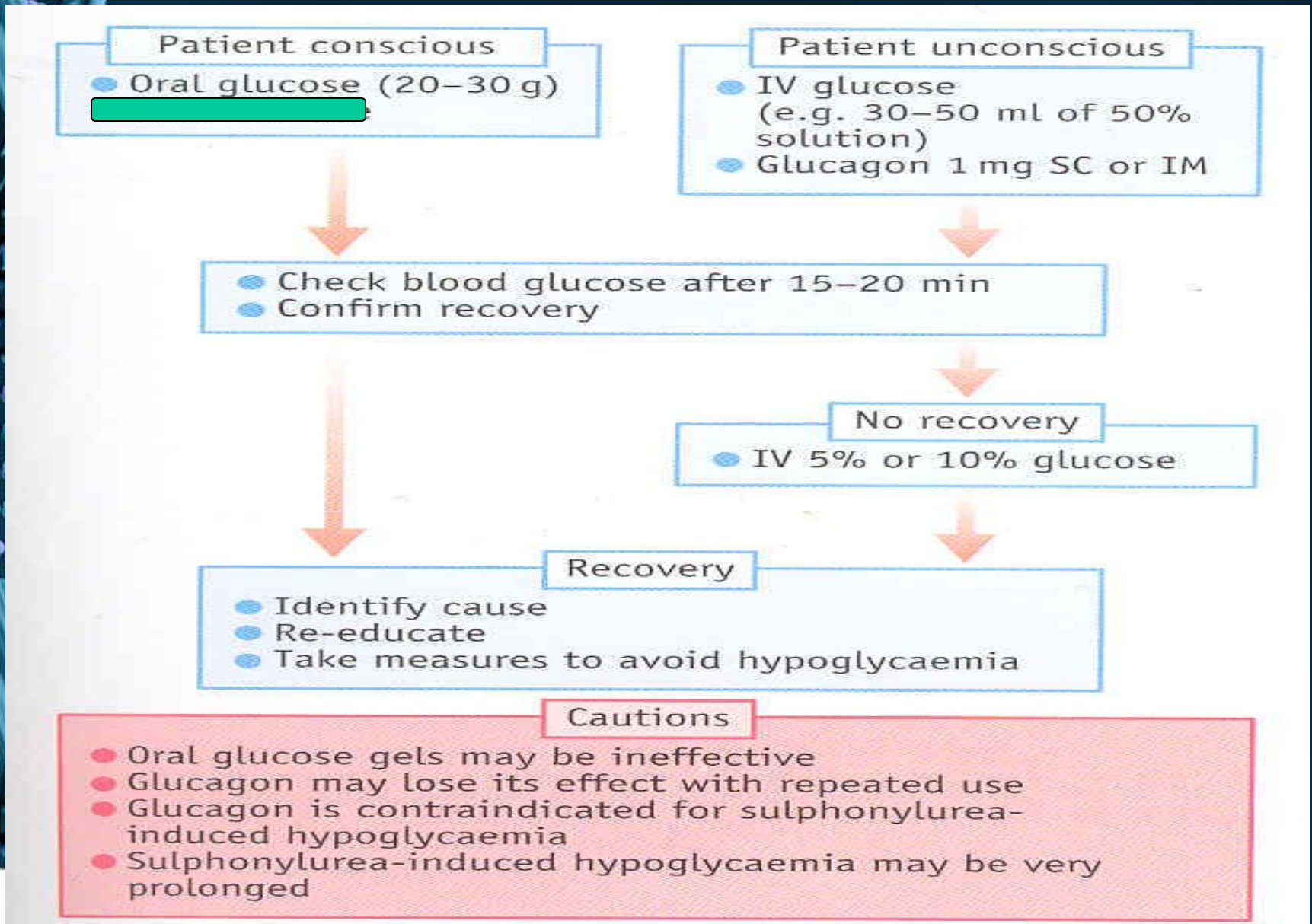
Main Causes of Hypoglycemia in DM

Mismatch of food and insulin/Drugs
Strict blood glucose control
Long duration of diabetes
Hypoglycemia unawareness
Exercise
↓ Endogenous glucose production (alcohol)
↓ Insulin clearance (renal failure)

