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The Body's Defense and Changes with Disease and Injury

DND Primary Care Paramedicine

Module: 02

Section: 04

Objectives and Overview

- Case approach to understanding physiological changes with disease.
- Cellular response to change and injury.
- Genetics and other causes of disease.
- Infectious agents
- The body’s response to infection

Case Study

- Dispatched for a 36 y/o M C/O an inability to weight bare on his left leg.
- Patient is homeless and currently with police who called for EMS assessment.
- On arrival the patient is seated on the rear bumper of a police van with wet, extremely damaged footwear.
- VS: HR 130, BP 90/54, T 37.0°C, BGL 16.2 mmol/L, RR 24, SpO_2 94% on room air.
- Broad differential diagnosis?

Pathophysiology

- Terminology recap:
  - Pathology
    - The study of disease and its causes
  - Pathophysiology
    - The study of how diseases alter normal physiology

The Body's Defence and Changes with Disease and Injury

CELLULAR CHANGE AND ADAPTATION

Cellular Adaptation

- Cells, tissues, organs and organ systems can adapt to both normal and injurious (pathological) conditions.
  - Ex. growth of the uterus during pregnancy is a response to a normal condition.
  - Ex. dilation of LV post MI is response to a pathological condition.
- When stimulated by external stressors, the body undergoes cellular adaptations that results in alteration of structure and function.

Types of Cellular Adaptations

- Atrophy
  - Decreased size resulting from a decreased workload.
  - Can also occur as a result of lack of stimulation, decreased nutrient/blood supply and/or ischemia
- Hypertrophy
  - An increase in cell size resulting from an increased workload
  - Thought to occur in cells that are unable to increase in # (hyperplasia), therefore increase in mass with increased workload
    - ex. LVH secondary to chronic HTN

Types of Cellular Adaptations

- Hyperplasia
  - An increase in the number of cells resulting from an increased workload.
  - Commonly occurs in conjunction with hypertrophy
- Metaplasia
  - Replacement of damaged cells of one type by a different type of cell that is not normal for that tissue.
    - Ex. Replacement of ciliated columnar epithelial cells of the trachea with stratified squamous cells secondary to chronic cigarette smoking.

Types of Cellular Adaptations

- Dysplasia
  - A change in cell size, shape, or appearance caused by an external stressor.
  - Related to hyperplasia, typically an abnormal/atypical hyperplasia.

Mechanisms of Cellular Injury

- Hypoxia
- Chemicals
- Physical agents
- Nutritional factors
- Genetic factors
- Infectious Agents
- Immunological/Inflammatory reactions

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Mechanisms of Cellular Injury

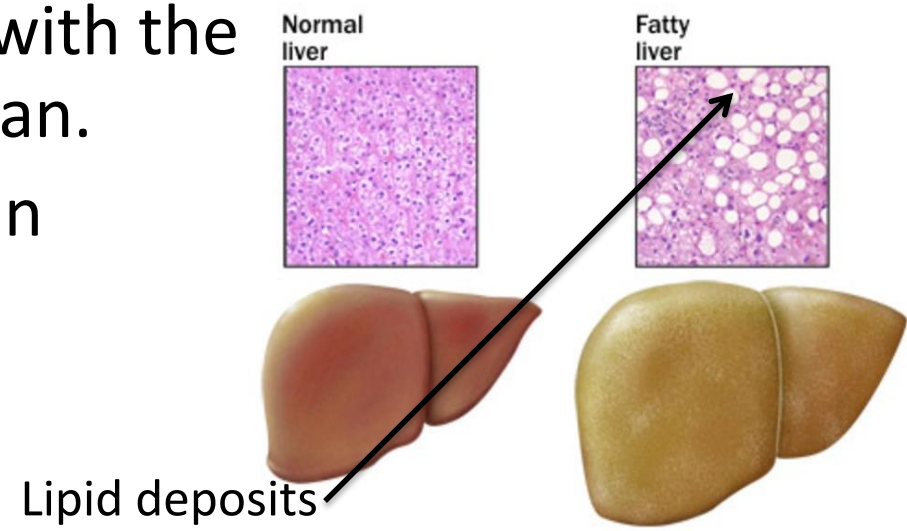
- Hypoxia
  - The most common cause of cellular injury
  - Blockage or reduction of oxygenated blood to cells results in cellular ischemia
  - Cells can no longer undergo aerobic metabolism, therefore switch to anaerobic
  - Results in increased production of lactate
  - Leads to destruction of Na^+/K^+ pumps resulting in increased intracellular Na^+ concentration
  - Leads to fluid shift and cellular swelling

Mechanisms of Cellular Injury

- Hypoxia
  - If oxygen is not supplied to tissue, process will continue and cell membranes will rupture
  - Causes spillage of harmful enzymes into interstitial space
  - Cellular injury now considered irreversible
  - This is now cellular/tissue death = **infarction**

Mechanisms of Cellular Injury

- Fatty change
  - In addition to cellular swelling, cellular injury can also result in fatty deposits
  - During the process, lipids invade the area of injury
  - Causes a disruption of the cellular membrane and metabolism, interfering with the vital functions of the organ.
  - Occurs most commonly in vascular organs, most frequently the liver.
    - ex. NAFLD



Mechanisms of Cellular Injury

- Hypoxia
- Chemicals
- Physical agents
- Nutritional factors
- Genetic factors
- Infectious Agents
- Immunological/Inflammatory reactions

Mechanisms of Cellular Injury

- Chemicals
  - Harmful chemicals can disrupt cellular membranes, alter coagulation and cause cell death
- Physical agents
  - Extremes of temperature and pressure, radiation, noise and/or trauma can all damage cells/tissue.

Mechanisms of Cellular Injury

- Hypoxia
- Chemicals
- Physical agents
- Nutritional factors
- Genetic factors
- Infectious Agents
- Immunological/Inflammatory reactions

Mechanisms of Cellular Injury

- Nutritional factors
  - Improper nutrition increases risk for atherosclerosis, DM and vitamin deficiencies.
  - Leads to hormone imbalances and metabolic derangements, eventually causing cellular injury
- Genetic factors
  - Genetic variances can result in changes to protein synthesis.
  - Results in modification of cellular structure and therefore function.
    - Ex. Sickle cell disease

Mechanisms of Cellular Injury

- Hypoxia
- Chemicals
- Physical agents
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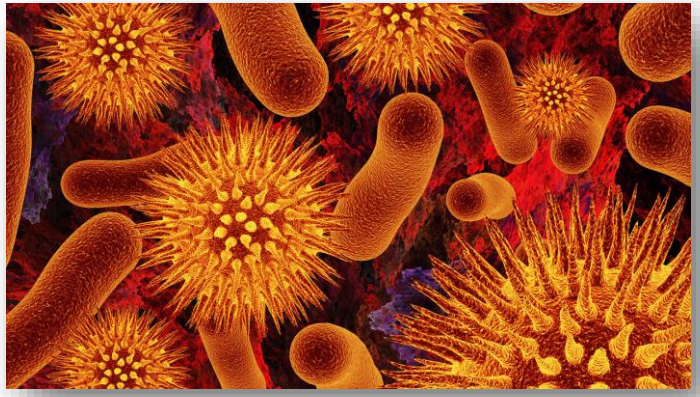
- Genetic factors
- Infectious Agents
- Immunological/Inflammatory reactions

Infectious Agents

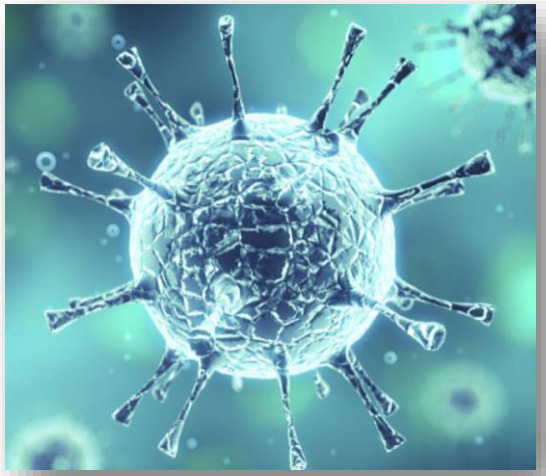
- Common cause of cellular injury
- Most infectious agents are harmless
- Those that cause infection or disease are called **Pathogens**
- Types include:
  - Bacteria
  - Viruses
  - Fungi
  - Prions
  - Other parasites

Bacteria

- Single-cell organisms with a cell membrane and cytoplasm but no organized nucleus.
- Cause many common infections, and usually respond to antibiotic treatment.
- Bacteria release toxins.
  - **Exotoxins** are secreted during bacteria growth.
  - **Endotoxins** are released when the bacteria dies.



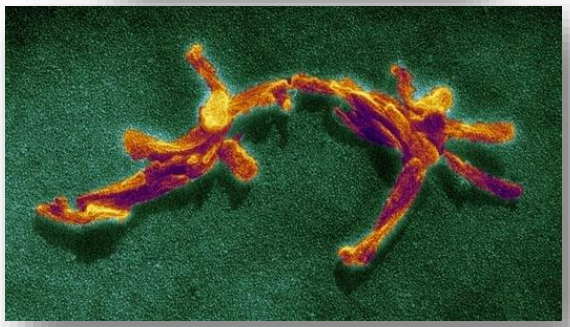
Viruses



- Smaller than bacteria and cause most infections.
- No organized cellular structure except a protein coat (capsid) surrounding the internal genetic material (RNA or DNA). Some have an outer envelope.
- Viruses do not produce toxins.
  - They replicate and may cause a malignancy.
  - They may attack immune cells and destroy the ability to ward off infection.

Other Agents of Infection

- Fungi
  - Don't usually cause anything more serious than minor skin infections
  - Typically opportunistic pathogens
- Prions
  - Most recently recognized class of infectious agents.
  - Misfolded proteins that propagate and have harmful activities
- Parasites
  - More common in developing nations
  - Treatment depends on the organism and its location



Mechanisms of Cellular Injury

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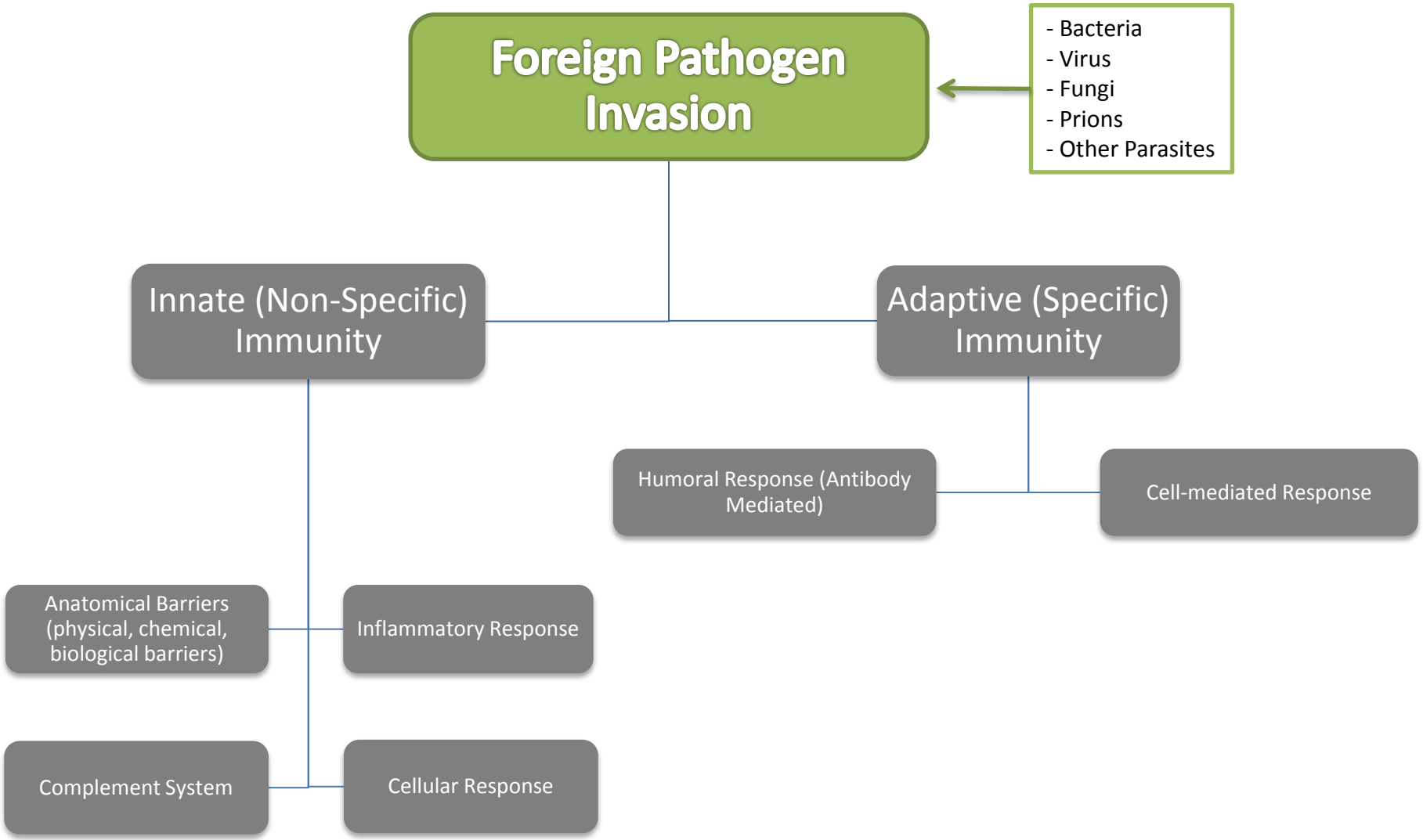
Immune Response Overview



