Diabetes Mellitus

Diabetes mellitus consists of hyperglycemia caused by from insulin deficiency, impairment of insulin action, or both. Five percent of the population is affected by diabetes, 10% of whom have type 1 diabetes. Acute hyperglycemia with ketoacidosis can lead to severe electrolyte disturbances, cerebral edema, and vascular collapse. Chronic hyperglycemia can cause damage to the eyes, kidneys, nerves, heart, and blood vessels. Overtreatment of hyperglycemia can cause hypoglycemia, resulting in seizures, loss of consciousness, and even death.

I. **Classification of Diabetes Mellitus**
   A. Diabetes mellitus is classified into two primary types: type 1 (previously referred to as insulin-dependent diabetes) and type 2 (previously referred to as noninsulin-dependent diabetes).
   B. **Type 1 Diabetes**
      1. Type 1 diabetes is caused by absolute insulin deficiency. Most cases among children and adolescents (95%) result from autoimmune destruction of the beta cells of the pancreas. The peak age at diagnosis is 12 years, and 75-80% of individuals develop type 1 diabetes before age 30 years. Some persons present with ketoacidosis at disease onset (usually children), while others manifest elevated glucose levels for years (more common in adults).
      2. Gender distribution is nearly equal. Caucasians have the highest incidence of type 1 diabetes compared with African-Americans, Asians, and Native Americans.
   C. **Type 2 Diabetes**
      1. Type 2 diabetes is caused by insulin resistance in combination with a relative insulin deficiency. Most individuals who have type 2 diabetes do not require exogenous insulin.
      2. Most patients who have type 2 diabetes are obese. Native Americans, Mexican-Americans, African-Americans, and Pacific Islanders are at increased risk.

II. **Pathogenesis of Type 1 Diabetes**
   A. Type 1 diabetes develops in individuals who are genetically susceptible, have come in contact with certain environmental exposures, and have immune-mediated destruction of the beta cells.
   B. Although 80-85% of patients who have type 1 diabetes have no other affected family member, the relative risk increases to 1 in 20 (from 1 in 300) for first-degree relatives. If the affected family member is the father or a sibling, the risk is 6%; if the affected family member is the mother, the risk is only 2% to 3%.

III. **Clinical Presentation of Diabetes**
   A. The classic signs and symptoms of diabetes--polyuria, polydipsia, and polyphagia--are caused by insulin deficiency. Extremely high glucose levels cause a severe diuresis that results in fluid, electrolyte, and calorie loss. Two thirds of patients are diagnosed at this stage before metabolic decompensation occurs.
   B. The diagnosis of type 1 diabetes is established by the presence of glycosuria coupled with a random serum glucose level greater than 200 mg/dL or a fasting level greater than 126 mg/dL obtained in a clinical laboratory.
   C. DKA may be confused with meningitis, acute abdomen, and sepsis; the

continuation of urination due to osmotic diuresis may lead to the false impression that dehydration is not present.

IV. **Management of Diabetic Ketoacidosis**

A. DKA can be seen at the time of diagnosis of type 1 diabetes or in the patient who has established disease if diabetes management is inadequate.

B. DKA is caused by severe insulin deficiency, which leads to hyperglycemia, ketogenesis, and elevated counterregulatory hormone levels.

C. Symptoms include polyuria, polydipsia, hyperpnea with shortness of breath, vomiting, and abdominal pain. Hyperosmolar dehydration and acid/base and electrolyte disturbances occur. In the advanced stages of DKA, the level of consciousness alters and can lead to coma.

D. **Rehydration**

1. The immediate evaluation should assess the degree of dehydration by determining capillary refill, skin temperature, and postural heart rate and blood pressure.
2. Significant elevation of urea nitrogen level indicates severe dehydration. Predicted sodium (correct sodium by adding 1.6 mEq for every 100 mg/dL that the serum glucose is >180 mg/dL) and blood glucose concentrations should be measured and monitored as dehydration is corrected.
3. Initial fluid resuscitation consists of a 10-mL/kg bolus of 0.9% saline over 30-60 minutes, repeated if hypovolemic shock persists. It is extremely rare for patients to require more than 20 mL/kg of fluid resuscitation in the initial phase of fluid management. Patients then should begin to receive maintenance fluid requirements (1,500 mL/m^2 per 24 h) added to the calculated fluid deficit (>2 y: 30 mL/kg for mild deficit, 60 mL/kg for moderate deficit, 90 mL/kg for severe deficit; <2 y: 50 mL/kg for mild deficit, 100 mL/kg for moderate deficit, 150 mL/kg for severe deficit). The deficit should be replaced slowly over 48 hours. The sodium concentration of the fluid should provide 50% of the sodium deficit in the first 12 hours and the remainder in the next 36 hours (75 to 125 mEq/L sodium chloride).
4. Excessive fluid administration and inadequate sodium replacement in the first 24 hours of therapy can lead to a decrease in serum osmolality and cerebral edema. As therapy progresses, effective serum osmolality should be monitored (effective serum osmolality = 2(Na^+)+ (glucose [mg/dL])/18), and fluid therapy should be administered to ensure that effective osmolality does not decrease rapidly. A decrease in serum sodium concentration is associated with a 15-20% risk of neurologic complications (headache, acute deterioration, or death).

