Chapter 7
General Principles of Pathophysiology

Objectives

Describe normal cell environment

Outline how alterations in water and electrolyte balance affect body function

Describe treatment of fluid/electrolyte imbalances

Describe body mechanisms to maintain acid-base balance

Objectives

Outline alterations in acid-base balance

Describe management of patients with acid-base imbalance

Describe cell or tissue alterations due to adaptation, injury, neoplasia, aging, death

Outline effect of cell injury on local/systemic body function
Objectives

- Describe alterations in body function due to genetic/familial disease factors
- Outline hypoperfusion syndrome
- Describe inflammatory and immune responses to cell injury or antigenic stimulation
- Explain how altered immunity and inflammation can harm body function
- Describe impact of stress on response to illness or injury

Scenario

Your patient appears acutely ill. His physician says he has a diagnosis of diabetic ketoacidosis. He is breathing rapidly, has a dry, furrowed tongue, and tenting skin. The physician tells you to watch for rhythm disturbances.

Consider

- What signs and symptoms of dehydration should you watch for?
- How should you treat the dehydration?
- Why is the patient breathing so fast?
- Should you attempt to slow his breathing?
- Why might this patient have increased potassium levels that can cause rhythm problems?
The Cell

- Fundamental unit found in higher life forms

Tissue Types

- Epithelial
- Connective
  - Including hematologic tissue
- Muscle
- Nervous

Intracellular Fluid (ICF)

- Fluid found in all body cells
- 40% of total body weight
Extracellular Fluid (ECF)

- Intravascular
  - Blood plasma
- Interstitial fluid
  - Between cells
    - Cerebrospinal fluid
    - Intraocular fluid
    - 20% of total body weight

Aging and Distribution of Body Fluids

- Water is the main component of body mass
  - Adults
    - 50% to 60% of total body weight
  - Newborn
    - About 80% of total body weight
  - Childhood
    - 60% to 65% of total body weight
  - Further declines with age

Water Movement Between ICF and ECF

- Osmosis
  - Flow of fluid across a semipermeable membrane from a lower solute concentration to a higher solute concentration
- Partial pressures of gases determine osmotic pressure
- Nongaseous particles (e.g., electrolytes)
  - Osmotic pressure determined by:
    - Number and molecular weights
    - Permeability of membrane
Osmosis

Solutions
- Hypertonic solution
- Hypotonic solution
- Isotonic solution

Diffusion
- Due to constant motion of atoms, molecules, ions in solution
  - Passive process
  - Moves particles from area of higher concentration to area of lower concentration
- Concentration gradient
Mediated Transport Mechanisms

- Carrier molecules
  - Proteins
  - Glucose
- Two kinds of mediated transport:
  - Active transport
  - Facilitated diffusion

Mediated Transport by a Carrier Molecule
Molecule Released on Other Side of Plasma Membrane

Water Movement between Plasma and Interstitial Fluid
- Fluid transfer between blood and interstitial fluid
- Due to pressure changes at arterial and venous ends of the capillary

Capillary Network
- Blood enters capillary network from arterioles
- Flows through capillary network into venules
- Arteriolar capillaries
- Venous capillaries
- True capillaries
- Thoroughfare channels
- Capillary sphincters
Sympathetic Innervation

- Sympathetic fibers innervate all blood vessels except:
  - Capillaries
  - Capillary sphincters
  - Most metarterioles
- Vasoconstrictor and vasodilator fibers

Diffusion across Capillary Wall

- Capillary flow
  - Hydrostatic pressure
  - Osmotic pressure
- Oncotic pressure
- Capillary and membrane permeability
**Starling Hypothesis**

Net filtration =
Forces favoring filtration − Forces opposing filtration

**Alterations in Water Movement**

- **Edema**
  - Fluid accumulation in interstitial spaces
  - Due to any condition that leads to:
    - Net movement of fluid out of capillaries into interstitial tissues