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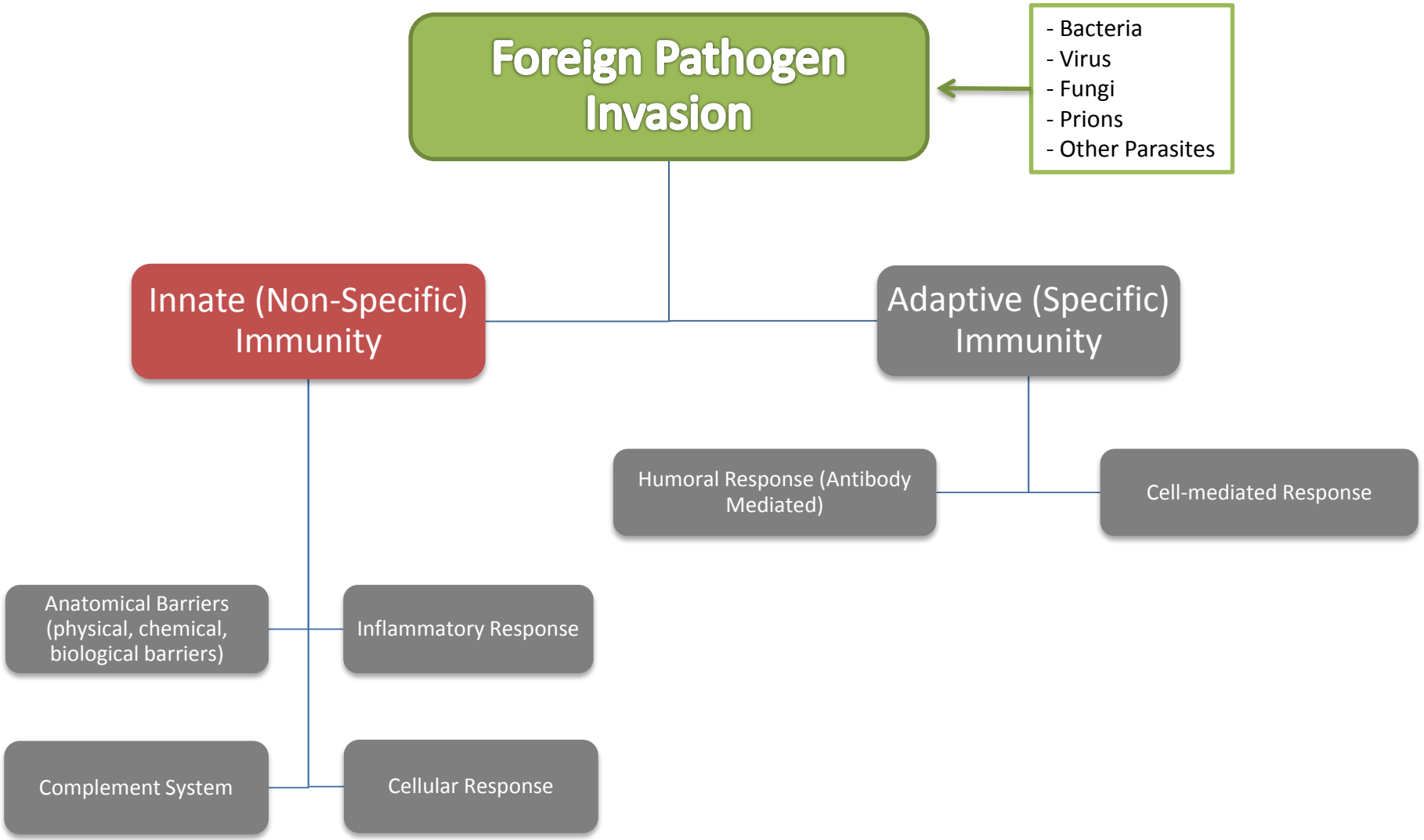
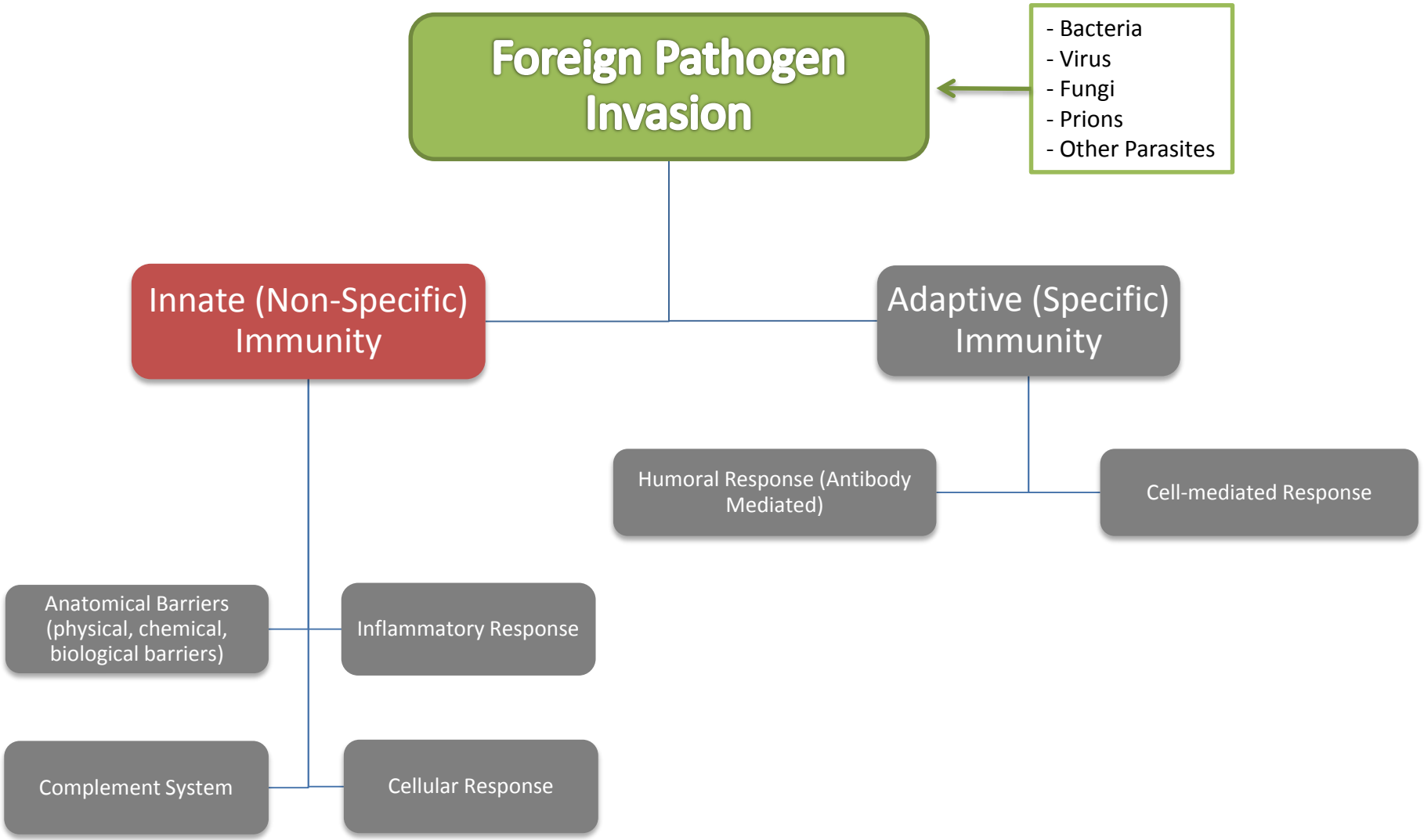
Immune Response Overview



Innate (Non-Specific) Immunity

- Rapid onset to attack foreign pathogens
- Generic, non-specific, response
- No ability to ‘remember’ pathogens for later exposure
- Provides initial rapid response to allow time for the adaptive response to develop

Immune Response Overview



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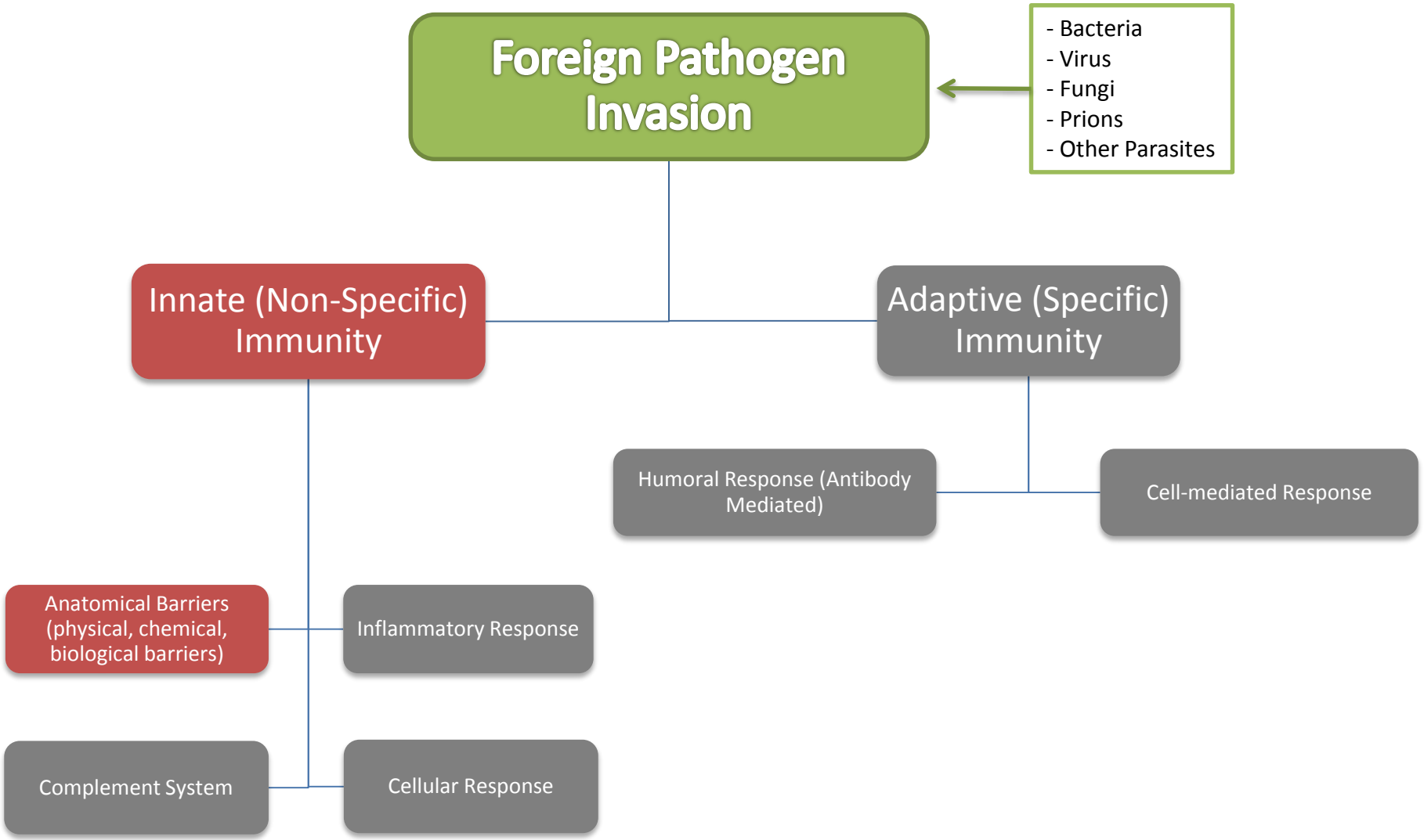

Anatomic Barriers

- Epithelium
- Sebaceous glands
- Sweat, tears, saliva
- Mechanical responses:
  - Respiratory: mucus, surfactant
  - Gastrointestinal: gastric acid, bile, gut flora

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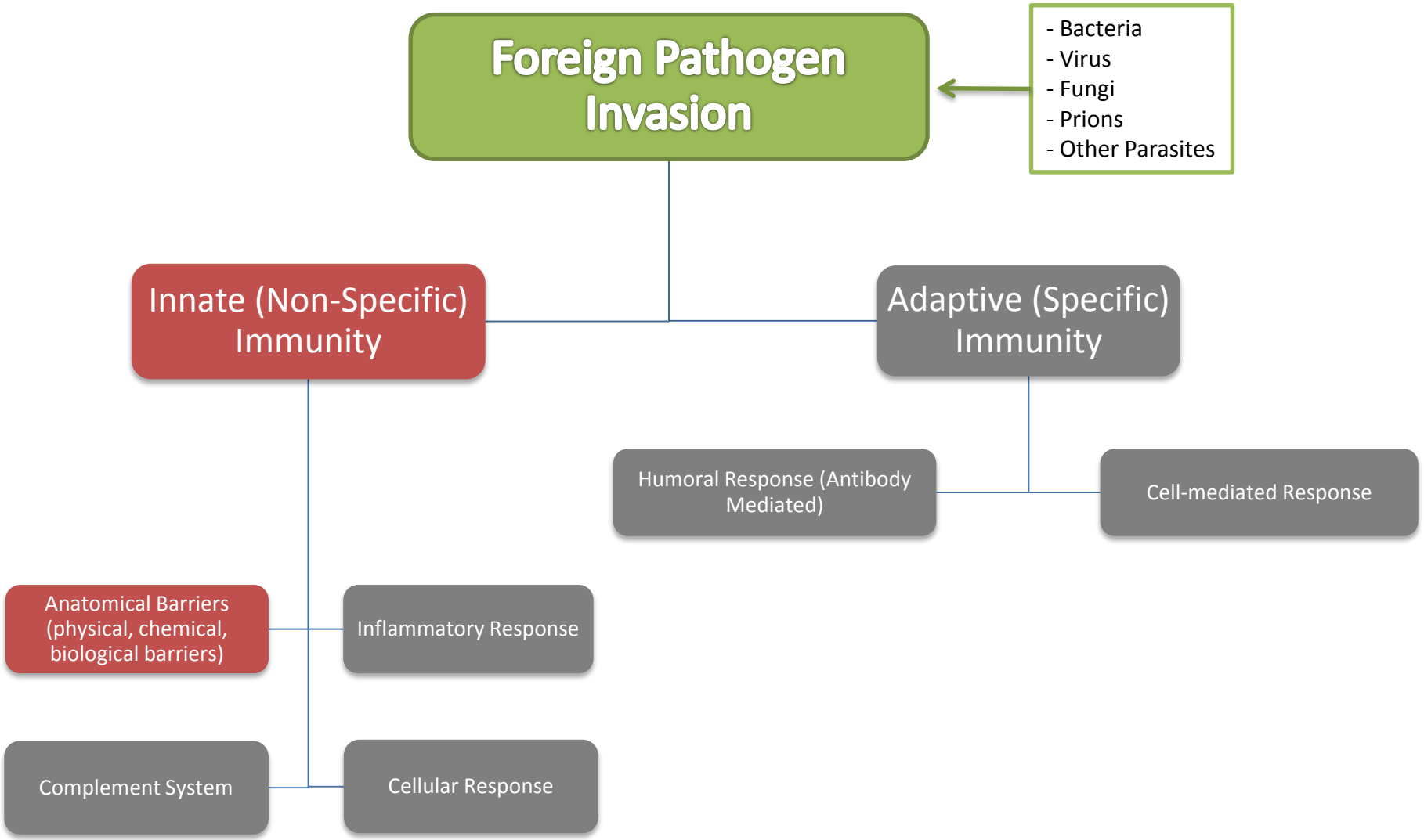
Immune Response Overview