Laboratory Monitoring During DKA	
Blood glucose:	At presentation, then hourly by fingerstick with glucose meter; a level of >500 mg/dL requires laboratory confirmation
Serum sodium and potassium:	At presentation, then at 4- to 6-h intervals
Acid/base status:	At presentation, then at 2- to 4-h intervals. Venous pH and serum carbon dioxide

Serum urea nitrogen, complete blood count, acetone and appropriate cultures can be obtained at presentation.

E. **Potassium Replacement**
   1. DKA is associated with total body potassium depletion. This deficit should be replaced by infusing potassium chloride at a rate of 3 mEq/kg per 24 hours after completion of the normal saline fluid resuscitation.
   2. The potassium infusion often needs to be increased to keep serum potassium levels above 3.5 mEq/L. Cardiac monitoring should assess for the development of U waves and arrhythmias.
   3. If the patient requires more than 4 mEq/kg of a potassium infusion, 50% can be administered as potassium phosphate to help prevent hyperchloremia acidosis. Supplemental potassium phosphate also can improve the associated hypophosphatemia. However, routine phosphate administration is not indicated in DKA because little morbidity is associated with hypophosphatemia and excessive phosphate administration can lead to hypocalcemia.

F. **Lowering the Glucose Level**
   1. Regular insulin should be initiated as an intravenous infusion of 0.1 U/kg per hour. The goal of therapy is to lower the glucose level by 50 to 100 mg/dL per hour.
   2. Once the glucose level is in the range of 250 to 350 mg/dL, 5% glucose should be initiated; when the glucose level is between 180 to 240 mg/dL, the infusate can be changed to 10% glucose.

G. **Correcting Acidosis**. Alkali therapy is not necessary to correct the acidosis associated with DKA. If acidosis is severe, with a pH less than 7.1, sodium bicarbonate can be infused slowly at a rate of 1 to 3 mEq/kg per 12 hours and discontinued when the pH exceeds 7.2.

H. **Cerebral Edema**
   1. Cerebral edema is the gravest complication of treating DKA. In 2-3% of cases, cerebral edema is potentially life-threatening. The typical presentation is acute neurologic deterioration 6 to 12 hours after the initiation of treatment, although some patients have antecedent headache, lethargy, incontinence, seizures, pupillary changes, and signs of intracranial hypertension, with decreasing heart rate and increasing blood pressure.
   2. Cerebral edema is treated with mannitol (0.25 to 1.0 g/kg), which should be administered rapidly when neurologic symptoms develop.

V. **Long-term Diabetes Management**

A. The **Diabetes Control and Complication Trial (DCCT)** demonstrated that

intensive management of diabetes results in a significant reduction in the development of diabetic complications: a 76% reduction in retinopathy, a 39% reduction in microalbuminuria, and a 60% reduction in clinical neuropathy. In addition, there is slower progression of pre-existing complications; intensive treatment slows the progression of retinopathy by 54%, proliferative retinopathy by 47%, and albuminuria by 54%.

Targeted Blood Glucose Range (Preprandial)

Age	Glucose Levels (mg/dL)
Infants, toddlers	120-220
Preschool children	100-200
School-age children	70-150

B. **Insulin Regimens**

1. The preferred insulin preparation is human insulin, which is less antigenic than animal-derived insulin. It is unusual for most preteens to require more than two to three injections per day. For preschool-and school-age children, two injections are usually all that is required to achieve targeted glycemia. Insulin is distributed as short-acting (regular insulin) and intermediate-acting (NPH) insulin before breakfast and a small dose of usually short- or intermediate-acting insulin alone at dinner.
2. If indicated to improve morning blood glucose levels, the evening dosage can be split so that the short-acting insulin is administered before dinner and the intermediate-acting is administered before bedtime.

