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Acute complications of diabetes

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UNIWERSYTET MEDYCZNY W ŁODZI

Acute metabolic complications of diabetes consist of

- diabetic ketoacidosis (DKA)
- Hyperosmolar non-ketotic coma (HNC)
- Lactic acidosis (LA)
- Hypoglycemia.

diabetic ketoacidosis (DKA)

- defined by **absolute** insulin deficiency with
  - hyperglycemia (>200 mg/dl)
  - increased lipolysis with increased ketone production, (ketone levels positive at 1:4 dilution of serum or greater or beta hydroxybutyrate >0.5 mmol/L)
  - acidosis (pH ≤7.3 or bicarbonate ≤15 mEq/L).

  - Normoglycemic ketoacidosis has been reported and milder forms of ketoacidosis with bicarbonate levels between 15-18 mEq/L.

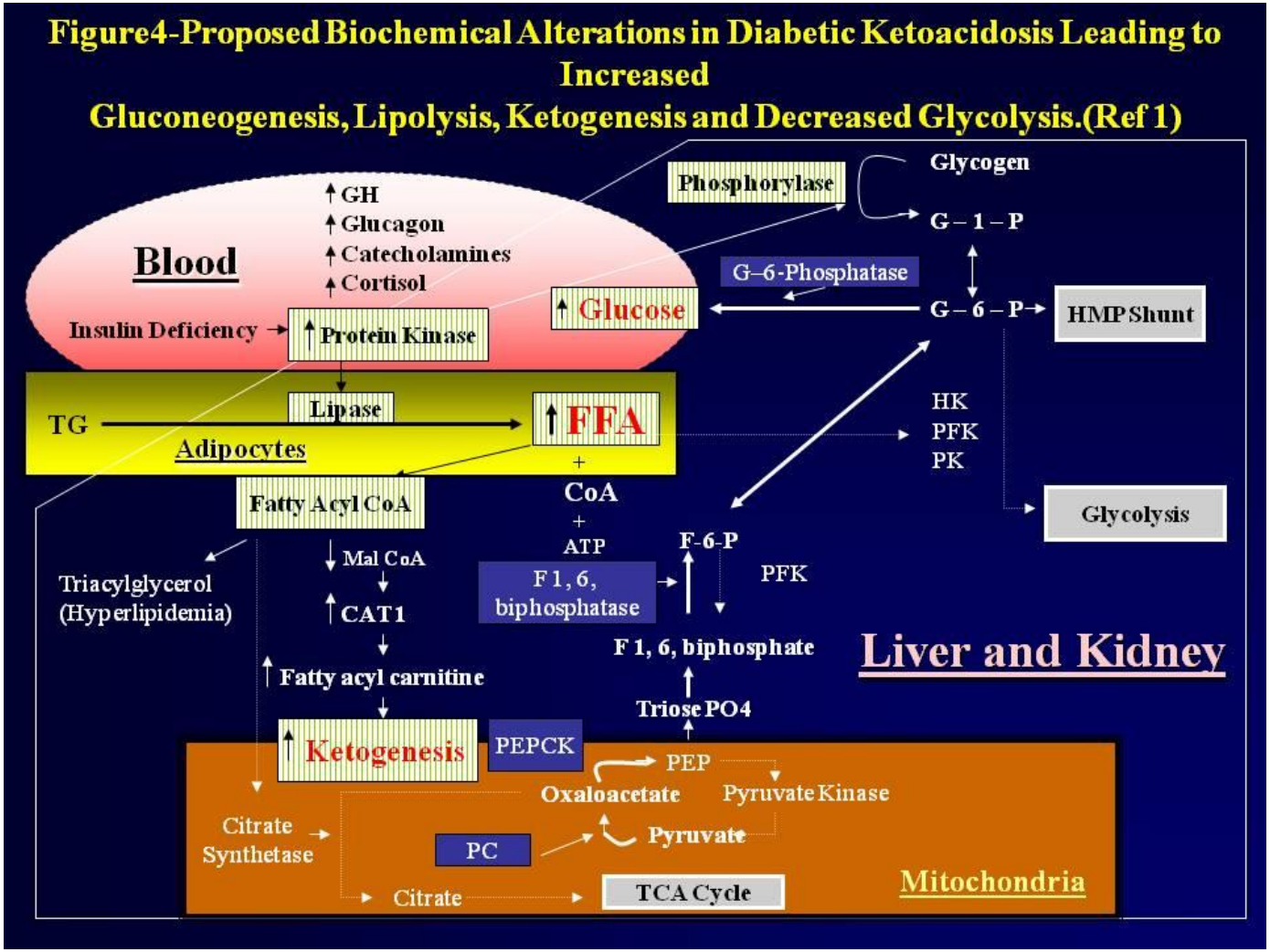
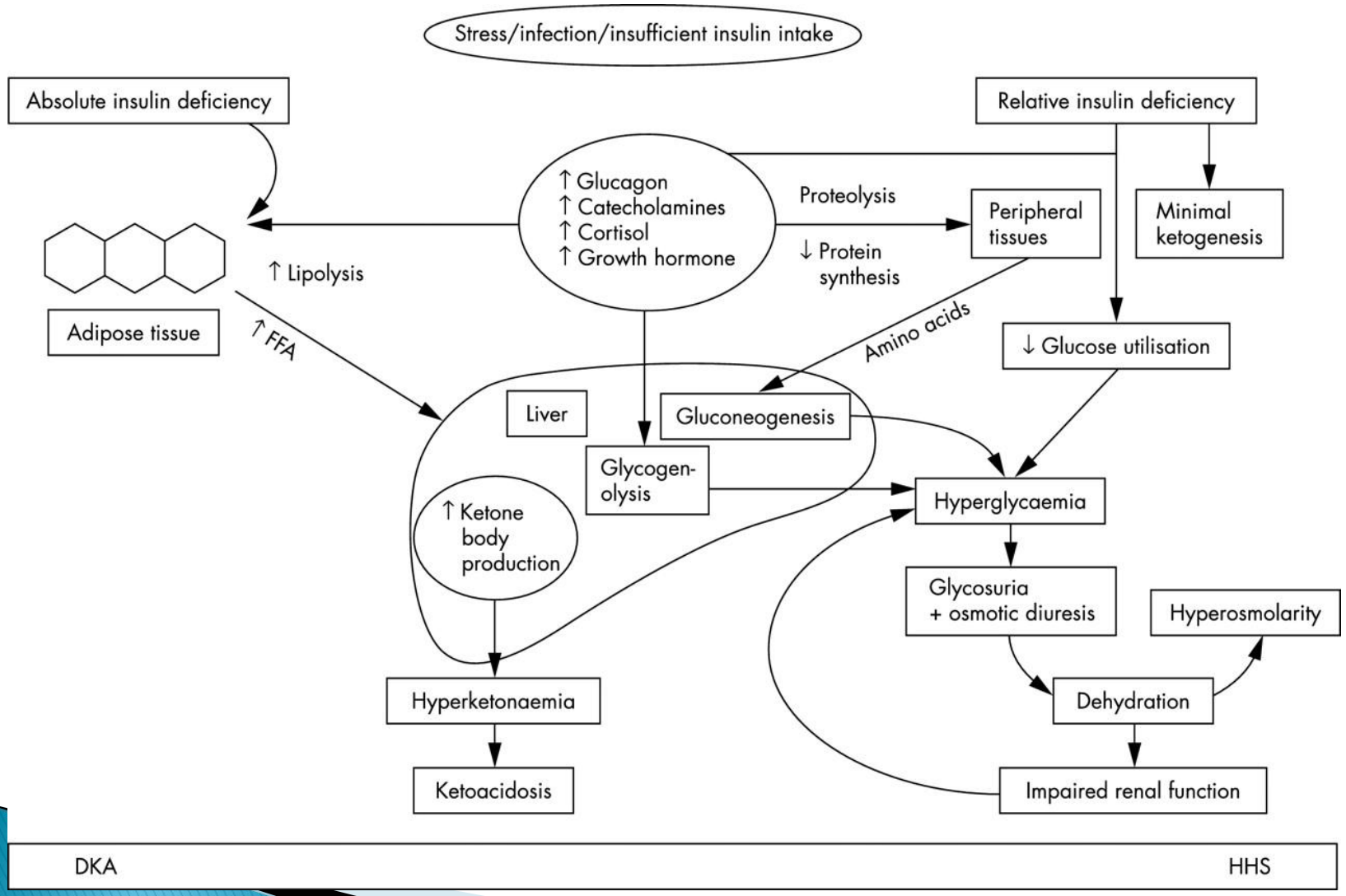