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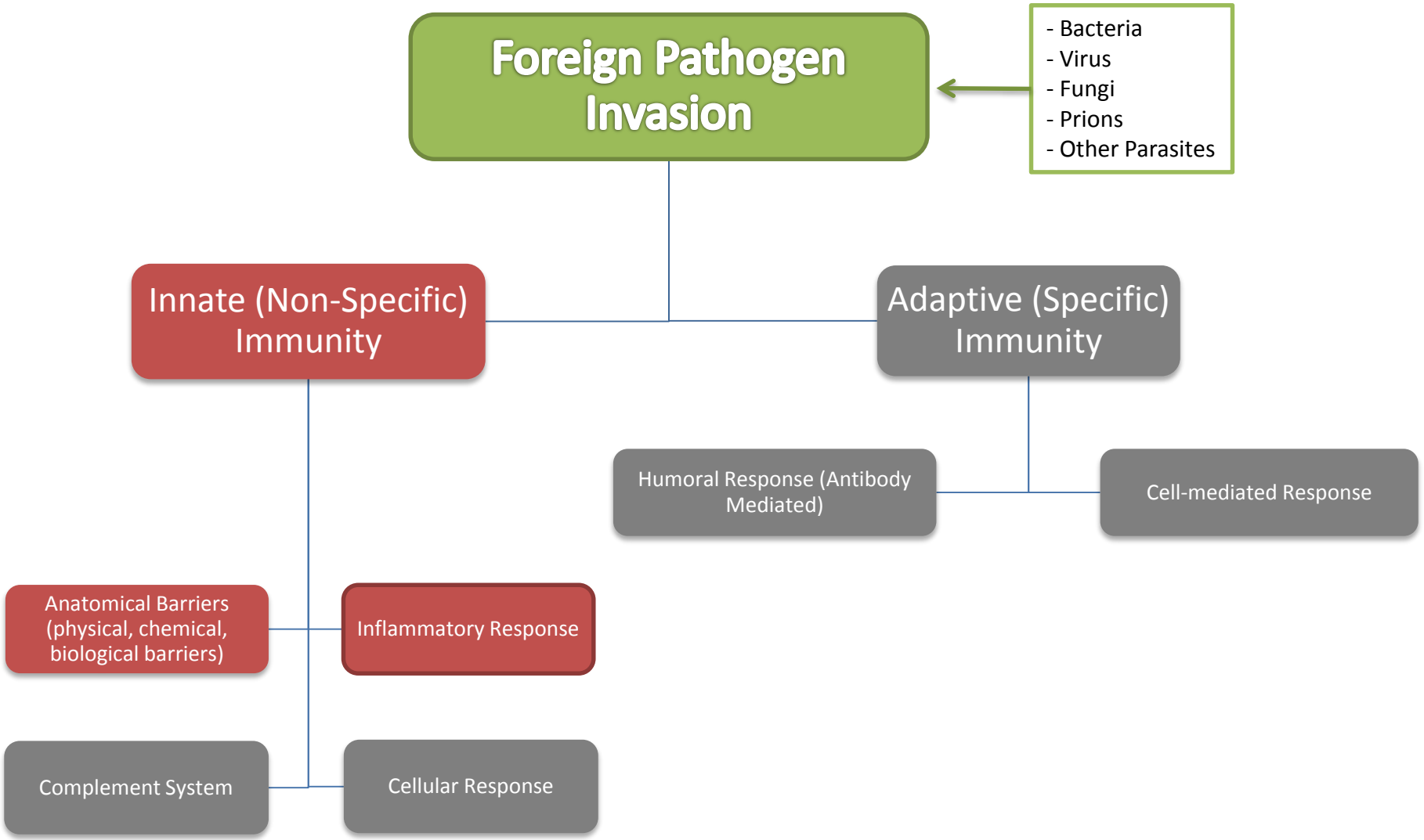

Inflammatory Response

- Begins within seconds of injury or invasion by a pathogen.
- Nonspecific
- Mediated by multiple plasma protein systems
  - Coagulation system
  - Kinin system
  - Release of leukotrienes, prostaglandins

- More later in presentation…

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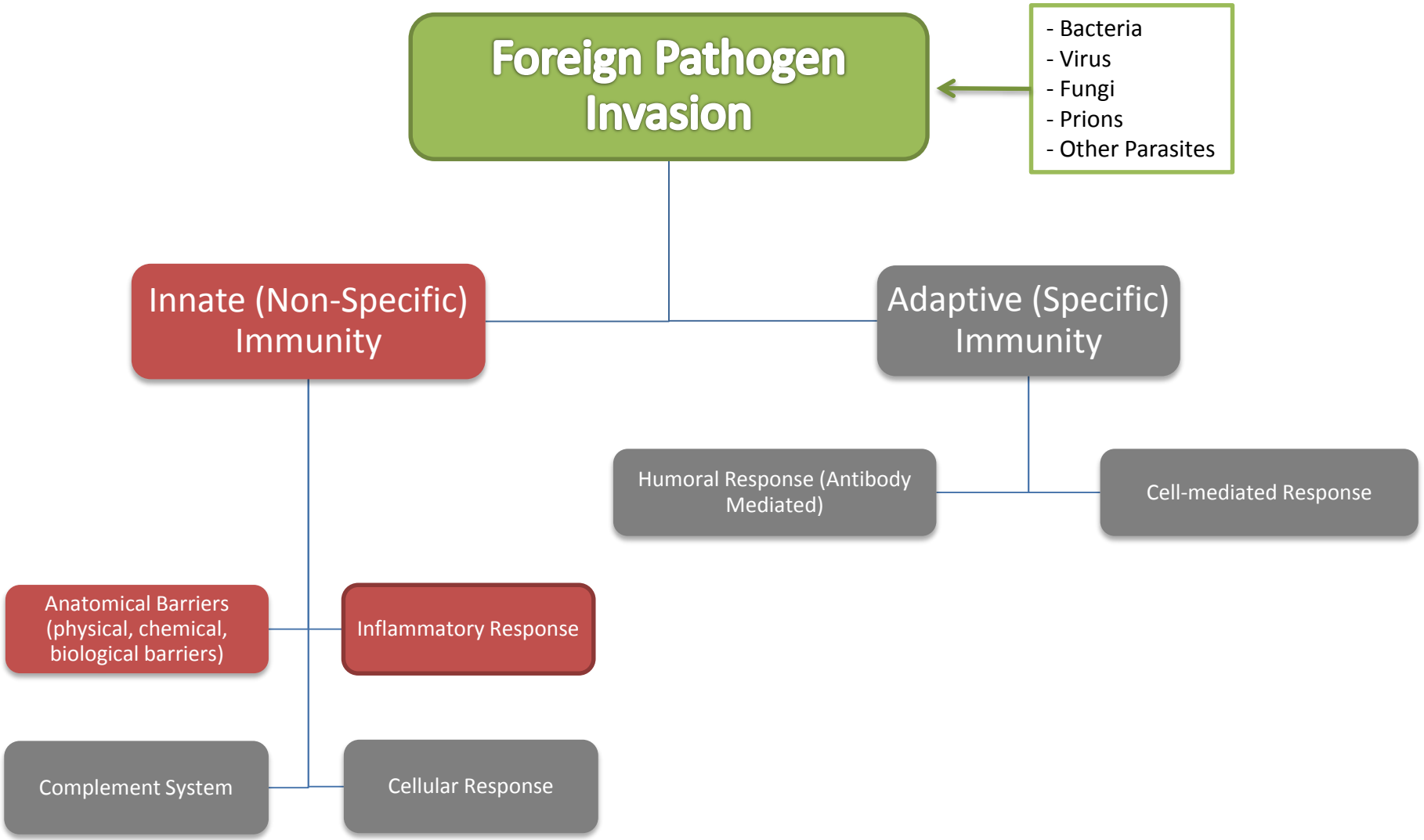
Immune Response Overview



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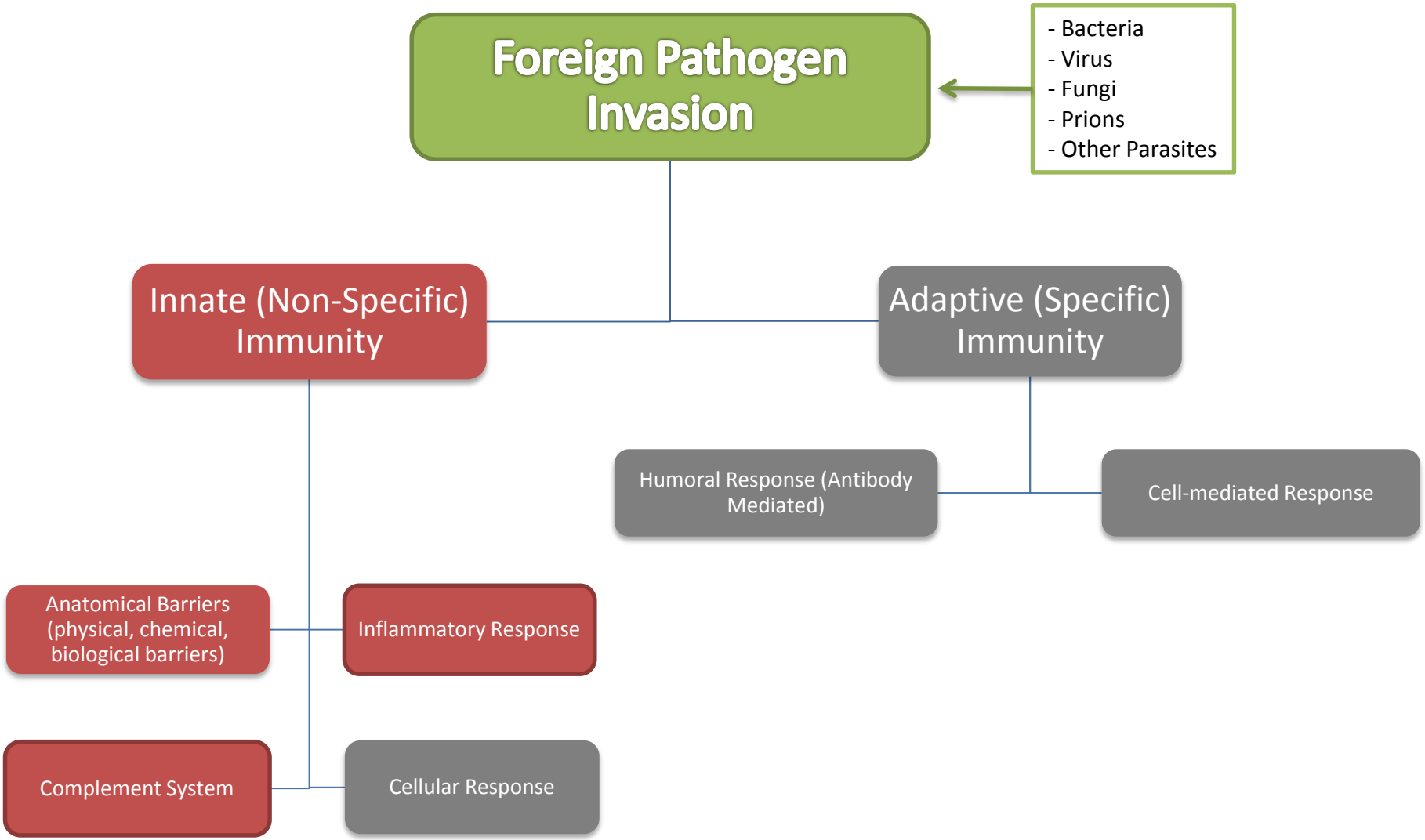
Immune Response Overview



Complement System

- Biochemical pathway that, once initiated, enhances ability of Ab and Phagocytes
- Nonspecific
- Pro-proteins (inactive) synthesized by the liver and are present at all times in bloodstream in inactive form
  - Activation can occur rapidly

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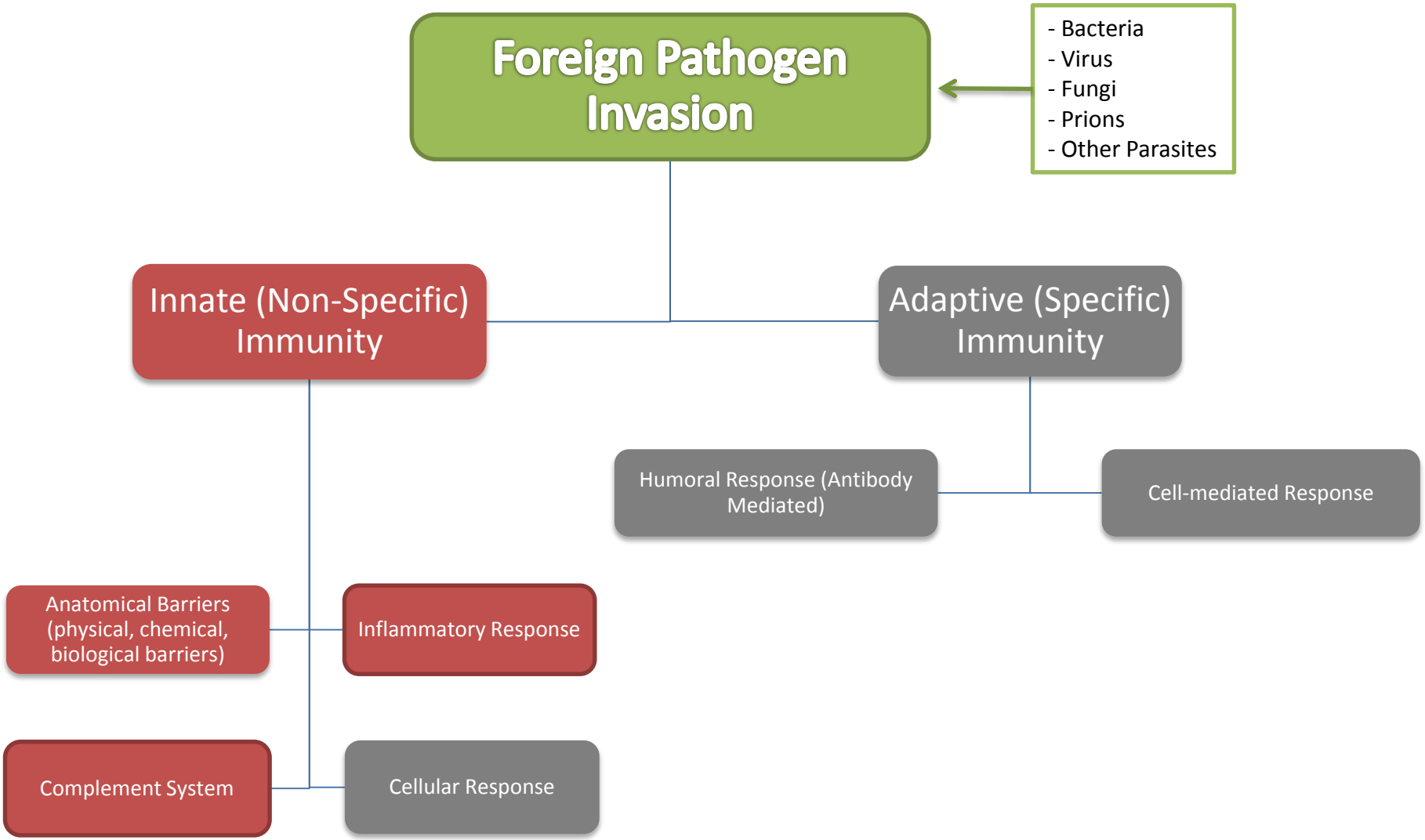
Immune Response Overview