Hypothesis of Hypoglycemia



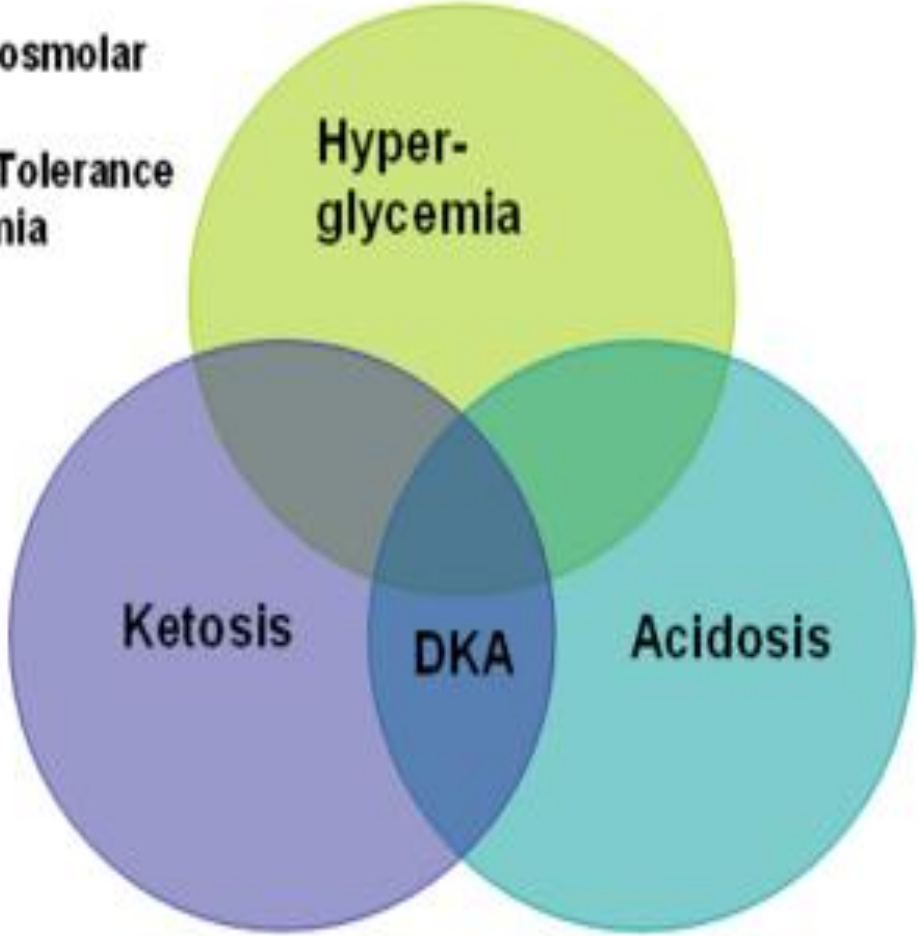
Algorithm for Treating Acute Hypoglycemia



Diabetic Ketoacidosis (DKA)

& Hyperglycemic Hyperosmolar State (HHS)

Other Hyperglycemic States
Diabetes Mellitus
Non-Ketotic Hyperosmolar Coma
Impaired Glucose Tolerance
Stress Hypoglycemia



Other Ketotic States:
Ketotic Hypoglycemia
Alcoholic Ketosis
Starvation Ketosis

Other Metabolic Acidotic States
Lactic Acidosis
Hyperchloremic Acidosis
Salicysm
Uremic Acidosis
Drug-Induced Acidosis

Epidemiology

- ***DKA accounts for 8- 29% of all hospital admissions with a primary diagnosis of diabetes***
- ***The annual incidence of DKA : 4 to 8 episodes per 1000 pt admissions with diabetes***
- ***The incidence of DKA continues to increase***

- *The mortality rate for DKA has been falling over the years*

- *Mortality rate of HHS has remained alarmingly high (15%), compared with < 5% in DKA*

Precipitating events of DKA

- 1) discontinuation or Inadequate insulin administration
- 2) Infection (pneumonia/UTI/gastroenteritis/sepsis)
- 3) Infarction (cerebral, coronary, mesenteric, peripheral)
- 4) Drugs (cocaine)
- 5) Pregnancy

Pathophysiology of DKA

- ***Both***

1) insulin deficiency

and

2) glucagon excess

are necessary for DKA to develop

.....Pathophysiology of DKA

1)insulin deficiency

and

2)hyperglycemia →

↓ hepatic level of fructose-2,6-phosphate, which alters the activity of phosphofructokinase and fructose-1,6-bisphosphatase