Figure4-Proposed Biochemical Alterations in Diabetic Ketoacidosis Leading to Increased
Gluconeogenesis, Lipolysis, Ketogenesis and Decreased Glycolysis.(Ref 1)
Blood
↑GH
↑Glucagon
↑Catecholamines
↑Cortisol
Insulin Deficiency
↑Protein Kinase
Phosphorylase
Glycogen
G – 1 – P
G–6-Phosphatase
↑Glucose
G – 6 – P
HMP Shunt
TG
Lipase
Adipocytes
↑FFA
+
CoA
HK
PFK
PK
Glycolysis
Fatty Acyl CoA
+
ATP
F-6-P
PFK
Triacylglycerol
(Hyperlipidemia)
Mal CoA
↑CAT1
F 1, 6,
biphosphatase
F 1, 6, biphosphate
Liver and Kidney
↑Fatty acyl carnitine
Triose PO4
↑Ketogenesis
PEPCK
PEP
Oxaloacetate
Pyruvate Kinase
Citrate
Synthetase
PC
Pyruvate
Citrate
TCA Cycle
Mitochondria

Pathogenesis of DKA and HHS



English P , Williams G Po[illegible] Med J 2004;80:253-261

- Ketosis – ◢ *in FFA release*
- Reduced insulin levels + ◢ in catecholamines and GH – increase lipolysis and the release of FFA
- In DKA, hyperglucagonemia alters hepatic metabolism to favor ketone body formation, through activation of **carnitine palmitoyltransferase I.**
- Enzyme is crucial for regulating fatty acid transport into the mitochondria, where beta oxidation and conversion to ketone bodies occur.

- occurs in the context of total insulin deficiency in IDDM
- occurs rarely in NIDDM under the stress of acute illness.
- When DKA occurs in patients with NIDDM, it may represent a transition to insulin deficiency.

TABLE 323-5 Manifestations of Diabetic Ketoacidosis

Symptoms
- Nausea/vomiting
- Thirst/polyuria
- Abdominal pain
- Shortness of breath

Precipitating events
- Inadequate insulin administration
- Infection (pneumonia/UTI/ gastroenteritis/sepsis)
- Infarction (cerebral, coronary, mesenteric, peripheral)
- Drugs (cocaine)
- Pregnancy

Physical findings
- Tachycardia
- Dry mucous membranes/reduced skin turgor
- Dehydration / hypotension
- Tachypnea / Kussmaul respirations/respiratory distress
- Abdominal tenderness (may resemble acute pancreatitis or surgical abdomen)
- Lethargy /obtundation / cerebral edema / possibly coma

Diagnostic Criteria for Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

	Mild DKA	*Moderate DKA*	*Severe DKA*	*HHS*
Plasma glucose (mg per dL [mmol per L])	> 250 (13.9)	> 250	> 250	> 600 (33.3)
Arterial pH	7.25 to 7.30	7.00 to 7.24	< 7.00	> 7.30
Serum bicarbonate (mEq per L)	15 to 18	10 to < 15	< 10	> 15
Urine ketones	Positive	Positive	Positive	Small
Serum ketones	Positive	Positive	Positive	Small
Beta-hydroxybutyrate	High	High	High	Normal or elevated[20]
Effective serum osmolality (mOsm per kg)*	Variable	Variable	Variable	> 320
Anion gap†	> 10	> 12	> 12	Variable
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

DKA = diabetic ketoacidosis; HHS = hyperosmolar hyperglycemic state.