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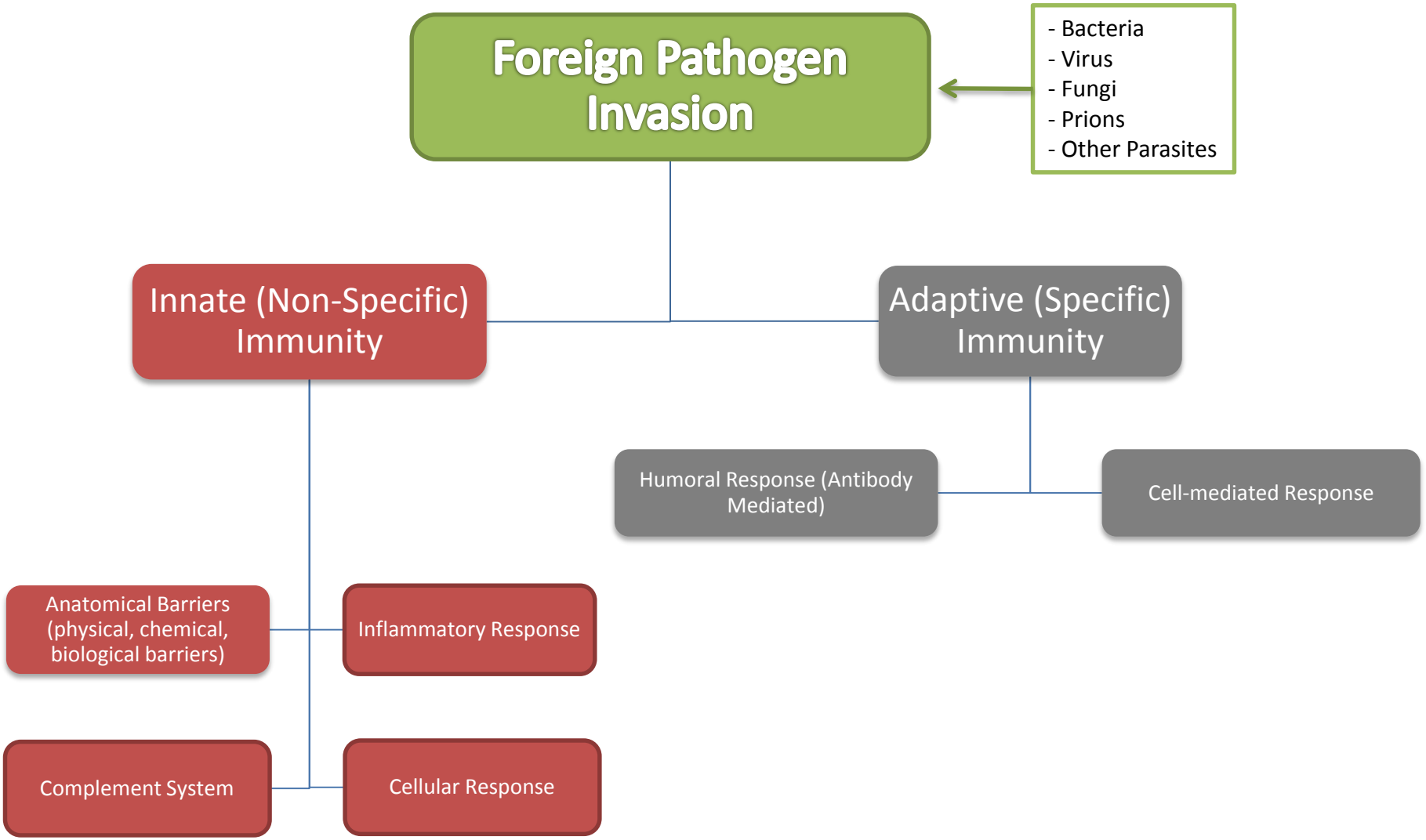

Cellular Response

- Various Leukocytes produce a rapid, non-specific response
  - NK cells: attack virus infected cells and tumors
  - Mast cells: release Heparin and Histamine
  - Macrophages: large phagocytic cells
  - Neutrophils: produce oxidizing agents (H_2O_2) to destroy bacteria and fungi
  - Dendritic cells: assist in presentation of antigens to the surface for marking

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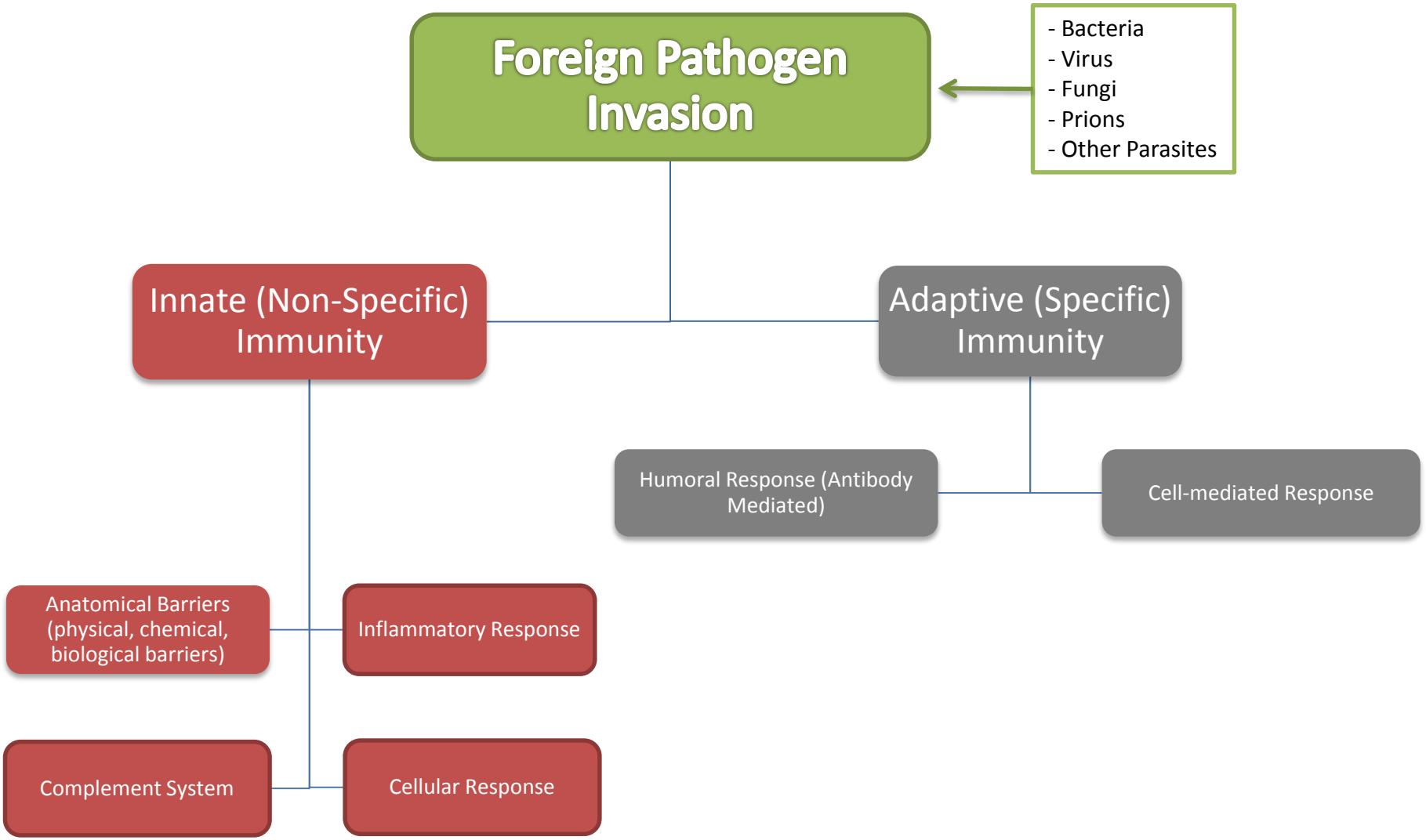

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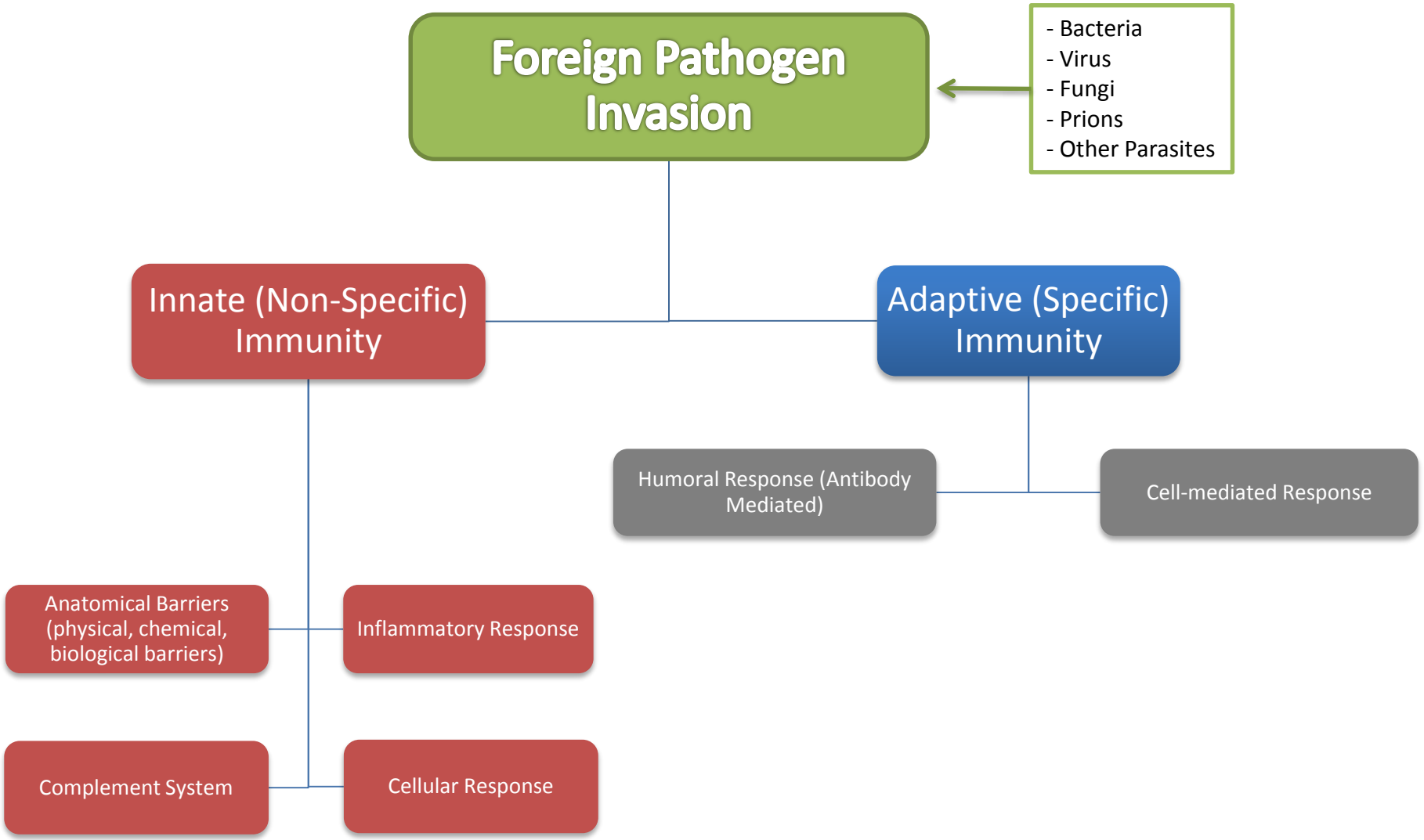

Adaptive (Specific) Immunity

- Develops more slowly
- Consists of non-specific and specific responses
- Specific
  - Will develop a specialized response for an individual invader
- Mediated by one plasma protein system
  - Immunoglobulin