**Pathophysiology of Edema**

- **Normal interstitial space fluid depends on:**
  - Capillary hydrostatic pressure
  - Oncotic pressure by blood plasma proteins
  - Capillary permeability
  - Lymphatic channels collect fluid forced from capillaries by blood hydrostatic pressure and return it to circulation
Mechanisms Responsible for Edema

- Increased hydrostatic pressure
- Decreased plasma oncotic pressure
- Increased capillary permeability
- Lymphatic obstruction
- Increased capillary hydrostatic pressure
  - Venous obstruction
  - Sodium and water retention

Clinical Manifestations of Edema

- Edema may be localized or generalized

Localized edema
- Usually limited to:
  - Injury site (e.g., a sprained ankle)
  - Organ system (e.g., cerebral edema, pulmonary edema)

Generalized Edema

- More widespread

- Dependent parts of body
  - Often:
    - Weight gain
    - Swelling
    - Puffiness
  - Other symptoms from underlying illness
Water Balance, Sodium, and Chloride

- Water follows osmotic gradient established by changes in sodium concentration
  - Sodium and water balance are closely related

Water Balance

- Regulated by antidiuretic hormone
  - Secretion of ADH
  - Perception of thirst

- Release of ADH initiated by:
  - Increase in plasma osmolality
  - Decrease in circulating blood volume
  - Lowered venous and arterial pressure

ADH

- Increased plasma osmolality
  - Stimulates hypothalamic neurons (osmoreceptors)
  - Causes thirst perception
  - Increases ADH release from posterior pituitary
ADH

- After ADH release:
  - Water is reabsorbed into plasma from distal renal tubules and kidney collecting ducts
  - Amount of water lost in urine decreases
  - Plasma osmolality returns to normal as water is reabsorbed

Sodium and Chloride Balance

- Sodium
  - Major ECF cation
  - Sodium balance regulated by aldosterone
    - Hormone secreted from the adrenal cortex
  - Regulates:
    - Osmotic forces
    - Water balance

- Chloride
  - Major ECF anion
  - Provides electroneutrality with sodium
  - Increases or decreases in chloride are proportional to changes in sodium
Sodium and Chloride Balance

- Aldosterone is secreted when sodium levels decrease or potassium levels increase
  - Increases reabsorption of sodium, secretion of potassium by distal tubules of kidneys
- Renin is secreted by kidneys when blood volume or water balance is reduced

Renin-Angiotensin

- Renin stimulates formation of angiotensin I:
  - Then converted to angiotensin II
- Angiotensin II is a potent vasoconstrictor
  - Stimulates ADH secretion
- Results in:
  - Reabsorption of sodium and water
  - Elevation in blood pressure
  - Activation of renin-angiotensin system

Role of Adrenal Medulla in Regulating BP
Renin-Angiotensin-Aldosterone Mechanism

Vasopressin (ADH) Mechanism

Natriuretic Hormone
- Promotes urinary secretion of sodium
- Decrease in sodium tubular reabsorption
- Loss of sodium and water
Sodium, Chloride, and Water Balance

- Homeostatic mechanisms
  - Maintain constant balance between water intake and excretion
  - Water gained each day approximately equals water lost

Alterations in Water Balance

- Gain water primarily by:
  - Drinking fluids
  - Ingesting food containing moisture
  - Forming water through oxidation of hydrogen in food during metabolic process

- Body loses water through:
  - Kidneys as urine
  - Bowel as feces
  - Skin as perspiration
  - Exhaled air as vapor
  - Excretion of tears and saliva
Alterations in Water Balance

- Abnormal states of body fluid balance
  - If the water lost exceeds the water gained, there is a water deficit (dehydration)
  - If the water gained exceeds the water lost, there is a water excess (overhydration)