**—Effective serum osmolality = 2 × measured Na (mEq per L) + (glucose [mg per dL] ÷ 18).*

†—*Anion gap = $Na^+ - (Cl^- + HCO_3^-$ [mEq per L]).*

For each ▲ of 100 mg/dl – ▼ of 1,6 mmol/l Na

Acetoacetate – false ▲ of Crea

False ▲ of amylase

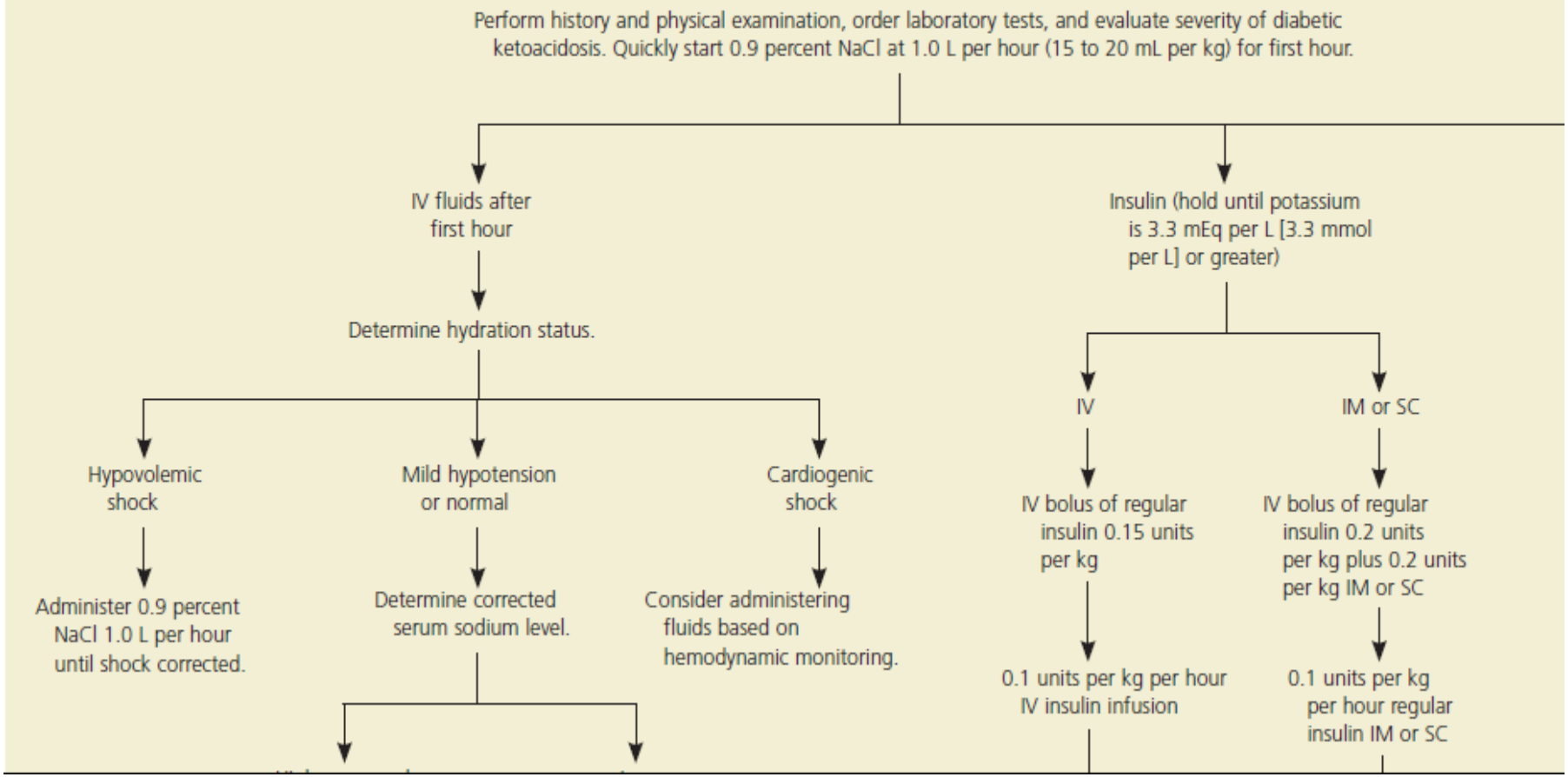
- **$pH = 6.1 + \log (HCO_3 / H_2 CO_3)$**
  - $H_2 CO_3 = pCO_2$ (mm Hg) X 0.03