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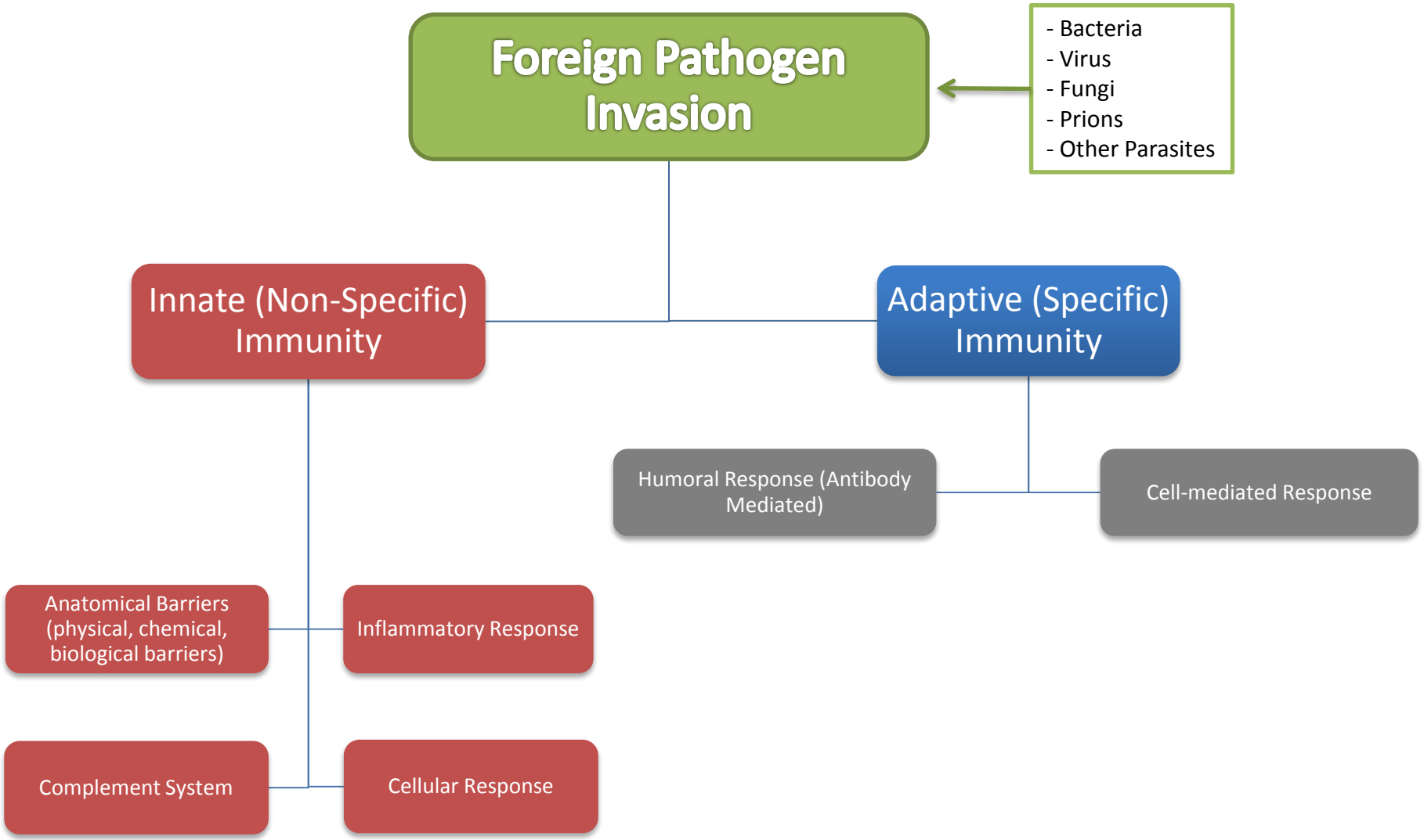
Immune Response Overview



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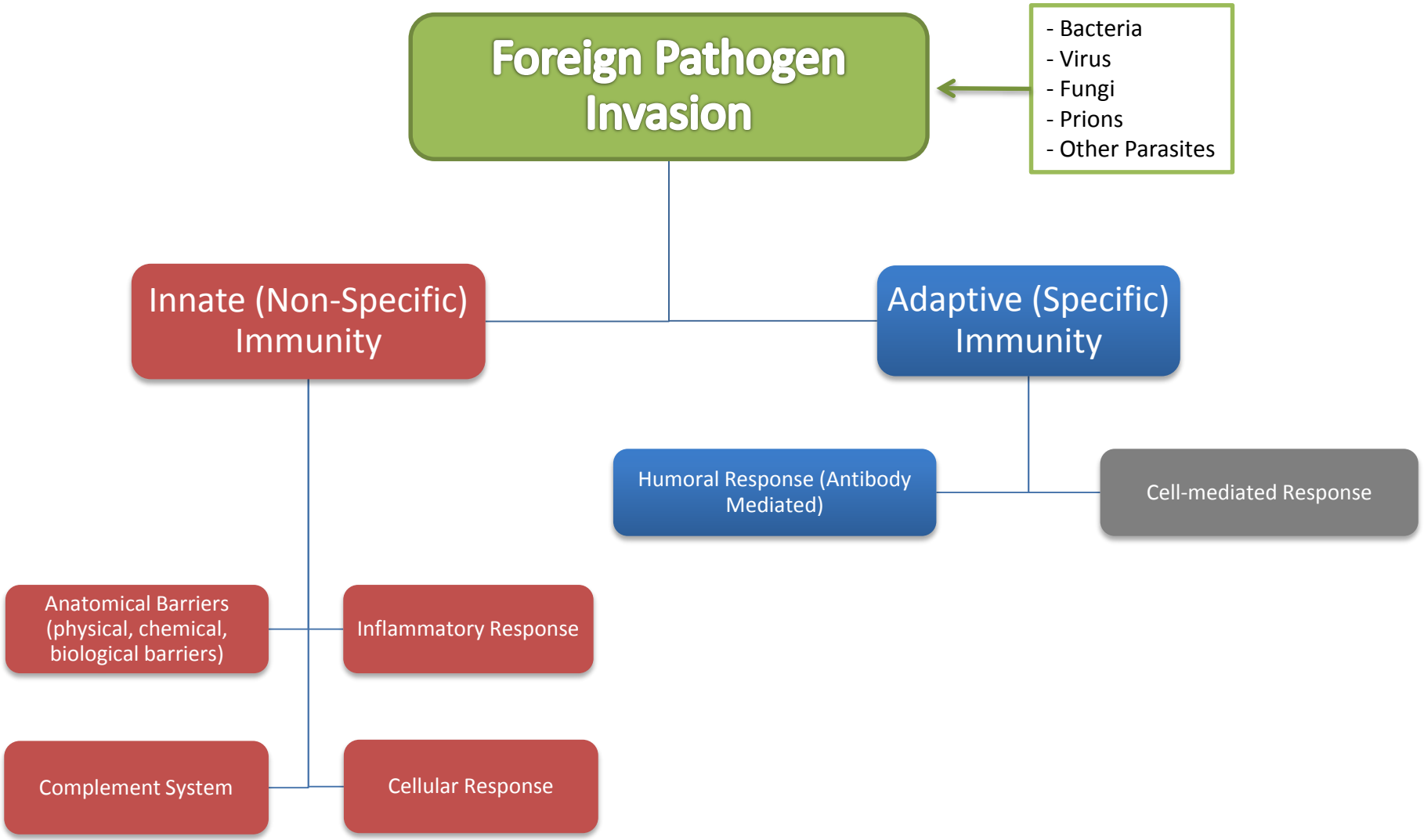
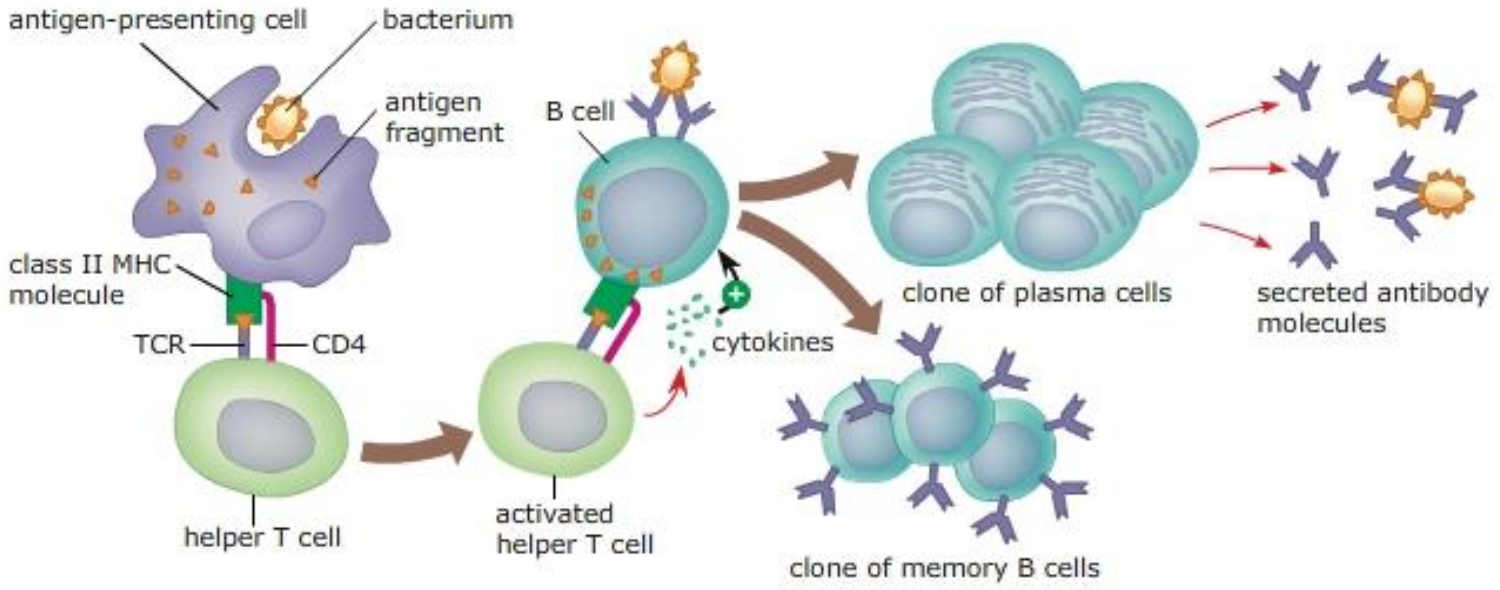


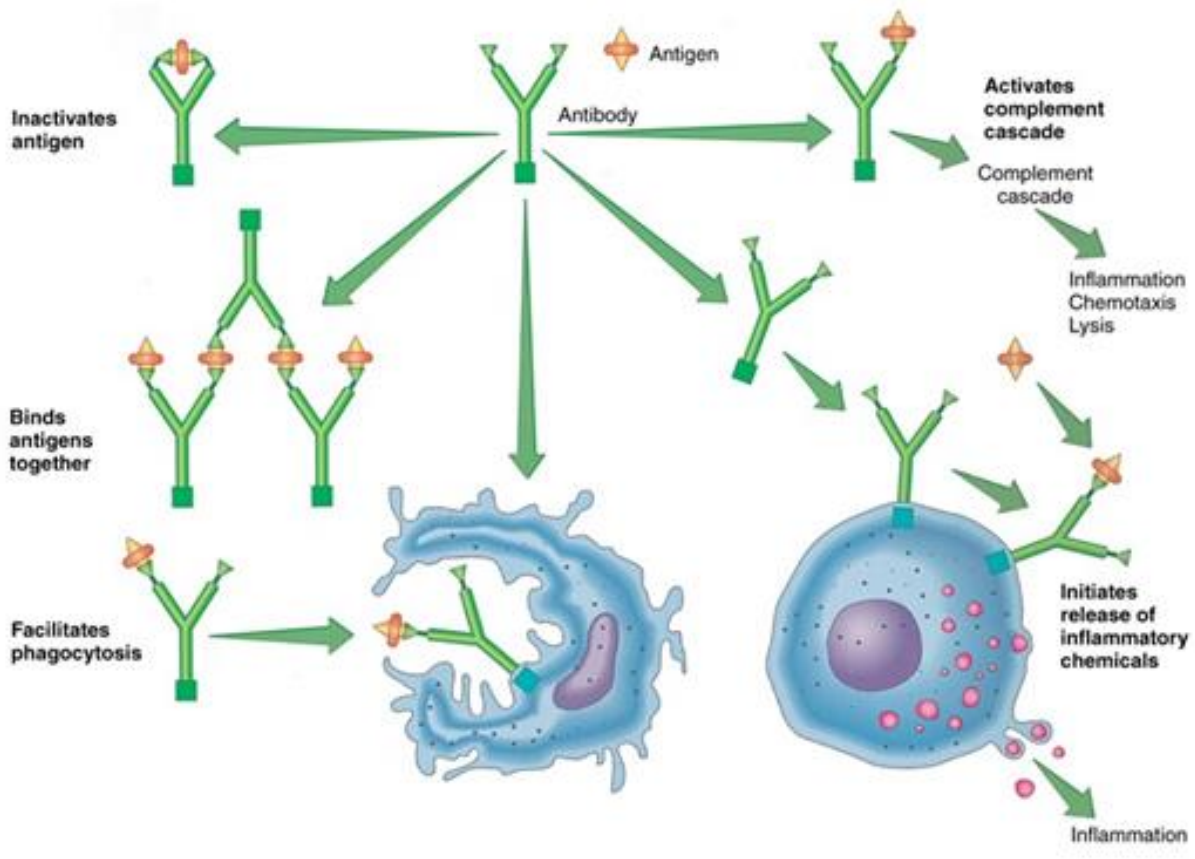
Humoral Immunity

- **Humoral immunity** is the long-term immunity to an antigen provided by antibodies produced by **B lymphocytes**.



Humoral Immunity

- Once the Ab are present, future exposure to the same pathogen eludes a more rapid response.