……Pathophysiology of DKA

- ↑ Glucagon → ↓ activity of pyruvate kinase

whereas

- ↓ insulin → ↑ activity of phosphoenolpyruvate carboxykinase

- These changes shift the handling of **pyruvate** toward glucose synthesis

.....Pathophysiology of DKA

- ***↑glucagon and catecholamines in the face of ↓ insulin leveis***

↑glycogenolysis

- ***Insulin deficiency :↓GLUT4***

↑ BS

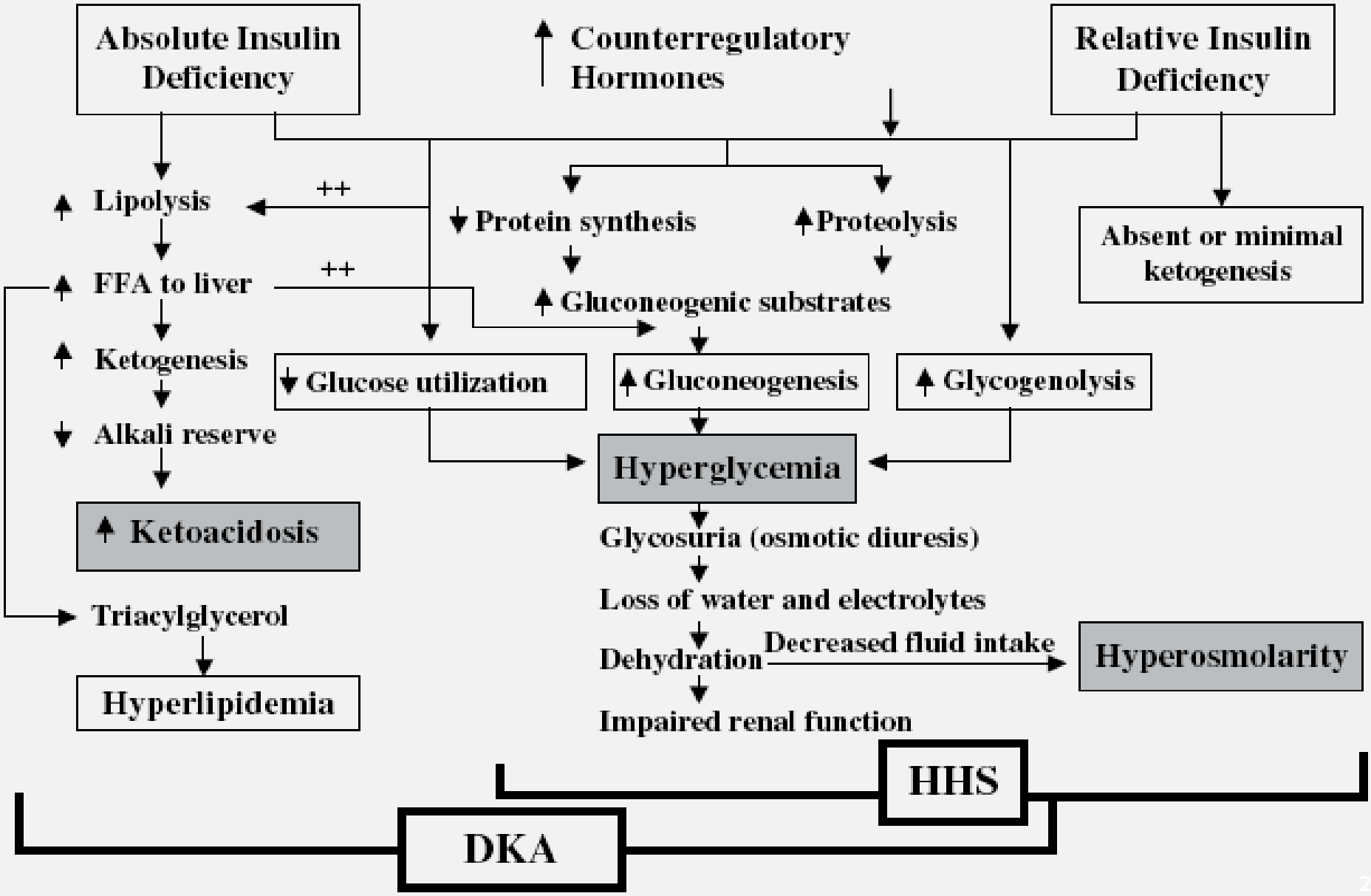
…….Pathophysiology of DKA

- In DKA, **hyperglucagonemia** → **activation** of the enzyme **carnitine palmitoyltransferase I** → **FFA** → **ketone body formation**
- **carnitine palmitoyltransferase I** is crucial for regulating fatty acid transport into the **mitochondria**, where beta oxidation and conversion to ketone bodies occur