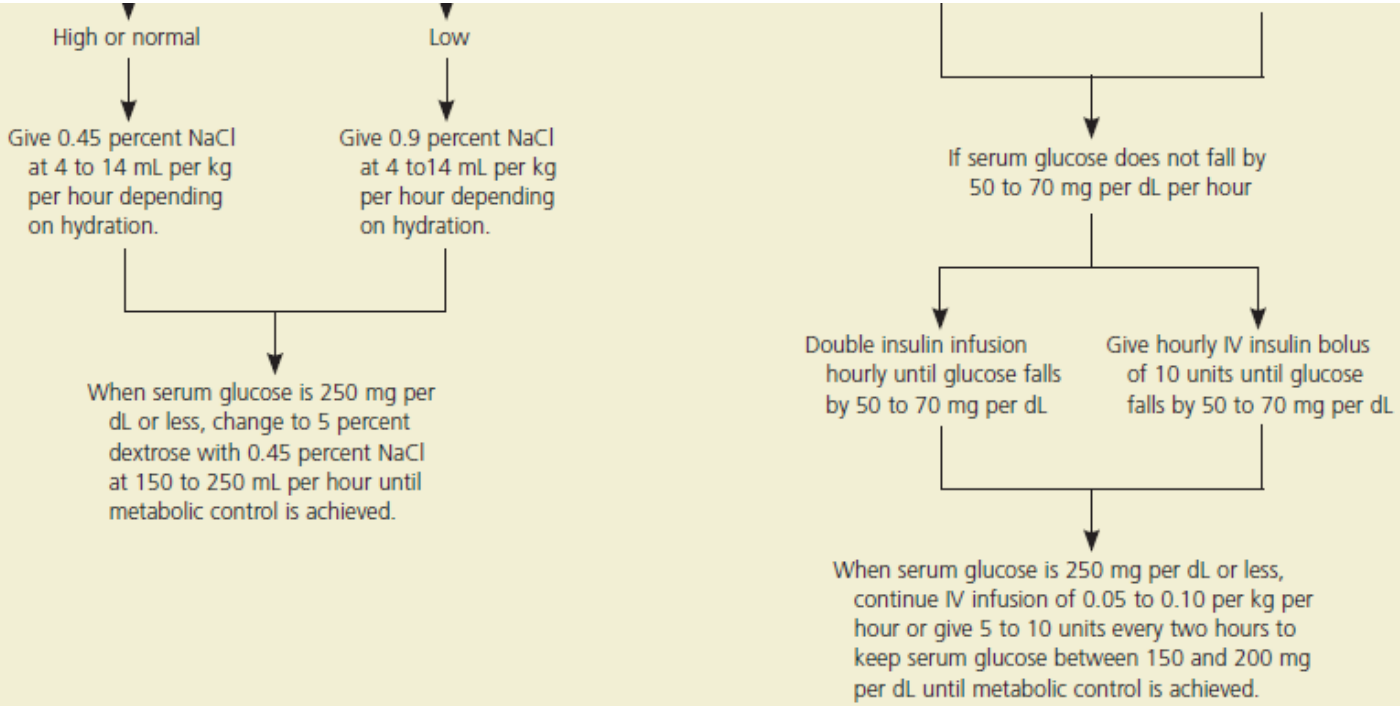
  - pH – 7,35 – 7,45
  - pO2 – 70 – 116 mm Hg (9,2 – 15,5 kPa)
  - pCO2 – 35 – 45 mm Hg (4,7 – 6,0 kPa)
  - HCO3 – 22 – 26 mmol/l
  - SpO2 – norma 95 – 99%
  - BE – +/– 2,5 mEq/l