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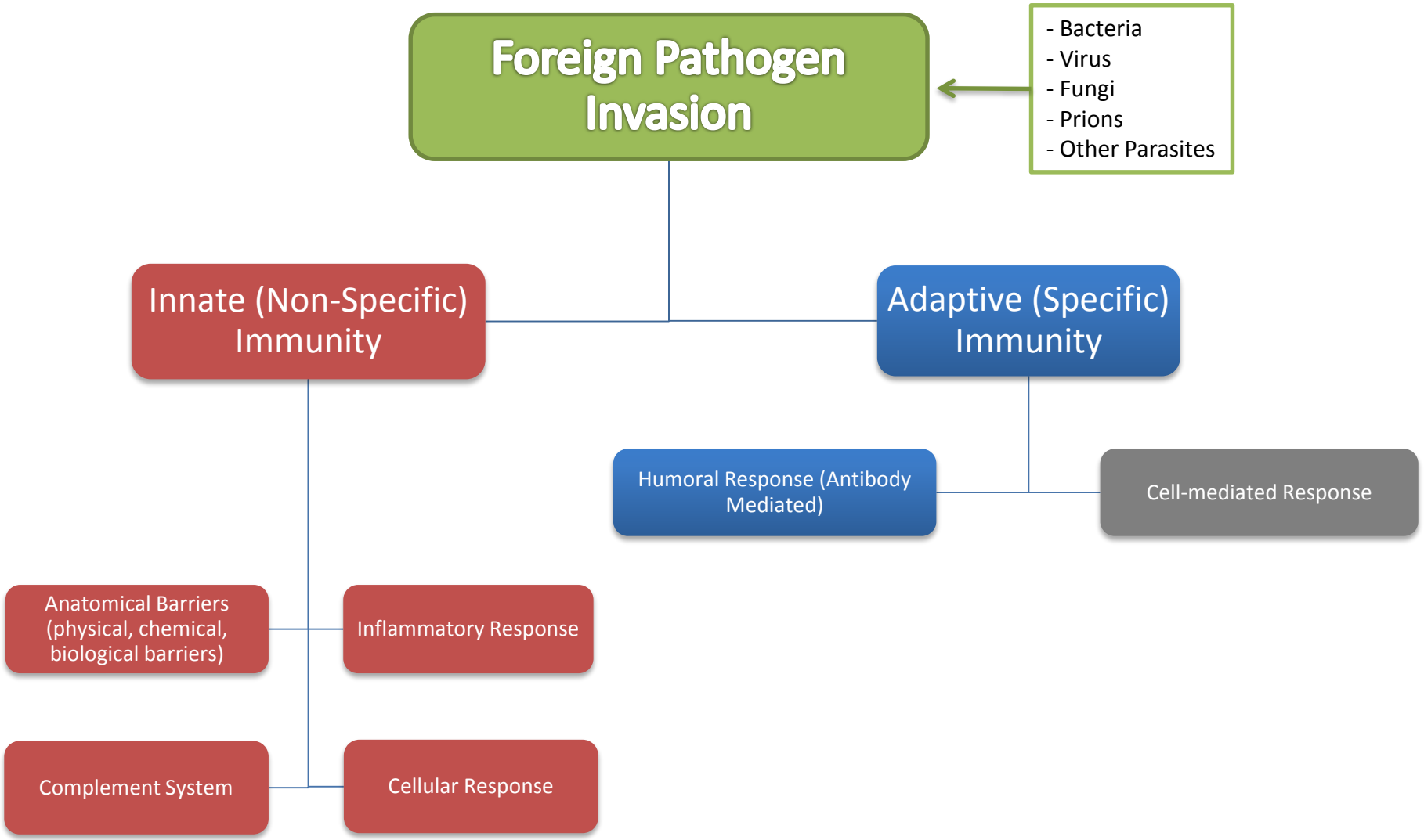

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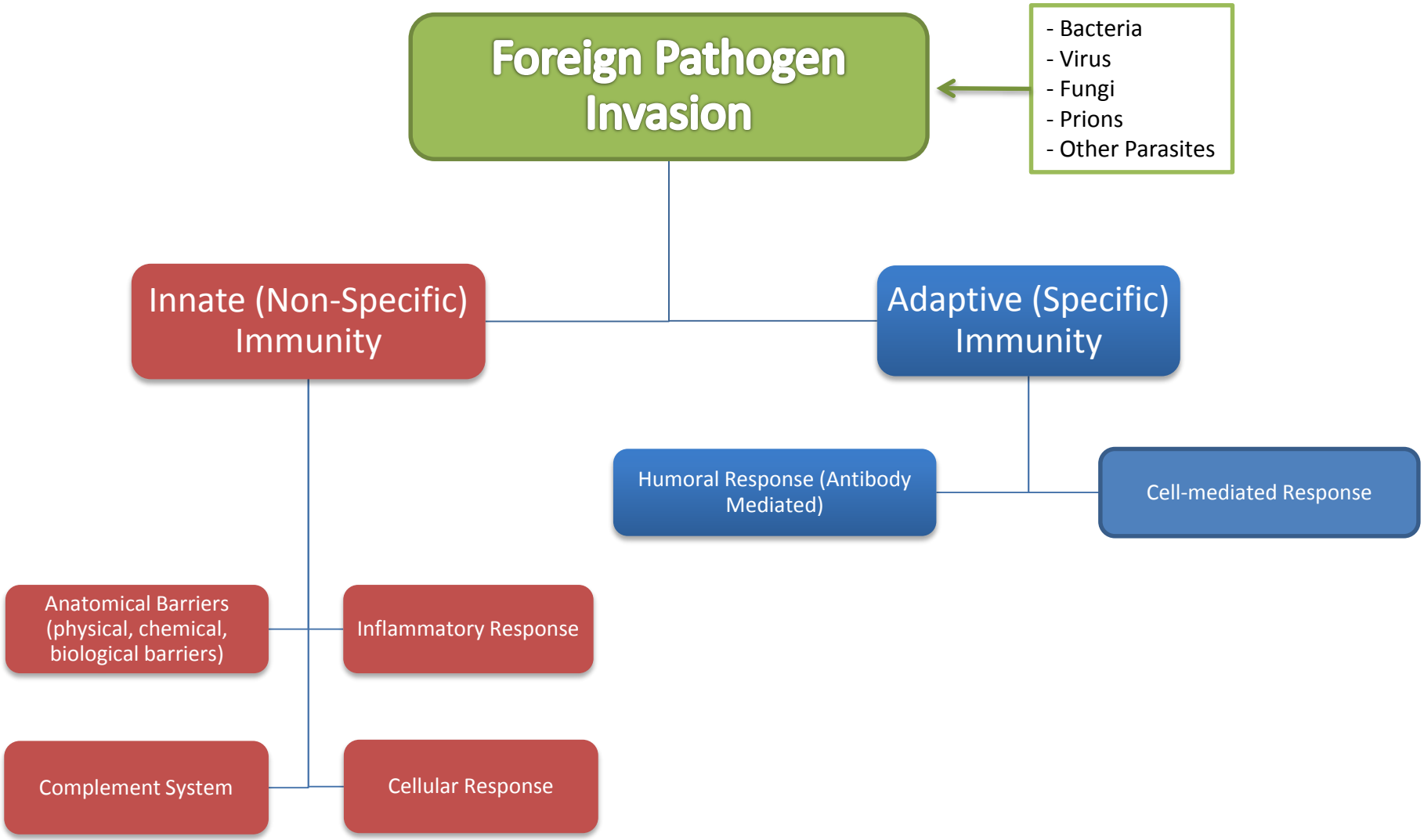
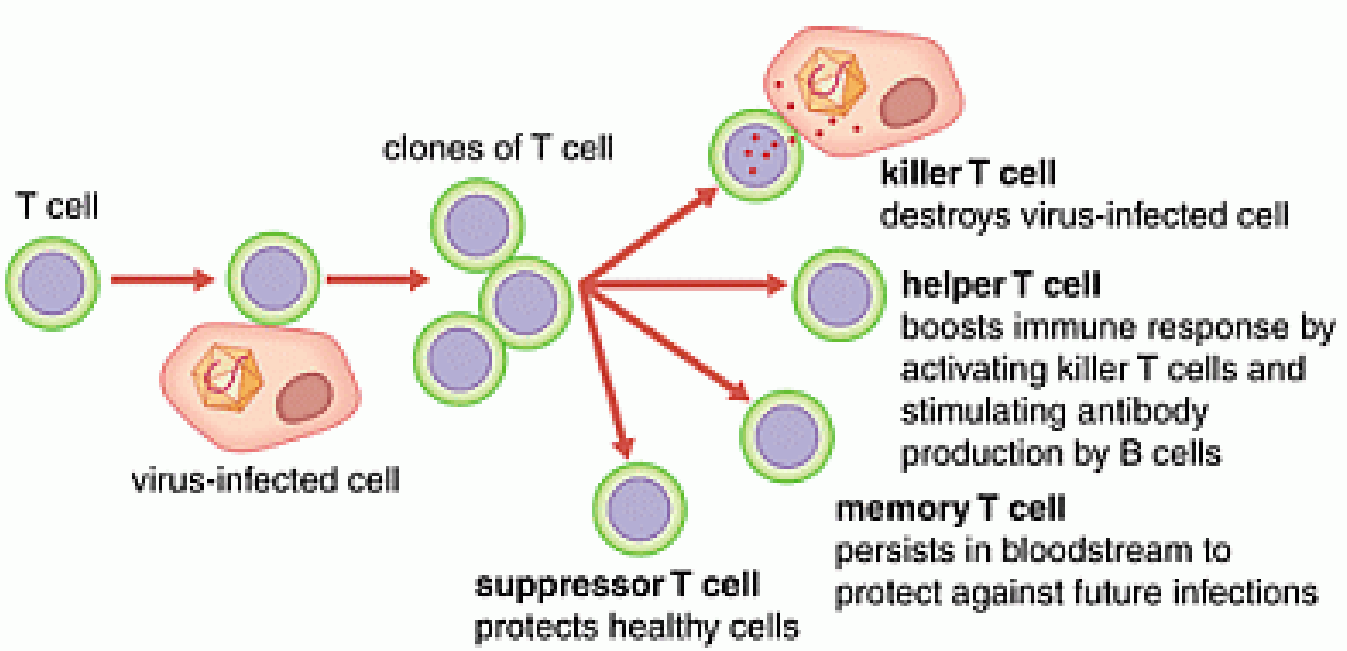


Cell-Mediated Immunity

- **Cell-mediated immunity** is immunity to an antigen provided by **T lymphocytes** that help phagocytes and B cells or directly kill infected cells.



Cell-Mediated Immunity

- Helper T cells – Assist other components
  - Assist B cells to differentiate into plasma cells
  - Assist cytotoxic T cells
- Cytotoxic (Killer) T cells – destroy virus infected or tumour cells
- Memory T cells – antigen specific cells that retain memory of pathogen
- Suppressor T cells – help to ‘turn off’ response when not needed

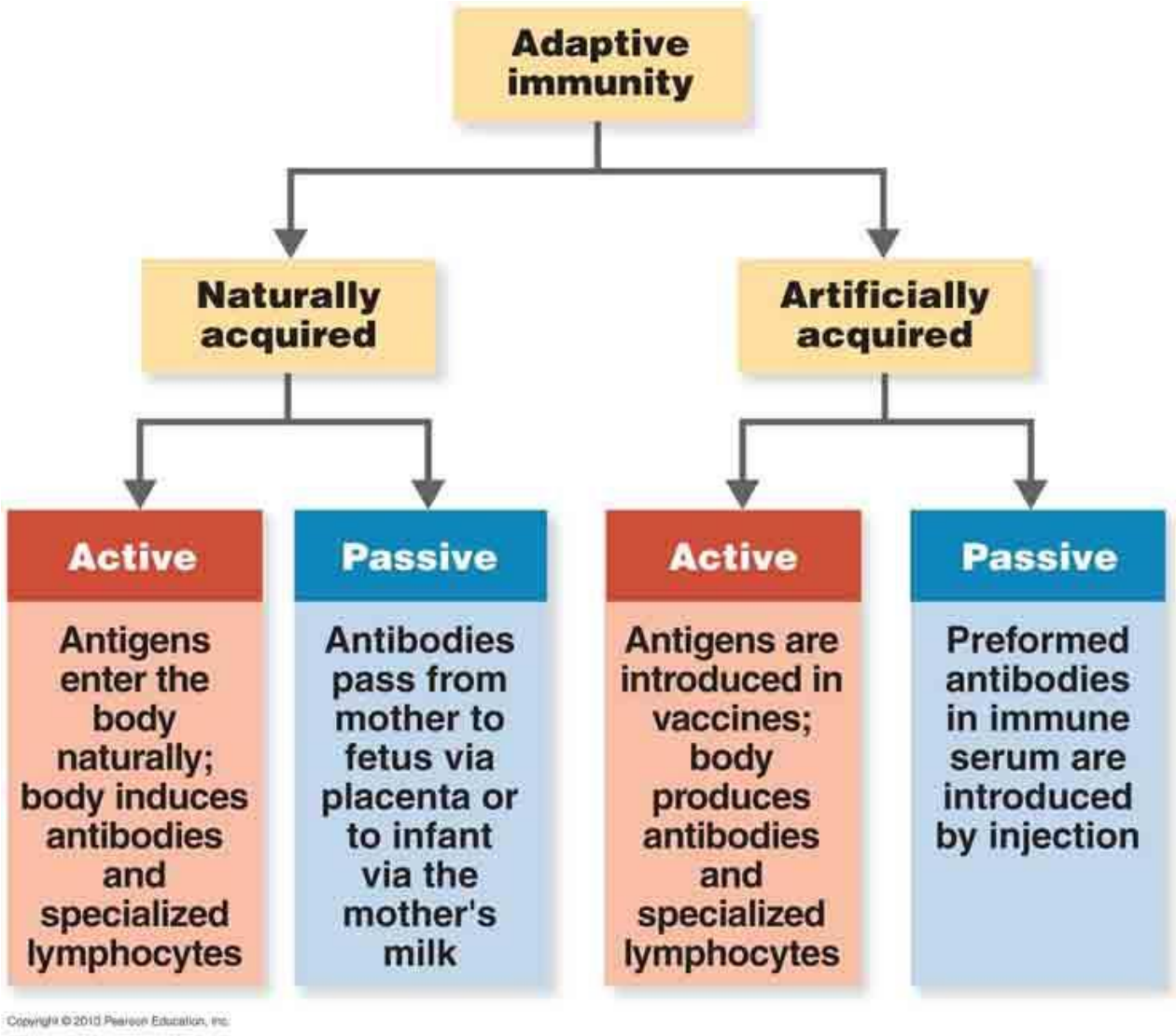
The Body's Defence and Changes with Disease and Injury

IMMUNITY

Immunity Types

- **Natural** immunity is part of genetic makeup
- **Artificial** immunity develops as a result of a deliberate action.
- **Active** immunity is generated by the immune system after exposure to an antigen
- **Passive** immunity is transferred to a person from an outside source.