Recommended Total Daily Insulin Dosage

<5 Years (U/kg)	5-11 Years (U/kg)	12-18 Years (U/kg)
0.6-0.8	0.75-0.9	0.8-1.5

Newly diagnosed patients and those who are in the remission phase may require less insulin. If the required dosage exceeds these guidelines, consider cryptic illness, causes of insulin resistance, or non-adherence.

Meal Plans

Calorie Content

2000 kcal/m^2 or 1000 kcal + 100 kcal/year of age

Distribution
- 25% Breakfast
- 25% Lunch
- 30% Dinner
- 20% Snacks

Food Type
- 50% carbohydrate
- 25% to 30% fat
- 20% to 25% protein

Outpatient Management of Type 1 Diabetes

Monitoring Schedule	**Daily**	**Intermittent (2 times/month)**
Blood testing	Before breakfast Before lunch Before dinner	Middle of the night Midmorning After school

Insulin Regimens
- Start with distribution of:
  - 2/3 total dose before breakfast
  - 1/3 total dose in PM
- Morning dose:
  - 1/3 short-acting or rapid-acting
  - 2/3 intermediate-acting
- Evening dose:
  - 1/2 short-acting or rapid-acting
  - 1/2 intermediate-acting
    - -either as one injection with both short- or rapid-acting and intermediate-acting before dinner OR short- or rapid-acting before dinner and intermediate-acting at bedtime
- Alternate regimens:
  - Long-acting 1 to 2 times per day
  - Short- or rapid-acting with meals
  - Continuous insulin infusion pump

Adjustment Algorithms

Immediate Correction of Abnormal Blood Glucose Level Out of Target (70to 150 mg/dL)

Add extra insulin for each 50 mg/dL above target:
- <5 years old: 0.25 U for each 50 mg/dL
- Grade school age: 0.5-1 U
- Adolescents: 1-2 U

Correction of Abnormal Established Pattern

Short/rapid- or intermediate-acting insulin adjusted after 3-day pattern established

Increase or decrease by 0.5, 1, or 2 U (10% of dose)

Time of Abnormal Test	Change this Insulin
Before breakfast	Evening intermediate
Before lunch	Morning short/rapid
Before dinner	Morning intermediate
Before bedtime	Evening short/rapid

C. **Blood Glucose Monitoring**
   1. Children and adolescents should test their blood glucose levels at least four times a day, before meals and at bedtime.
   2. Additional testing should be performed intermittently, particularly in the middle of the night and at times of unusual behavior in very young children.

D. **Health-care Assessment**
   1. Diabetic children should be seen quarterly to assess height and weight, pubertal progression, and blood pressure. The eyes, thyroid gland, abdomen (hepatomegaly), skin, joints, and injection sites should be examined.
   2. Quarterly measurement of hemoglobin A1c (HbA1c) assesses glycemic control and reflects the average blood glucose concentration over the last 120 days.

Assessment of HbA1c Values

HbA1c Values	Level of Glycemic Control
HbA1c >10%	Poor or minimal
HbA1c 8.0% to 10.0%	Average
<8.0%	Excellent or intensive

   3. Urinary microalbumin excretion should be assessed with an albumin-to-creatinine ratio. If albumin is high--exceeding 30 mg/g on at least two occasions--the adequacy of glycemic control should be reevaluated. If glycemic control is the best that can be achieved, an ACE-inhibitor should be initiated, even if the patient's blood pressure is normal. Any ACE-inhibitor can be used. Angiotensin-converting enzyme (ACE)-inhibiting drugs have renal protective effects when microalbuminuria or hypertension begins.
   4. Thyroid function tests should be obtained at diagnosis and when symptoms develop. There is an increased risk of autoimmune thyroiditis, and 6% of diabetic children also have hypothyroidism. Lipid profiles may be obtained in adolescent patients. Five years after diagnosis, annual dilated ophthalmologic examination by an ophthalmologist should be initiated.

E. **Insulin Analogs**

1. Insulin analogs have a more rapid onset of action than regular insulin because they are monomers of insulin rather than insulin aggregates. Lispro insulin has a rapid onset of action of 10 minutes and a short duration of action (2 hours).
2. The ability to administer it 10 minutes prior to eating improves lifestyle. In very young children, it might be as efficacious if given after the meal, when the exact quantity of food ingested can be determined. §