…….Pathophysiology of DKA

- ***At physiologic pH, ketone bodies exist as ketoacids, which are neutralized by bicarbonate***
- ***As bicarbonate stores are depleted, metabolic acidosis ensues***
- ***↑lactic acid production also contributes to acidosis***
- ***↑FFA increase TG and VLDL production.***
- ***↓ VLDL clearance because of ↓ the activity of insulin-sensitive LPL in muscle and fat***
- ***Hyper-TG may be severe enough to cause pancreatitis***

Pathogenesis of DKA and HHS



CLINICAL PRESENTATION

- Diabetic ketoacidosis (DKA) usually evolves rapidly, over a 24-hour period.

- In contrast, symptoms of hyperosmolar hyperglycemic state (HHS) develop more insidiously with polyuria, polydipsia, and weight loss, often persisting for several days before hospital admission.

Neurologic symptoms

- Mental obtundation and coma are more frequent in HHS than DKA because of the usually greater degree of hyperosmolality in HHS
- focal neurologic signs (hemiparesis or hemianopsia) and/or seizures .
- Mental obtundation may occur in patients with DKA, who have lesser degrees of hyperosmolality, when severe acidosis exists

- Patients with diabetic ketoacidosis (DKA) may present with nausea, vomiting, and abdominal pain;
- Possible causes of abdominal pain include delayed gastric emptying and ileus induced by the metabolic acidosis and associated electrolyte abnormalities

Physical examination

- Signs of volume depletion are common in both DKA and HHS and include decreased skin turgor, dry axillae and oral mucosa, low jugular venous pressure, tachycardia, and, if severe, hypotension.

- Neurologic findings, noted above, also may be seen, particularly in patients with HHS.

- Patients with DKA may have a fruity odor (due to exhaled acetone; and deep respirations reflecting the compensatory hyperventilation (called Kussmaul respirations).

Diagnostic criteria and typical total body deficits of water and electrolytes in diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome

	Diabetic ketoacidosis			Hyperglycemic hyperosmolar syndrome
	Mild	Moderate	Severe	
Diagnostic criteria and classification				
Plasma glucose (mg/dL)	>250	>250	>250	>600
Arterial pH	7.25–7.30	7.00–<7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15–18	10–<15	<10	>15
Urine ketone[a]	Positive	Positive	Positive	Small
Serum ketone[a]	Positive	Positive	Positive	Small
Effective serum osmolality[b]	Variable	Variable	Variable	>320
Anion gap[c]	>10	>12	>12	Variable
Mental status	Alert	Alert/drowsy	Stupor/coma	Variable
Typical deficits				
Total water (L)	6			9
Water (mL/kg)[d]	100			100–200
Na+ (mEq/kg)	7–10			5–13
Cl− (mEq/kg)	3–5			5–15
K+ (mEq/kg)	3–5			4–6
PO4 (mmol/kg)	5–7			3–7
Mg++ (mEq/kg)	1–2			1–2
Ca++ (mEq/kg)	1–2			1–2

[a] Nitroprusside reaction method.

[b] Calculation: effective serum osmolality: 2[measured Na^+ (mEq/L)+glucose (mg/dL)/18 [mOsm/Kg].

[c] Calculation: anion gap: $(Na^+)-(Cl^-+HCO3^-$ (mEq/L) [normal = 12 ± 2].

[d] per kg of body weight.