Dehydration

- Dehydration classifications
  - Isotonic
    - Excessive loss of sodium and water in equal amounts
  - Hypernatremic
    - Loss of water in excess of sodium
  - Hyponatremic
    - Loss of sodium in excess of water

Isotonic Dehydration

- Vomiting, diarrhea, infection, bowel obstruction

- Signs and symptoms
  - Skin turgor, oliguria, anuria, weight loss

- Treatment
  - Isotonic fluids
Hypernatremic Dehydration
- Diuretic use, sodium intake without water, diarrhea
- Dry, sticky mucus membranes, flushed skin, thirst, oliguria, increased thirst, altered LOC
- Treat with isotonic fluids

Hyponatremic Dehydration
- Diuretic use, perspiration, renal problems, increased water intake
- Muscle cramps, seizures, rapid pulse, diaphoresis, cyanosis
- Treatment with NS or LR
  - Rarely, use hypertonic saline

Overhydration
- Increased body water
- Excess intake, impaired cardiac or renal function, endocrine dysfunction
- Dyspnea, edema, polyuria, crackles, weight gain
- Treatment varies by cause:
  - Fluid restriction
  - Diuretics
Electrolyte Imbalances

- In addition to water and sodium imbalances, other electrolyte imbalances may occur
  - Potassium
  - Calcium
  - Magnesium

Potassium

- Major intracellular cation
- Needed for nerve, cardiac, skeletal function
- Excess excreted by kidneys
- Imbalance can cause sudden death

Hypokalemia

- Poor absorption, vomiting, diarrhea, renal disease, diuretics
- Malaise, weakness, dysrhythmias, decreased reflexes, faint heart sounds, hypotension, anorexia, vomiting
- Hospital treatment
  - Oral or IV potassium

Hyperkalemia
- Renal failure, burns, crush injuries, infections, excessive use, acidosis
- Dysrhythmias, irritability, abdominal distention, nausea, diarrhea, oliguria, weakness, paralysis
- Treatment
  - Life threats – calcium, glucose, insulin IV, albuterol
  - Hospital – K+ restriction, exchange resins, dialysis

Calcium
- Essential for:
  - Neuromuscular transmission
  - Cell membrane permeability
  - Hormone secretion
  - Bone growth
  - Muscle contraction

Hypocalcemia
- Endocrine dysfunction, renal disease, malabsorption
- Paresthesia, tetany, cramps, neural excitability, seizure, abnormal behavior
- Treatment
  - Calcium administration in hospital
Hypercalcemia

- Tumors, endocrine dysfunction, diuretics, excess vitamin D
- Muscle weakness, renal stones, altered mental status, seizures, bone pain, arrhythmias
- Treatment
  - Underlying problem
  - Diuresis with furosemide and NS

Magnesium

- Activates enzymes
- 50% in bone
- Excreted by kidneys
- CNS effect similar to calcium

Hypomagnesemia

- Alcoholism, diabetes, malabsorption, starvation, diarrhea, diuresis, disease with hypocalcemia, hypokalemia
- Tremors, nausea, vomiting, diarrhea, hyperactive reflexes, confusion, seizures, dysrhythmias
- Treatment
  - Magnesium sulfate
Hypermagnesemia

- Patients with chronic renal insufficiency
- Ingestion of magnesium-containing compounds
- CNS depression, dysrhythmias, muscle weakness, confusion, sedation, respiratory paralysis
- Most effective treatment: hemodialysis
- Also IV glucose and insulin

Acid-Base Balance

- Acids
  - Release hydrogen ions
- Bases
  - Receive hydrogen ions
- A solution increases in:
  - Acidity as hydrogen ions increase
  - Alkalinity as hydrogen ions decrease

Hydrogen Ion Concentration

- Hydrogen ion concentration
  - Expressed by pH
    - pH is negative logarithm (base 10) of hydrogen ion concentration
  - Strength of acid or base changed by 10 times with each unit change of pH
Buffer Systems