Immunity Types



The Body's Defence and Changes with Disease and Injury

INFLAMMATORY RESPONSE

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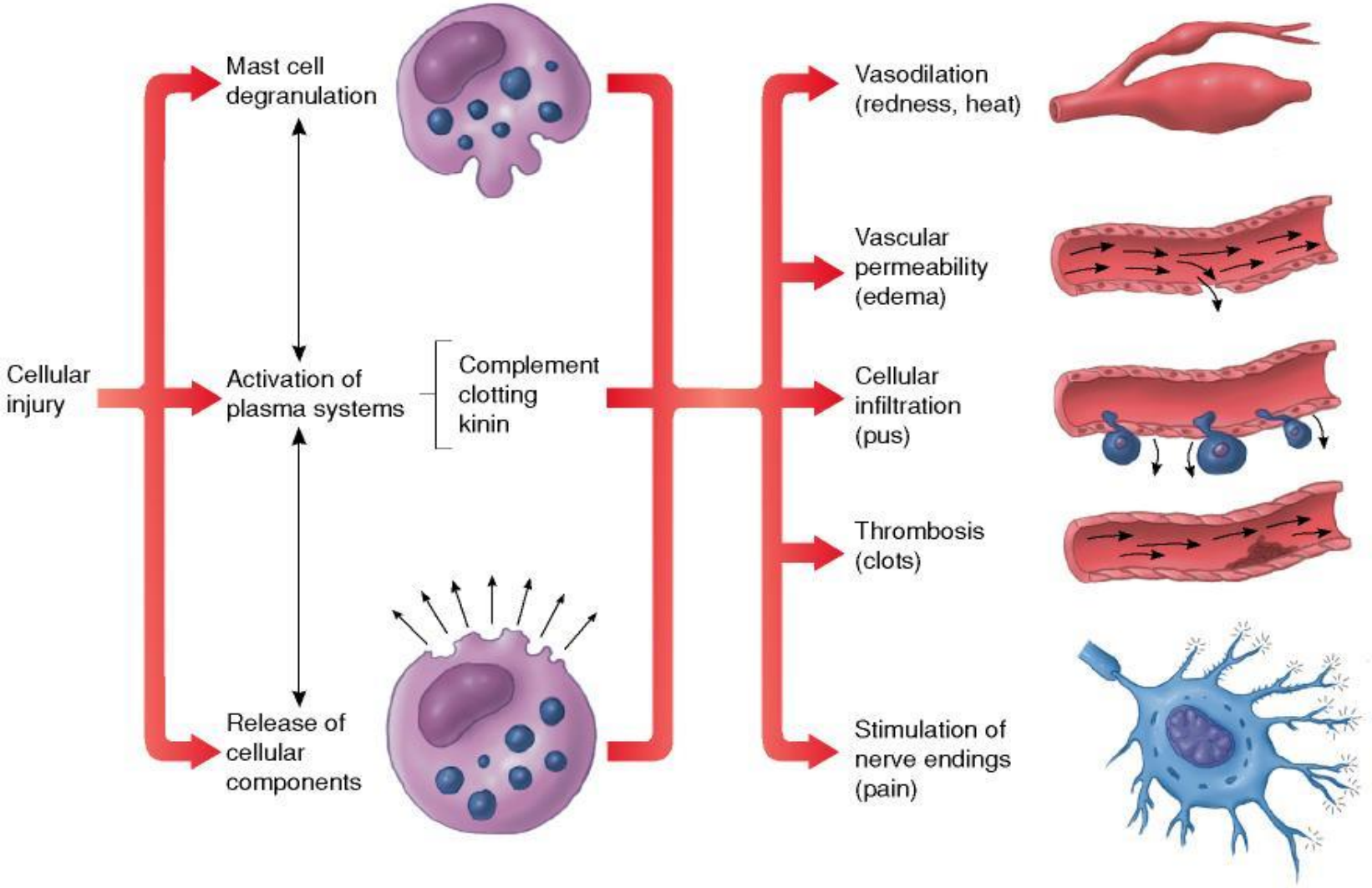
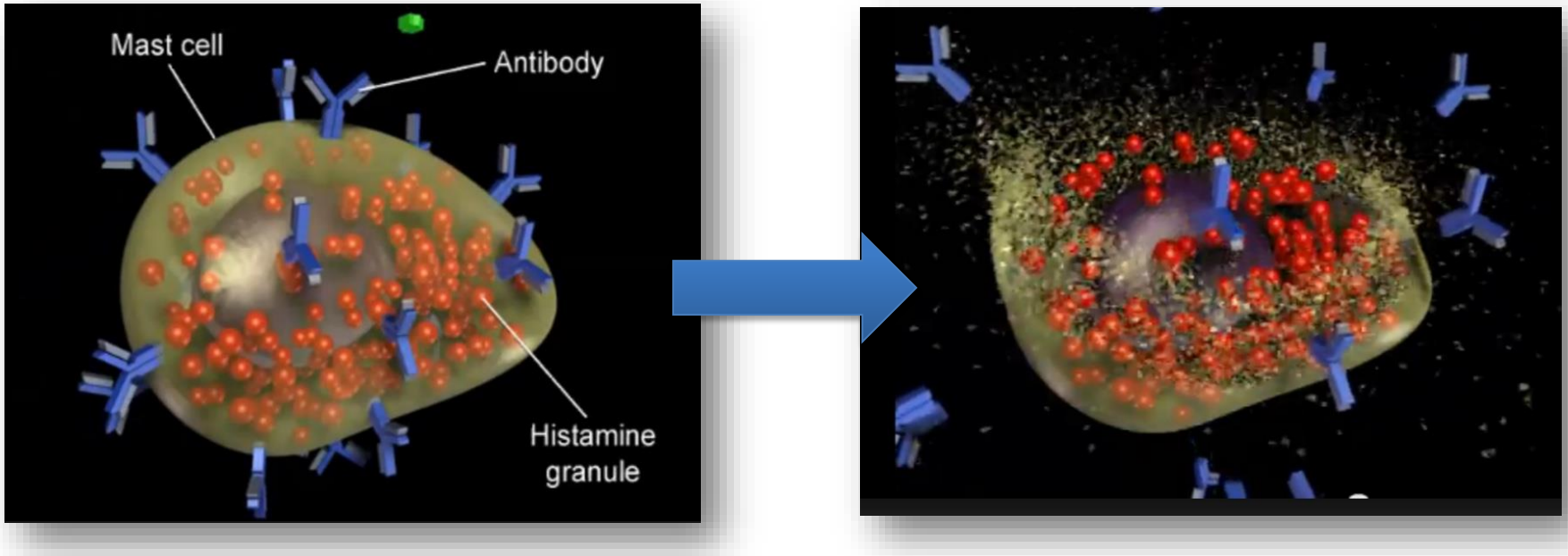
The Acute Inflammatory Response



Mast Cells

- Key activators of the inflammatory response.
- Activate the inflammatory response through degranulation and synthesis of immune mediators.



Degranulation

- Process by which mast cells empty granules from their interior into the extracellular environment.
- Occurs when the mast cell is stimulated by one of the following:
  - Physical injury
  - Chemical agents
  - Immunologic and direct processes

Biochemical Agents Stored and Released During Degranulation

- Vasoactive amines
  - Ex. Histamine
- Chemotactic factors
  - ex. Bradykinin, etc.
- Heparin

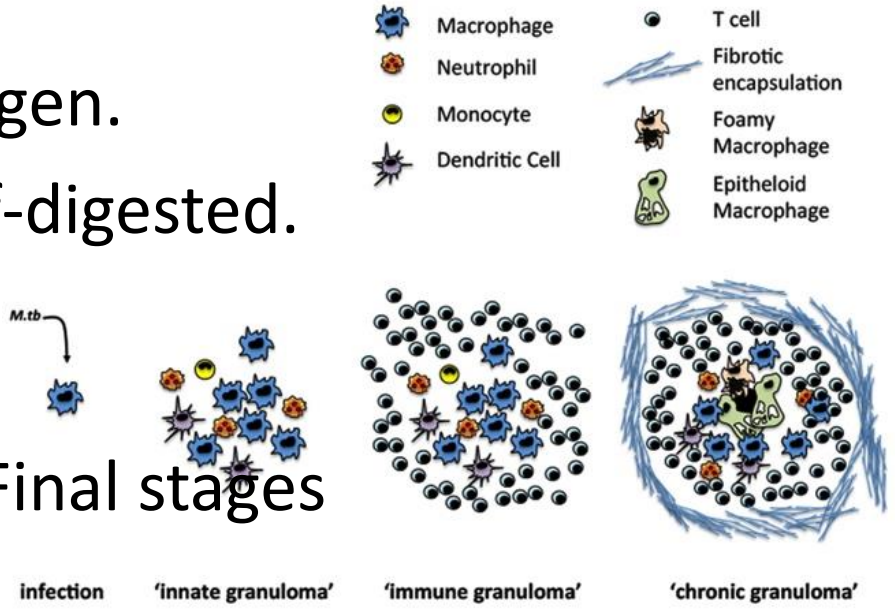
Synthesis

- Mast cells construct substances that play important roles in inflammation:
  - Leukotrienes
  - Prostaglandins
- Prostaglandin synthesis results in pain and fever
  - Synthesis involves Cyclooxygenase 1 & 2 pathways
  - Which medications block this?

Chronic Inflammatory Responses

- Defined as inflammation that lasts longer than 2 weeks.
  - Neutrophils continue to degranulate and die.
  - Lymphocytes infiltrate.
  - Fibroblasts secrete collagen.
  - Pus is produced and self-digested.
  - A granuloma may form.
  - Tissue repair.
  - Scar formation.

Final stages



Local Inflammatory Responses

- Local inflammatory symptoms result from:
  - Vascular changes
    - Redness, swelling, heat and pain
  - Exudation
    - Dilutes the toxins released by bacteria and toxic products of dying cells
    - Brings plasma proteins and leukocytes to the site to attack the invaders
    - Carries away the products of inflammation, e.g. toxins, dead cells, pus.

Systemic Inflammatory Responses

- Systemic Inflammatory Responses Syndrome (SIRS)
  - Progression of a localized infection to a more serious, systemically involved response
  - Results in:
    - Fever
    - Leukocytosis
    - Increased circulating plasma proteins

SIRS

- SIRS Criteria
  - Body Temperature: > 38°C or < 36°C
  - Heart Rate: > 90bpm
  - Respiratory Rate: > 20rrpm
  - WBC: > 12 x 10^9cells/L or < 4 x 10^9cells/L

- Two or more criteria results in a patient that is SIRS positive

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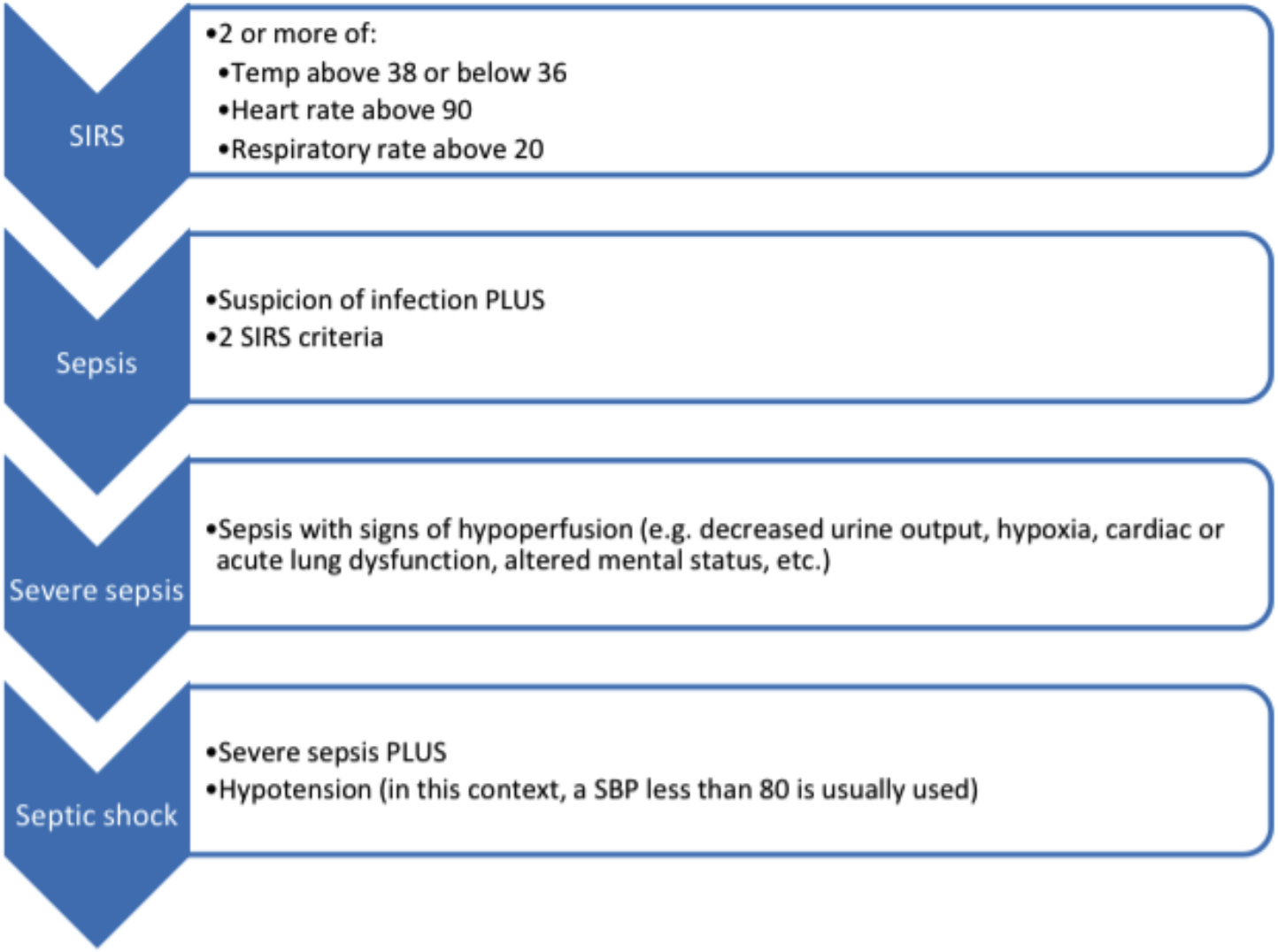
Sepsis Spectrum



Signs and Symptoms of Cellular Change

- When localized cellular injury spreads and chemical mediators enter the bloodstream, systemic effects are felt.
- Common presenting S/S associated with systemic involvement include:
  - Fatigue and malaise
  - Altered appetite
  - Fever
  - Increased heart rate
  - Pain