Flowchart for the Investigation of Diabetic Ketoacidosis

History

- Precipitating cause?
- If known diabetic patient: current treatment and problems
- Medication

Physical examination

- Dehydration
- Hypotension (postural), shock
- Ketosis (acetone on breath)
- Acidosis (Kussmaul breathing)
- Precipitating cause, e.g. pneumonia, urinary infection
- Diabetic complications, especially cardiovascular disease
- Hypothermia (low-reading thermometer)
- Gastric stasis

Bedside investigations

- Blood glucose (test strip)
- Urinary ketones (Ketostix)

Laboratory investigations

Venous blood

- Glucose
- Na^+, K^+, Cl^-, HCO_3^-
- Urea (BUN), creatinine
- Osmolality (measured or calculated)
- Ketone bodies (if available)
- Calculate anion gap
- Lactate, if significant lactic acidaemia suspected
- Visual inspection (hypertriglyceridaemia) of plasma

Arterial or capillary blood:

- pH, standard HCO_3^-, base excess
- PO_2, PCO_2

Others

- ECG, ± cardiac enzymes
- Full blood count
- Chest radiograph
- Blood, urine and sputum for culture

f diabetic ketoacidosis

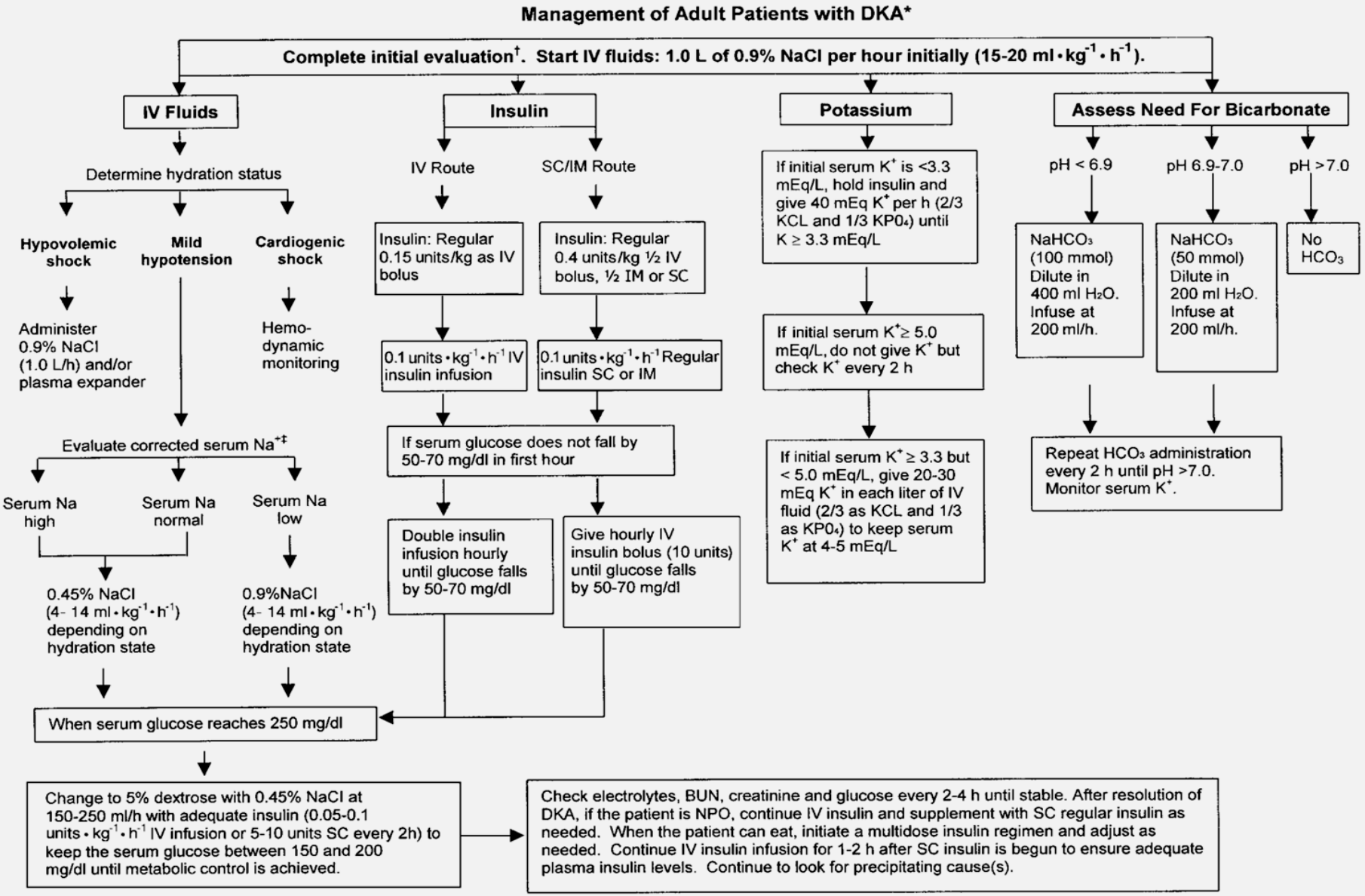


Figure 1—*Protocol for the management of adult patients with DKA. *DKA diagnostic criteria: blood glucose >250 mg/dl, arterial pH <7.3, bicarbonate <15 mEq/l, and moderate ketonuria or ketonemia. Normal ranges vary by lab; check local lab normal ranges for all electrolytes. †After history and physical examination, obtain arterial blood gases, complete blood count with