- Carbonic acid–bicarbonate buffer
- Protein buffering
- Renal buffering

Acid-Base Imbalance

- Any condition that increases carbonic acid or decreases base bicarbonate causes acidosis
- Any condition that increases base bicarbonate or decreases carbonic acid causes alkalosis

Respiratory Acidosis

- Carbon dioxide retention
- PCO₂ increase
- Increase ventilation
Respiratory Acidosis

- Possible causes
  - Respiratory depression
  - Respiratory arrest
  - Cardiac arrest
  - Medications
  - Chest wall injuries
  - Pulmonary illnesses, obstructed airway

Metabolic Acidosis

- Causes
  - Build-up of acid or loss of base

- Common forms
  - Lactic acidosis
  - Diabetic ketoacidosis
  - Acidosis related to renal failure
  - Acidosis related to ingestion of toxins

- Treat cause

Lactic Acidosis

- Causes
  - Ischemia, circulatory failure, shock
  - Extreme exertional states (seizures)

- Associated complications
  - Decreased cardiac contraction, hypotension, cardiac muscle refractory to defibrillation

- Treatment
  - Identify and treat underlying cause
  - Reestablish perfusion, cardiac output
  - Hyperventilation (possible), vigorous rehydration, sodium bicarbonate (possible) for cardiac arrest
**Diabetic Ketoacidosis**

- **Causes**
  - Complication of diabetes mellitus, alcoholism
  - Lack of adequate insulin

- **Treatment**
  - Administer NS

**Renal Failure Acidosis**

- **Causes**
  - Failure of kidneys to keep acid-base balance
  - Inability to efficiently excrete waste products

- **Treatment**
  - Identify and treat underlying cause

**Ingestion of Toxins**

- **Types**
  - Ethylene glycol, methanol, salicylate

- **Treatment**
  - GI evacuation, hemodialysis, diuresis, hydration, specific antidotes
Respiratory Alkalosis
- Hyperventilation decreases PCO₂
- Sepsis, shock, peritonitis, respiratory problems
- Treat cause, oxygenate, calm

Metabolic Alkalosis (Rare)
- Loss of hydrogen ions (usually stomach)
- Sodium bicarbonate or calcium carbonate ingestion
- Excess IV alkali
- Diuretics
- Treat cause

Mixed Acid-Base Disturbances
- Combination of respiratory and metabolic disorders
- Shock
- Cardiac arrest
- Others
Alterations in Cells and Tissues

- Cellular adaptation
  - Atrophy
  - Hypertrophy
  - Hyperplasia
  - Metaplasia
  - Dysplasia

Cellular Injury

- Cell unable to maintain homeostasis because of
  - Hypoxic injury
  - Chemical injury
  - Infectious injury (bacteria, viruses)
  - Immunologic and inflammatory injury
  - Genetic factors
  - Nutritional imbalances
  - Physical agents

Manifestations of Cellular Injury

- Accumulation of excess lipids, electrolytes, fluids
- Phagocytes engulf dying cells
- Cell swells
- Fatty changes
Cellular Injury—Systemic Manifestations

- Fever
- Malaise
- Loss of well-being
- Altered appetite
- Altered heart rate
- Leukocytosis
- Pain

Cellular Death/Necrosis

- Cell dies if it is irreparably damaged
- After cell death, structural changes occur in the nucleus and cytoplasm
- Lysosome membrane breakdown
- Enzymes digest cell
- Necrosis

Hypoperfusion

- Inadequate blood and nutrients to tissues

Cardiac output

- Depends on several factors
  - Strength of contraction
  - Rate of contraction
  - Amount of venous return (preload)

Compensatory mechanisms

**Negative Feedback Mechanisms**

- Baroreceptor reflexes
- Chemoreceptor reflexes
- Central nervous system ischemic response
- Hormonal mechanisms
- Reabsorption of tissue fluids
- Splenic discharge of stored blood