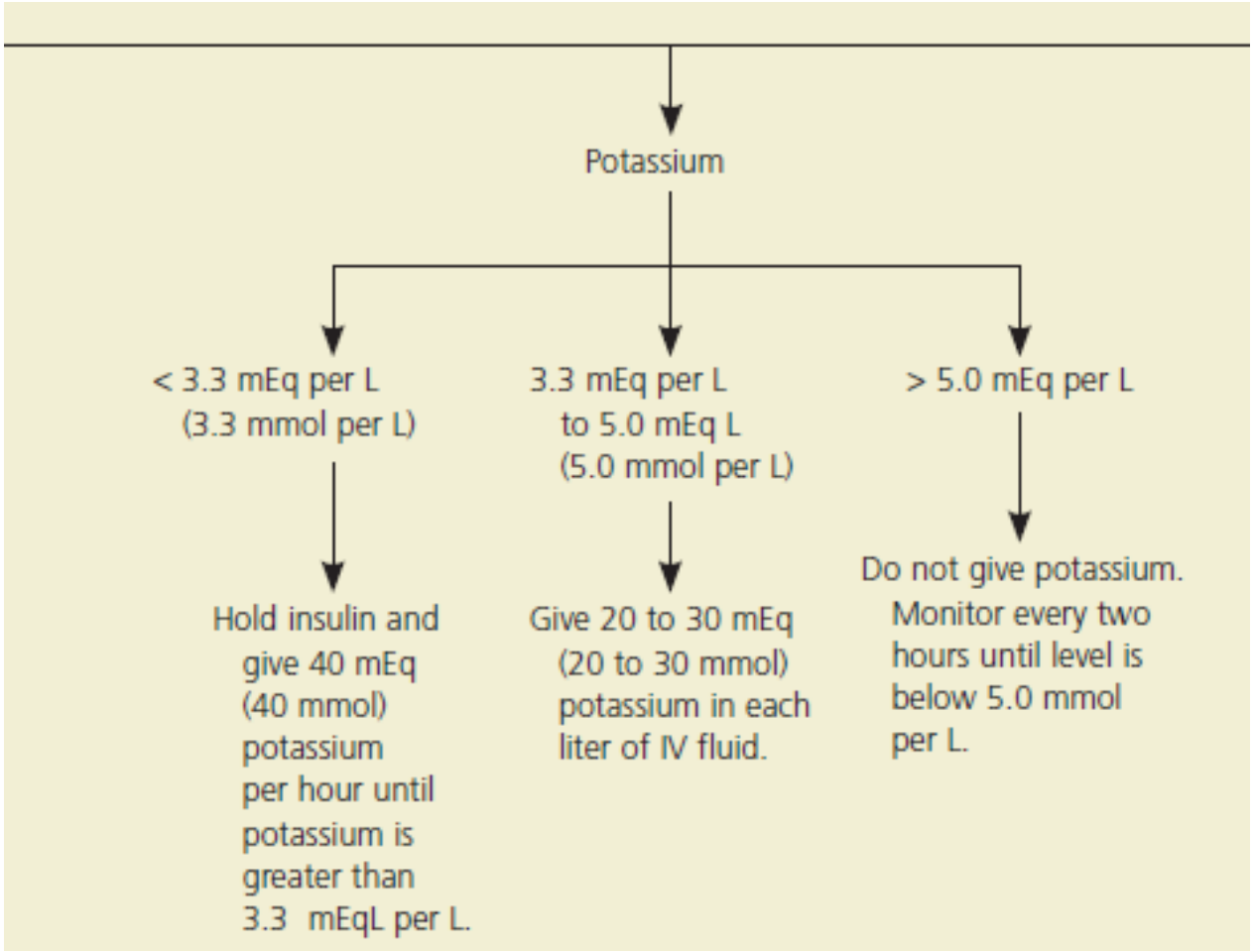
treatment

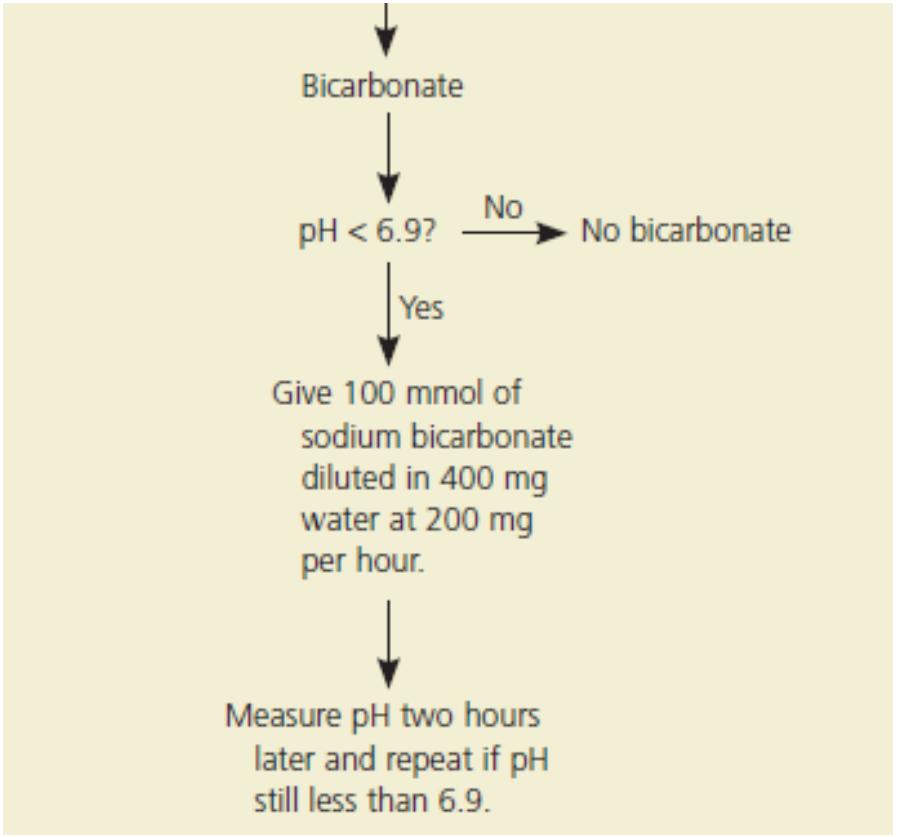
- Fluid replacement
- Insulin therapy
- Electrolyte replacement

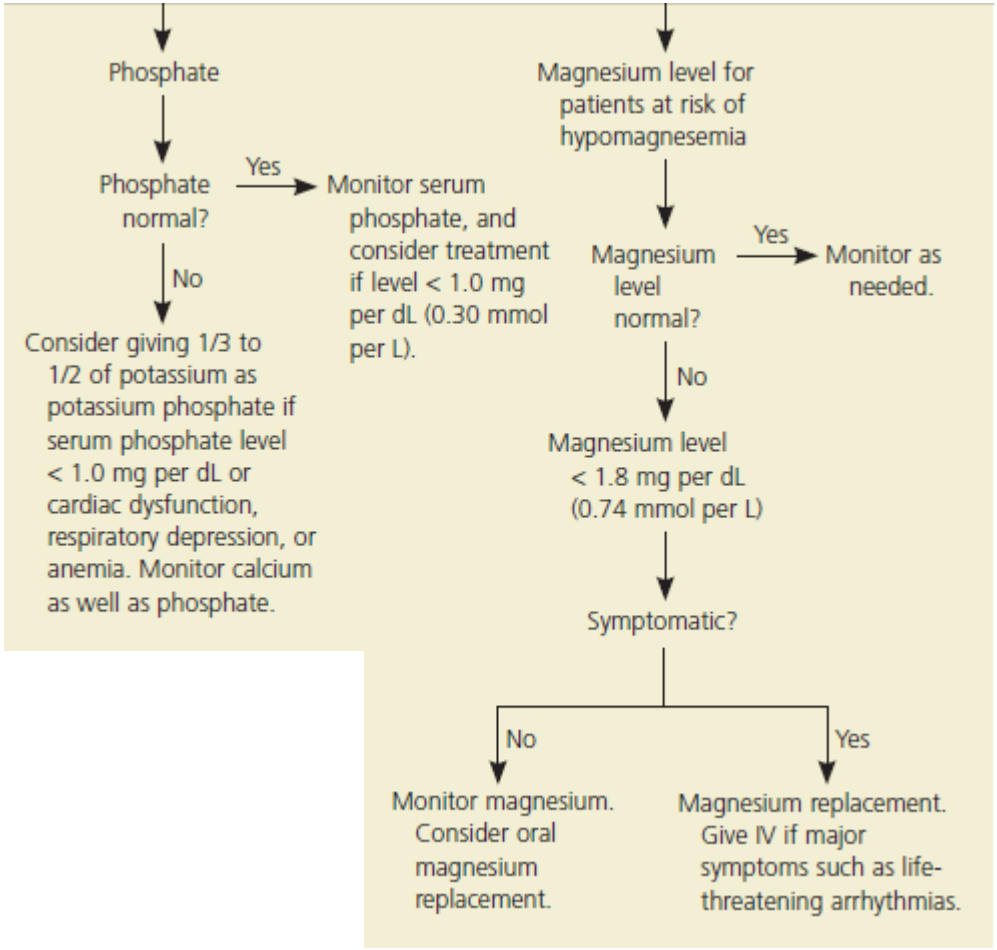
Management of Adults with Diabetic Ketoacidosis