differential, urinalysis, blood glucose, blood urea nitrogen (BUN), electrolytes, chemistry profile, and creatinine levels STAT as well as an electrocardiogram. Obtain chest X-ray and cultures as needed. ‡Serum Na should be corrected for hyperglycemia (for each 100 mg/dl glucose >100 mg/dl, add 1.6 mEq to sodium value for corrected serum sodium value). IM, intramuscular; IV, intravenous; SC subcutaneous.*

Hyperglycemic Hyperosmolar State

Hyperglycemic Hyperosmolar State

- Clinical Features
- The prototypical patient with HHS is an elderly individual with type 2 DM, with a several-week history of polyuria, weight loss, and diminished oral intake that culminates in mental confusion, lethargy, or coma.
- The physical examination reflects profound dehydration and hyperosmolality and reveals hypotension, tachycardia, and altered mental status.

Precipitating factors

- myocardial infarction or stroke
- Sepsis, pneumonia, and other serious infections
- a debilitating condition (prior stroke or dementia) or social situation that compromises water intake

Pathophysiology of HHS

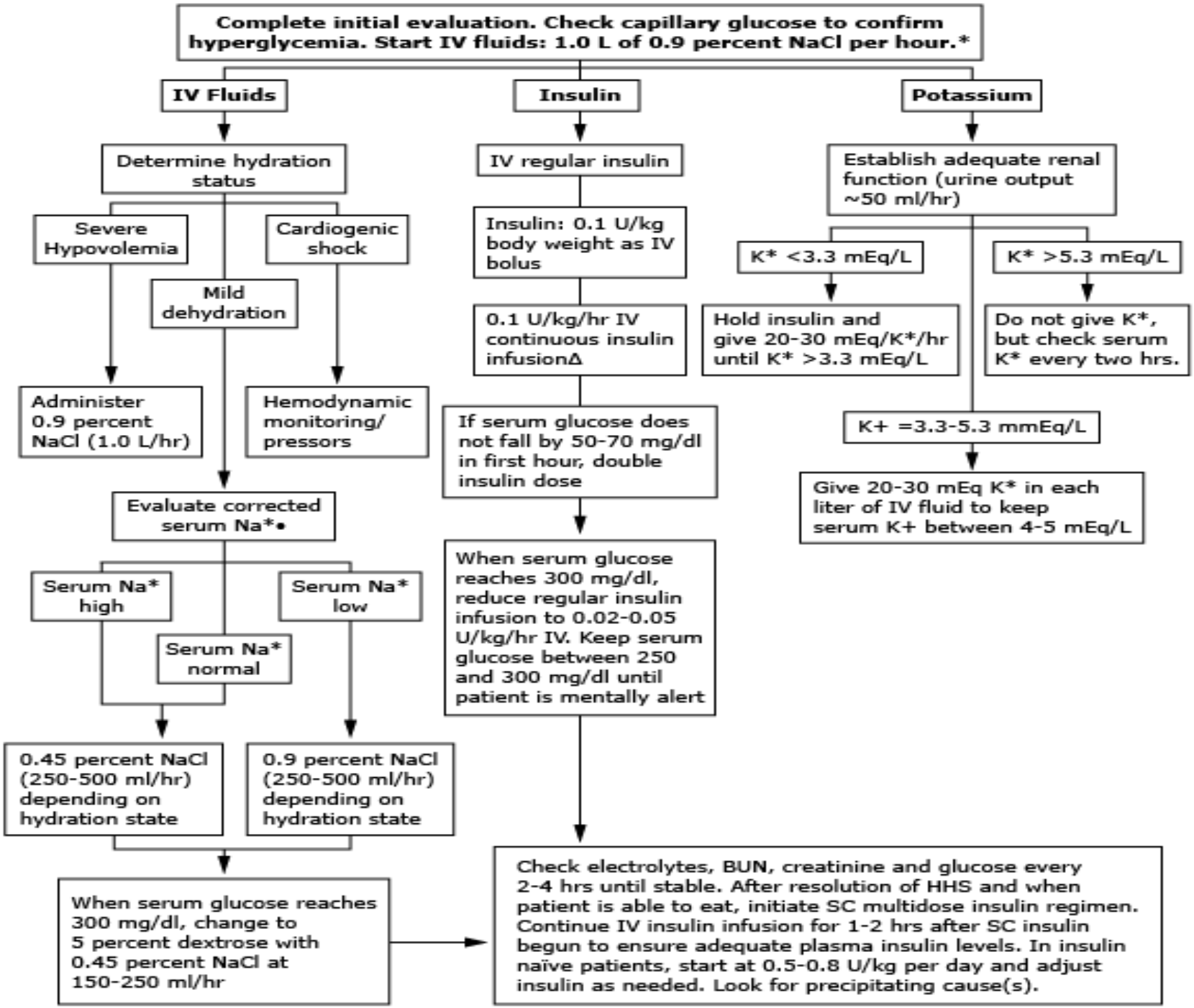
- Relative insulin deficiency and inadequate fluid intake
- Insulin deficiency increases hepatic glucose production (through glycogenolysis and gluconeogenesis) and impairs glucose utilization in skeletal muscle
- Hyperglycemia induces an osmotic diuresis that leads to intravascular volume depletion, which is exacerbated by inadequate fluid replacement