**Baroreceptor Reflexes**

- Maintain BP by negative feedback mechanisms
  - Lower BP if arterial pressure increases
  - Increase BP if arterial pressure decreases

**Chemoreceptor Reflexes**

- Low arterial pressure stimulates peripheral chemoreceptor cells in carotid and aortic bodies
- If oxygen or pH decreases, vasomotor center of medulla is stimulated
CNS Ischemic Response

- Activated with BP< 50 mm Hg
- Ischemia in medullary vasomotor center
- Activates vasomotor center
- Elevates arterial pressure
- If it persists, vagal centers are activated

Hormonal Mechanisms

- Adrenal-medullary mechanism
  - Epinephrine, norepinephrine release
  - Increased heart rate, stroke volume
  - Vasoconstriction

- Renin-angiotensin-aldosterone mechanism
  - Vasoconstriction
  - Water, sodium conservation

Hormonal Mechanisms

- Vasopressin mechanism
  - ADH causes vasoconstriction
  - Decreases urine production
Compensatory Mechanisms

- Reabsorption of fluids
  - Decreased capillary hydrostatic pressure
  - Fluid moves from interstitial to vascular space
- Splenic discharge of blood
  - Blood stored in venous sinuses
  - >200 mL can be released after vasoconstriction

Types of Shock

- Classified by primary cause
  - Two or more types may be combined
  - Primary problem is inadequate tissue perfusion

- Hypovolemic
- Cardiogenic
- Neurogenic
- Anaphylactic
- Septic
Multiple Organ Dysfunction Syndrome (MODS)

- Failure of two or more organ systems after severe illness or injury
- Septic shock is a common cause

MODS Pathophysiology

- Inflammatory response is triggered
- Fluid and cells leak into interstitial space
- Hypotension/hypoperfusion
- Complement, coagulation, kallikrein/kinin
- Thrombus formation, tissue ischemia
- Edema, cardiovascular instability, clotting abnormalities
- Tissue hypoxia, organ failure

Glucose

- Important fuel for producing energy
- Krebs cycle
  - Breaks down pyruvic acid into carbon dioxide and water
  - Much more efficient in producing ATP than glycolysis
  - Needs oxygen
Body’s Self-Defense Mechanisms

- Defense against illness and injury
  - First-line external barriers include:
    - Skin
    - Mucous membranes of the respiratory, digestive, and genitourinary (GU) tract
  - Second—Inflammatory response
  - Third—Immune response

Stages of Inflammatory Response

- Cellular response to injury
  - Energy depletion, autolysis

- Vascular response to injury
  - Hyperemia, vessel dilation
  - Leukocyte migration

- Phagocytosis
  - Leukocytes destroy pathogens
  - Exudate (pus) forms

Inflammatory Responses

- Acute inflammation
  - Local responses
  - Systemic responses
- Chronic inflammation
  - Inflammation ≥ 2 wks
Immune Response

- Types of immunity
  - Natural (native)
  - Acquired
    - Humoral immunity
    - Cell-mediated immunity

- Age and the immune response

Induction of Immune Response

- Antigen
  - Reacts with preformed components of immune system

- Immunogen
  - Antigen that can also induce formation of antibodies

To be immunogenic, the antigenic molecule must be
- Sufficiently foreign to the host
- Sufficiently large
- Sufficiently complex
- Present in sufficient amounts

- B lymphocytes
- T lymphocytes
Blood Group Antigens

- When combined with foreign plasma, red blood cells either clump together (agglutinate), or they do not.

- Two distinct agglutinins (substances on red blood cells acting as antigens) are responsible for this clumping.