High or normal
Low
Give 0.45 percent NaCl at 4 to 14 mL per kg per hour depending on hydration.
Give 0.9 percent NaCl at 4 to14 mL per kg per hour depending on hydration.
When serum glucose is 250 mg per dL or less, change to 5 percent dextrose with 0.45 percent NaCl at 150 to 250 mL per hour until metabolic control is achieved.
If serum glucose does not fall by 50 to 70 mg per dL per hour
Double insulin infusion hourly until glucose falls by 50 to 70 mg per dL
Give hourly IV insulin bolus of 10 units until glucose falls by 50 to 70 mg per dL
When serum glucose is 250 mg per dL or less, continue IV infusion of 0.05 to 0.10 per kg per hour or give 5 to 10 units every two hours to keep serum glucose between 150 and 200 mg per dL until metabolic control is achieved.


Potassium
< 3.3 mEq per L (3.3 mmol per L)
3.3 mEq per L to 5.0 mEq L (5.0 mmol per L)
> 5.0 mEq per L
Hold insulin and give 40 mEq (40 mmol) potassium per hour until potassium is greater than 3.3 mEqL per L.
Give 20 to 30 mEq (20 to 30 mmol) potassium in each liter of IV fluid.
Do not give potassium. Monitor every two hours until level is below 5.0 mmol per L.


Bicarbonate
pH < 6.9?
No
No bicarbonate
Yes
Give 100 mmol of sodium bicarbonate diluted in 400 mg water at 200 mg per hour.
Measure pH two hours later and repeat if pH still less than 6.9.

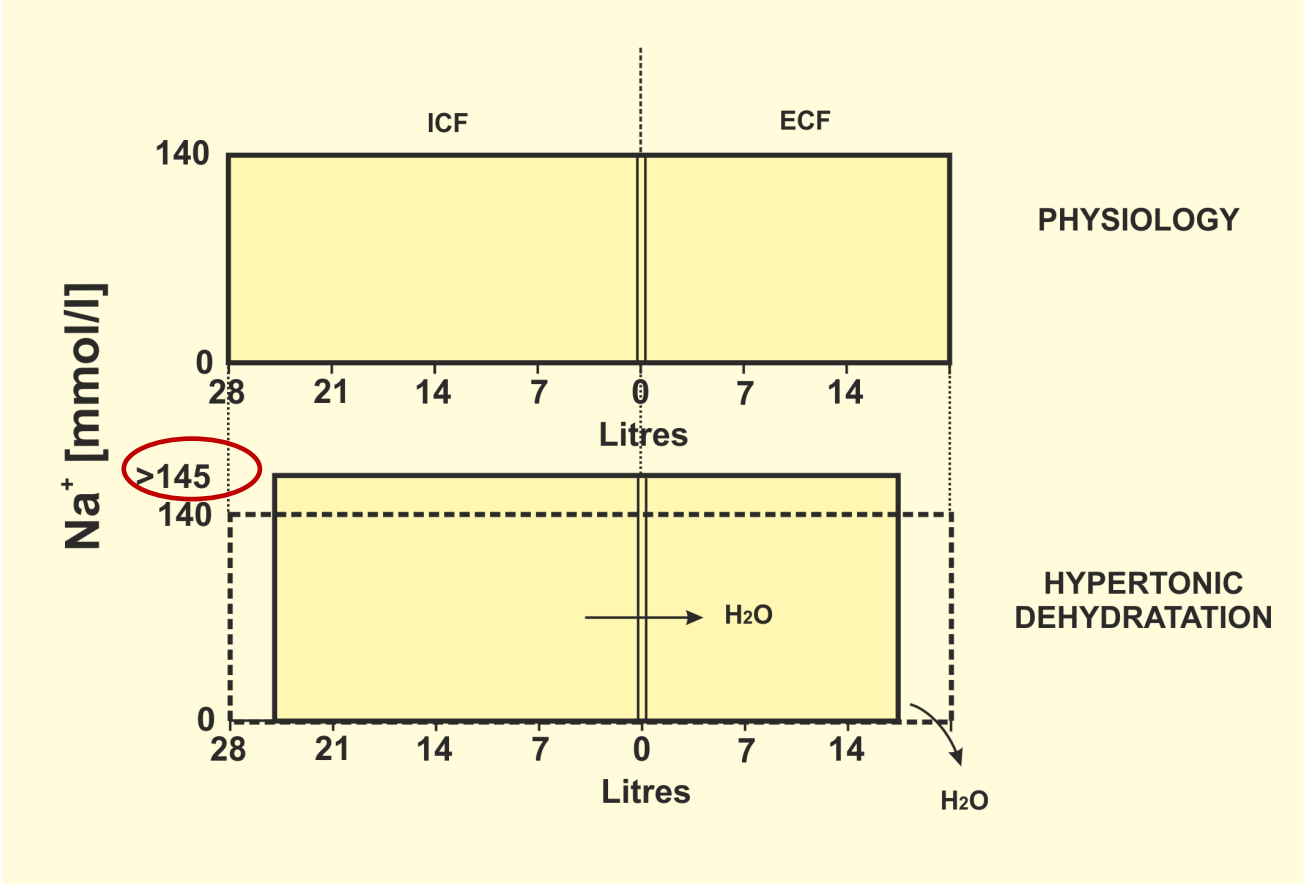

Phosphate
Phosphate normal?
Yes
Monitor serum phosphate, and consider treatment if level < 1.0 mg per dL (0.30 mmol per L).
No
Consider giving 1/3 to 1/2 of potassium as potassium phosphate if serum phosphate level < 1.0 mg per dL or cardiac dysfunction, respiratory depression, or anemia. Monitor calcium as well as phosphate.
Magnesium level for patients at risk of hypomagnesemia
Magnesium level normal?
Yes
Monitor as needed.
No
Magnesium level < 1.8 mg per dL (0.74 mmol per L)
Symptomatic?
No
Monitor magnesium. Consider oral magnesium replacement.
Yes
Magnesium replacement. Give IV if major symptoms such as life-threatening arrhythmias.