Laboratory Abnormalities and Diagnosis

- marked hyperglycemia [plasma glucose may be >1000 mg/Dl
- hyperosmolality (>350 mosmol/L), and prerenal azotemia.
- The measured serum sodium may be normal or slightly low despite the marked hyperglycemia.
- The corrected serum sodium is usually increased [add 1.6 meq to measured sodium for each 5.6-mmol/L (100 mg/dL) rise in the serum glucose].
- In contrast to DKA, acidosis and ketonemia are absent or mild.
- A small anion-gap metabolic acidosis may be present secondary to increased lactic acid.
- Moderate ketonuria, if present, is secondary to starvation.

Complications

- ***Hypoglycemia & Hypokalemia***
- ***Hyperchloremic Acidosis***
- ***Cerebral edema***
- ***ARDS***
- ***Thromboembolism***
- ***Acute gastric dilatation/ erosive gastritis***


Complete initial evaluation. Check capillary glucose to confirm hyperglycemia. Start IV fluids: 1.0 L of 0.9 percent NaCl per hour.*
IV Fluids
Insulin
Potassium
Determine hydration status
IV regular insulin
Establish adequate renal function (urine output ~50 ml/hr)
Severe Hypovolemia
Mild dehydration
Cardiogenic shock
Insulin: 0.1 U/kg body weight as IV bolus
K* <3.3 mEq/L
K* >5.3 mEq/L
0.1 U/kg/hr IV continuous insulin infusionΔ
Hold insulin and give 20-30 mEq/K*/hr until K* >3.3 mEq/L
Do not give K*, but check serum K* every two hrs.
Administer 0.9 percent NaCl (1.0 L/hr)
Hemodynamic monitoring/ pressors
If serum glucose does not fall by 50-70 mg/dl in first hour, double insulin dose
K+ =3.3-5.3 mmEq/L
Give 20-30 mEq K* in each liter of IV fluid to keep serum K+ between 4-5 mEq/L
Evaluate corrected serum Na*•
Serum Na* high
Serum Na* low
Serum Na* normal
When serum glucose reaches 300 mg/dl, reduce regular insulin infusion to 0.02-0.05 U/kg/hr IV. Keep serum glucose between 250 and 300 mg/dl until patient is mentally alert
0.45 percent NaCl (250-500 ml/hr) depending on hydration state
0.9 percent NaCl (250-500 ml/hr) depending on hydration state
When serum glucose reaches 300 mg/dl, change to 5 percent dextrose with 0.45 percent NaCl at 150-250 ml/hr
Check electrolytes, BUN, creatinine and glucose every 2-4 hrs until stable. After resolution of HHS and when patient is able to eat, initiate SC multidose insulin regimen. Continue IV insulin infusion for 1-2 hrs after SC insulin begun to ensure adequate plasma insulin levels. In insulin naïve patients, start at 0.5-0.8 U/kg per day and adjust insulin as needed. Look for precipitating cause(s).


Thank you