Blood Group Antigens

- Four types of human blood have been identified: A, B, AB, and O:
  - Type A blood has anti-B antibodies in the plasma and will clump type B blood.
  - Type B blood has anti-A antibodies and will clump type A blood.
Rh Factor

- Presence or absence of Rh antigen on surface of red blood cells
- 85% of Americans are Rh positive

Hypersensitivity

- Altered immunologic reactivity to antigen
- Causes pathologic immune response after reexposure
- Abnormal responses include:
  - Allergy
  - Autoimmunity
  - Isoimmunity

Mechanisms of Hypersensitivity

- Immediate hypersensitivity reactions
  - Itching, hives
  - Anaphylaxis
- Delayed hypersensitivity reactions
  - Take several hours to 1 to 2 days to appear
  - At maximum several days after antigen reexposure
Immunoglobulins

- Antibodies, or immunoglobulins (Ig), respond to antigenic stimulation
  - IgG
  - IgM
  - IgA
  - IgD
  - IgE

Immunoglobulins

- IgG
  - Secondary immune response
- IgM
  - ABO incompatibilities
- IgA
  - Defends body surface against organisms
- IgE
  - Immediate hypersensitivity reactions
- IgD
  - Function unknown

Immunity and Inflammation Deficiencies

- Body's self-defense mechanisms fail to function at normal capacity

- Sources of the deficiency:
  - Congenital
  - Acquired
    - Infection (e.g., HIV)
    - Cancer (e.g., leukemia)
    - Immunosuppressive drugs
    - Aging
**Acquired Immune Deficiencies**

- Nutritional deficiencies
- Iatrogenic deficiencies
- Deficiencies caused by trauma
- Deficiencies caused by stress
- Acquired immunodeficiency syndrome (AIDS)

**Neuroendocrine Regulation of Stress**

- Sympathetic nervous system activated by stress
- Adrenal gland releases catecholamines
- Hypothalamus stimulates pituitary gland to release:
  - ADH
  - Prolactin
  - Growth hormone
  - ACTH

**Catecholamines**

- Stimulate:
  - Alpha-adrenergic receptors
    - Alpha-1 and alpha-2
  - Beta-adrenergic receptors
    - Beta-1 and beta-2
Alpha Receptors

- Alpha-1 receptors
  - Postsynaptic
  - On the effector organs
  - Stimulate contraction of smooth muscle

- Alpha-2 receptors
  - Presynaptic nerve endings
  - Stimulate alpha-2 receptors
  - Inhibit release of norepinephrine

Beta Receptors

- Beta-1 receptors
  - Primarily in heart

- Beta-2 receptors
  - Bronchial and arteriolar smooth muscle

- Beta receptors
  - Stimulate the heart
  - Dilate bronchioles
  - Dilate blood vessels in the skeletal muscle, brain, and heart
  - Aid in glycogenolysis

Cortisol (Hydrocortisone)

- Circulates in the plasma
- Mobilizes substances needed for cellular metabolism
- Stimulates gluconeogenesis
  - Decreases glucose utilization
- Immunosuppressant
- Decreases migration of macrophages
  - Decreases phagocytosis
Role of the Immune System
- Immunologic conditions may be triggered by stress
- Immune, nervous, and endocrine systems may be affected by stress reaction

Stress, Coping, Illness Interrelationships
- Ill-effects of stress determined by:
  - Nature, intensity, and duration of stressors and individual’s perception
  - Individual coping skills
- Person must:
  - Recognize signs and symptoms of stress
  - Use stress management techniques:
    - Meditation
    - Imagery

Factors Causing Disease
- Genetic factors
  - Chromosomal
  - Polygenic
- Environmental factors
  - Microorganisms
  - Lifestyle
  - Physical environment
  - Psychosocial environment
Analyzing Disease Risk

- Disease rates

- Statistics commonly used to assess societal impact of disease:
  - Incidence rate
  - Prevalence rate
  - Mortality rate

Causal and Noncausal Risk Factors

Disease Risk

- Familial disease tendency

- Aging and age-related disorders
Conclusion

Paramedics should appreciate the correlation of pathophysiology with disease processes to better understand, anticipate, direct, and provide appropriate care to patients.