Hyperosmolar non-ketotic coma (HNC)

- Relative insulin deficiency and hyperglycemia, usually > 600 mg/dl + elevated serum osmolality (>300 mosm/kg)
- **Dehydration**
- stupor, progressing to coma if uncorrected
- No/small presence of ketosis or acidosis
  - Circulating insulin sufficient to prevent lipolysis and ketosis.

- mortality rate ranges from **10 to 50 %** – (2,6–10 x higher rate than that of DKA (1.2 to 9 %).
- true mortality data difficult to interpret due to high incidence of coexisting diseases
- Age, degree of dehydration, hemodynamic instability, underlying precipitating causes, and degree of consciousnessa – powerful predictorsvof a fatal outcome.

- reduction in the effective circulating insulin with a concomitant elevation of counter-regulatory hormones (glucagon, catecholamines, cortisol, and GH) + increased gluconegenesis
- Impaired glc utilisation.
- Osmotic diuresis (glucosuria)
  - **Hypertonic dehydratation**



For each ▲ of 100 mg/dl - ▼ of 1,6 mmol/l Na **!!!!**

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†—Anion gap = Na^+ – (Cl^- + HCO_3^- [mEq per L]).

For each ▲ of 100 mg/dl – ▼ of 1,6 mmol/l Na

TABLE 2
Precipitating Factors in Hyperosmolar Hyperglycemic State

- Coexisting diseases
  - Acute myocardial infarction
  - Adrenocorticotropic hormone-producing tumors
  - Cerebrovascular accident
  - Cushing's syndrome
  - Hyperthermia
  - Hypothermia
  - Mesenteric thrombosis
  - Pancreatitis
  - Pulmonary embolus
  - Renal failure
  - Severe burns
  - Thyrotoxicosis
- Infection
  - Cellulitis
  - Dental infections
  - Pneumonia
  - Sepsis
  - Urinary tract infection
- Medications
  - Calcium channel blockers
  - Chemotherapeutic agents
  - Chlorpromazine (Thorazine)
  - Cimetidine (Tagamet)
  - Diazoxide (Hyperstat)
  - Glucocorticoids
  - Loop diuretics
  - Olanzapine (Zyprexa)
  - Phenytoin (Dilantin)
  - Propranolol (Inderal)
  - Thiazide diuretics
  - Total parenteral nutrition
- Noncompliance
- Substance abuse
  - Alcohol
  - Cocaine
- Undiagnosed diabetes

TABLE 3
Electrolyte Losses in Hyperosmolar Hyperglycemic State

Electrolytes	*Losses*
Sodium	7 to 13 mEq per kg
Chloride	3 to 7 mEq per kg
Potassium	5 to 15 mEq per kg
Phosphate	70 to 140 mmol per kg
Calcium	50 to 100 mEq per kg
Magnesium	50 to 100 mEq per kg
Water	100 to 200 mL per kg

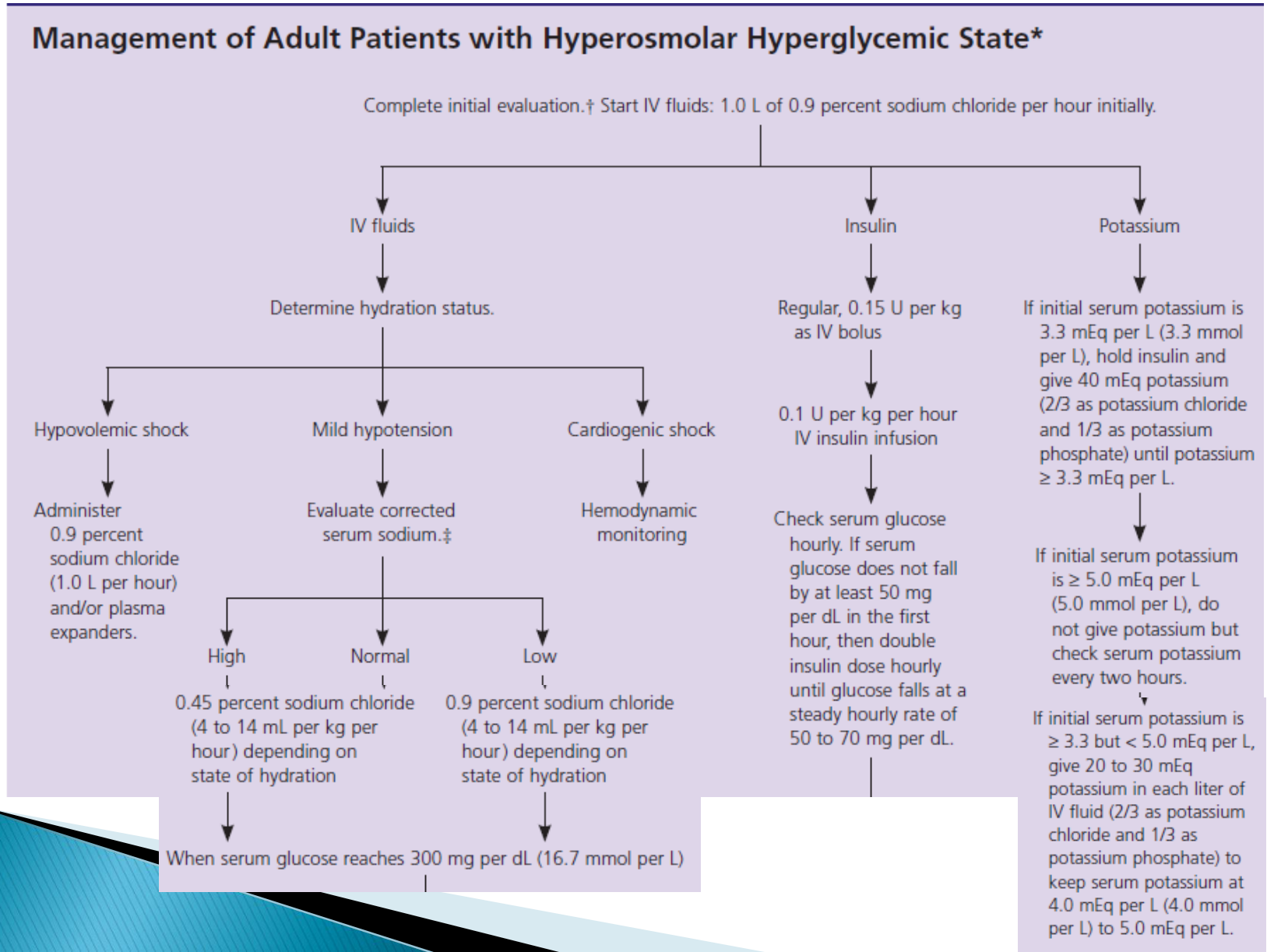
- K^+ – elevated or normal
- Creatinine, (BUN), and hematocrit – almost always **elevated**
- Hyperosmolar hyperglycemic state
- Na^+ – elevated or normal (false result – make correction!)

$$\text{Corrected serum sodium} = \underset{(\text{mEq per L})}{\text{sodium}} + \frac{1.65 \times (\text{glucose [mg per dL]} - 100)}{100}$$

$$\text{Effective serum osmolarity} = (2 \times 150) + \frac{1{,}100}{18} = 300 + 51 = 351 \text{ mOsm per kg}$$

treatment

- (1) vigorous intravenous rehydration
  - first and most important step **aggressive fluid replacement**, should begin with an estimate of the fluid deficit (usually **100 to 200 mL/kg**, or an average total **of 9 L**
- (2) electrolyte replacement
- (3) administration of intravenous insulin
- (4) diagnosis and management of precipitating and coexisting problems,
- (5) prevention


Management of Adult Patients with Hyperosmolar Hyperglycemic State*
Complete initial evaluation.† Start IV fluids: 1.0 L of 0.9 percent sodium chloride per hour initially.
IV fluids
Determine hydration status.
Hypovolemic shock
Administer 0.9 percent sodium chloride (1.0 L per hour) and/or plasma expanders.
Mild hypotension
Evaluate corrected serum sodium.‡
High
0.45 percent sodium chloride (4 to 14 mL per kg per hour) depending on state of hydration
Normal
Low
0.9 percent sodium chloride (4 to 14 mL per kg per hour) depending on state of hydration
When serum glucose reaches 300 mg per dL (16.7 mmol per L)
Cardiogenic shock
Hemodynamic monitoring
Insulin
Regular, 0.15 U per kg as IV bolus
0.1 U per kg per hour IV insulin infusion
Check serum glucose hourly. If serum glucose does not fall by at least 50 mg per dL in the first hour, then double insulin dose hourly until glucose falls at a steady hourly rate of 50 to 70 mg per dL.
Potassium
If initial serum potassium is 3.3 mEq per L (3.3 mmol per L), hold insulin and give 40 mEq potassium (2/3 as potassium chloride and 1/3 as potassium phosphate) until potassium ≥ 3.3 mEq per L.
If initial serum potassium is ≥ 5.0 mEq per L (5.0 mmol per L), do not give potassium but check serum potassium every two hours.
If initial serum potassium is ≥ 3.3 but < 5.0 mEq per L, give 20 to 30 mEq potassium in each liter of IV fluid (2/3 as potassium chloride and 1/3 as potassium phosphate) to keep serum potassium at 4.0 mEq per L (4.0 mmol per L) to 5.0 mEq per L.

Lactic Acidosis

- Severe defined as a high **anion gap** metabolic acidosis (anion gap >10) with a blood lactate concentration ≥5.0 mmol/l (N: 0.4–1.2 mmol/l)
  - AG = $[Na^+]-([Cl^-]+[HCO3^-])$, should be < 7–9 mmol/l
- The pathological elevation of lactate and hydrogen ions may result from:
  - Overproduction
  - Delayed clearance of lactate
  - Combination of both.

Table 4 Causes of lactic acidosis

Type A (anaerobic/hypoxic)	Type B (aerobic)
Shock:	Systemic disease:
Cardiogenic	Diabetes
Endotoxic	Neoplasia
Hypovolaemic	Liver disease
Cardiac failure	Drugs/toxins:
	Biguanides
Asphyxia	Ethanol
	Methanol
Carbon monoxide poisoning	Salicylates
	Inborn errors of metabolism:
	Type 1 glycogen storage disease
	Fructose 1,6-diphosphatase deficiency

Adapted from Stacpoole *et al.*[80]

- Type A – concurrent complicating illness without the accumulation of metformin;
- Type B – marked metformin accumulation without concurrent hypoxic factors

- Bicarbonate therapy is one of the principal management modalities for lactic acidosis
- bicarbonate in combination with haemodialysis has been successful in the management of metformin associated lactic acidosis