Cell Death

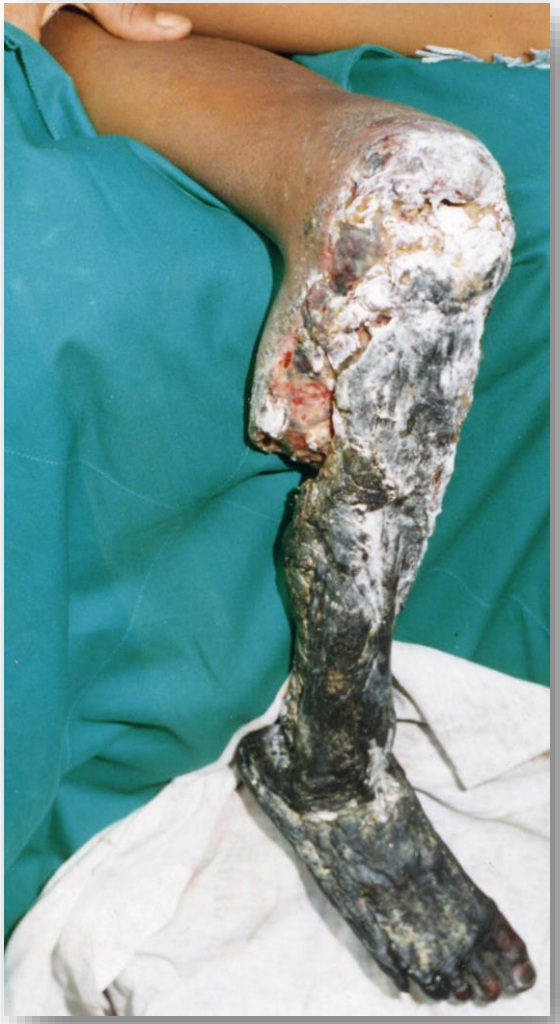
- Eventually if cause of cellular injury is not fixed, cellular death will occur.
- This occurs via one of two mechanisms:
  - Apoptosis
  - Necrosis

Apoptosis

- Programmed cell death
- Highly regulated process
  - Ex. cell death of tissue between fingers during embryonic development.
- Typically occurs if cell is stressed in any way (injury, infected)
- Injured cell releases enzymes that engulf and destroy the cell
- Eliminating damaged and dead cells allows tissues to repair and possibly regenerate

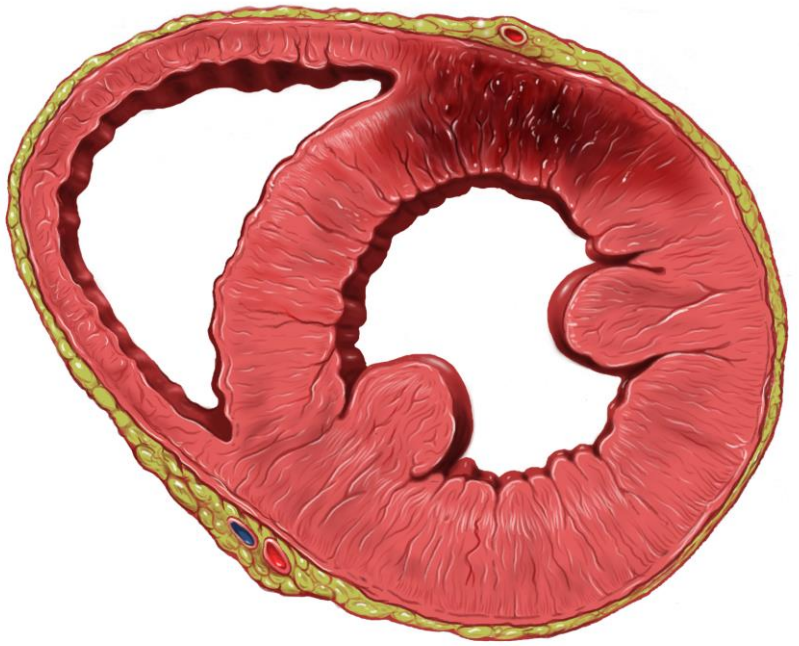
Necrosis

- Always a pathological process
  - Traumatic cell death
  - Result of infection, toxins, trauma
- Five types of necrotic cell death
  - Coagulative
  - Liquefactive
  - Caseous
  - Fatty
  - Fibrinoid
  - Gangrenous



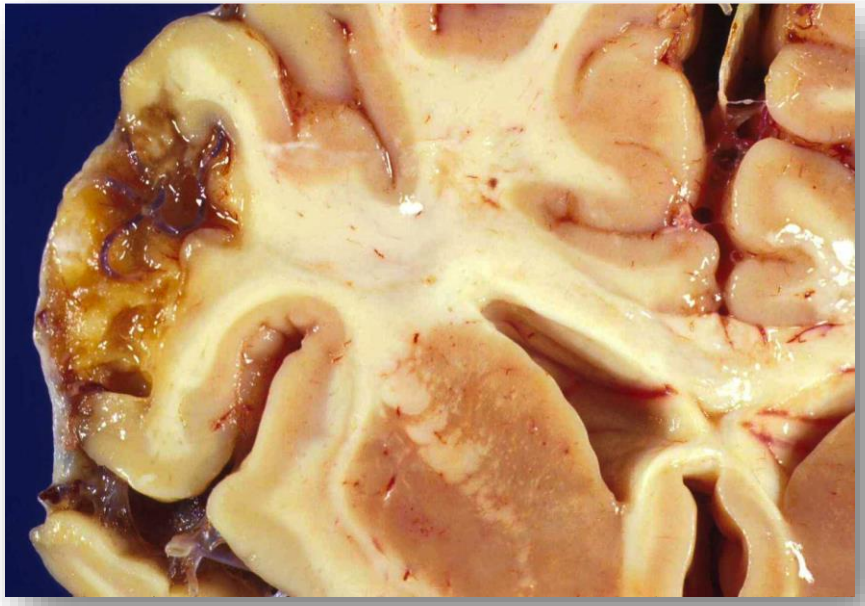
Coagulative Necrosis

- Type of necrosis caused by ischemia and subsequent infarction.
- Denatures proteins and lysozymes
  - Blocks proteolysis of damaged cells
  - Leads to inability to "self-fix" damage



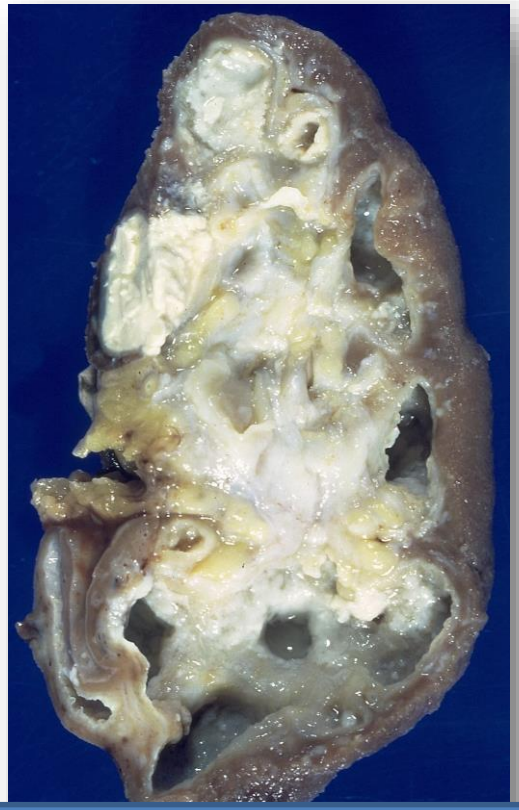
Liquefactive Necrosis

- Typically a result of bacterial or fungal infections
- Hydrolytic enzymes digest dead cells leaving mix of pus
  - Yellow pus color result of dead leukocytes
  - Common in the CNS



Caseous Necrosis

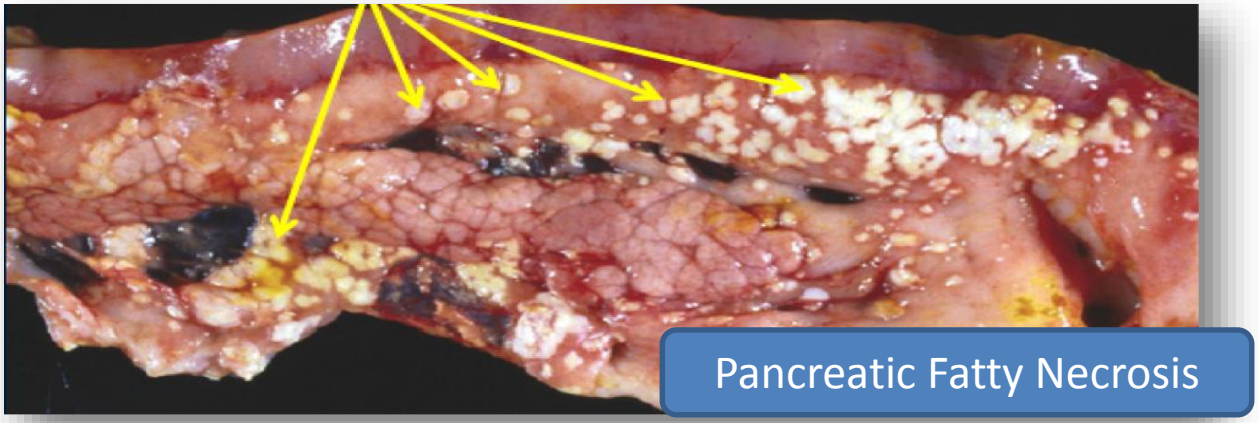
- White-coloured proteinaceous dead-cell mass
- Dead tissue appears cheese-like
- Combination of Coagulative and liquefactive forms



Caseous Necrotic Kidney

Fatty Necrosis

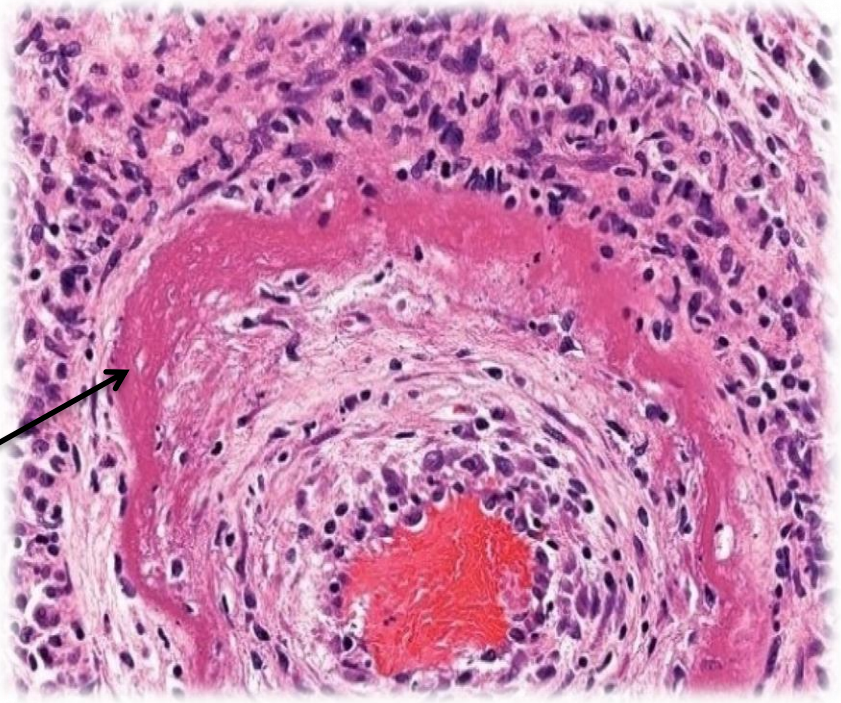
- Specific to adipose (fatty) tissue
- Lipase digest TG to FA
  - FA combine with Ca^{2+}
  - Soaps form which result in white, chalky deposits in tissue
  - Common post pancreatic trauma



Pancreatic Fatty Necrosis

Fibrinoid Necrosis

- Deposits of immune complexes (Antigen-Ab complex) and fibrin in tissue, typically vasculature walls
- Common with immune vasculitis and preeclampsia

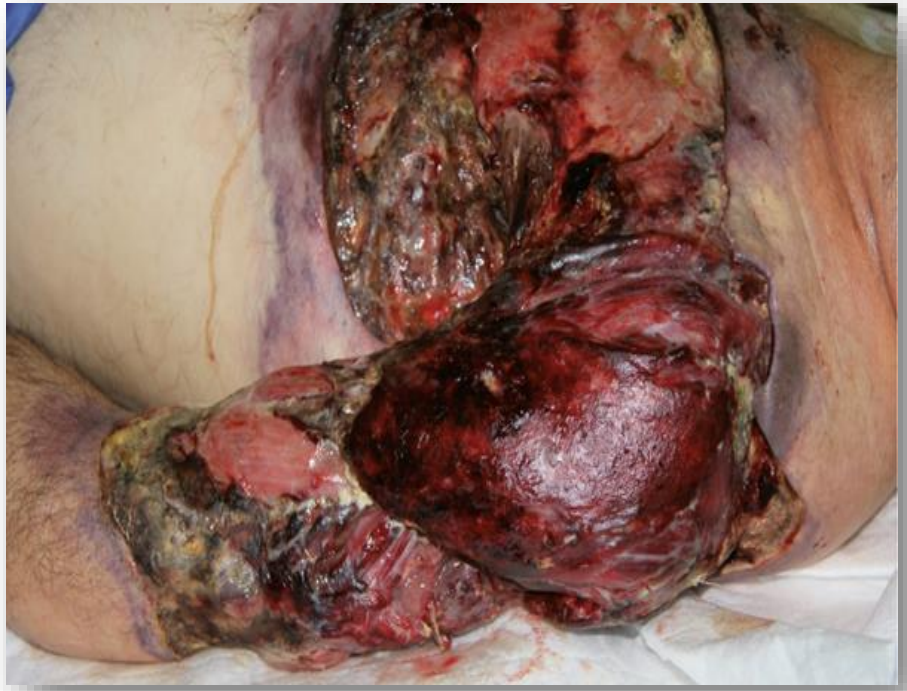


Gangrenous Necrosis

- Not a specific type but rather a wide spread progression of other necrosis types
- Can be caused by injury or illness
- Resembles mummified tissue
- Types
  - Dry gangrene
  - Wet gangrene
  - Gas gangrene
  - Nec Fasc

Necrotizing Fasciitis

- A.K.A. “Flesh-eating disease”
- Deep tissue, into fascia
- Secondary necrosis of subcutaneous tissue also occurs.
- Rapid progression, easier in immunocompromised patients



Multiple Organ Dysfunction Syndrome

- MODS is the progressive impairment of two or more organ systems from an uncontrolled inflammatory response to a severe illness or injury
  - Found in acutely ill patients in which some external intervention is required to maintain homeostasis
- Also known as multiple organ failure, multiple system organ failure

The Body's Defence and Changes with Disease and Injury

MODS STAGES

Primary MODS

- Organ damage results directly from a specific cause such as ischemia or inadequate tissue perfusion from shock, trauma or major surgery.
- Stress and inflammatory responses may be mild and undetectable
- During this response, neutrophils, macrophages, and mast cells are released

Secondary MODS

- Often occurs weeks after initial insult
- The host's inflammatory response enters a self-perpetuating cycle causing damage and vasodilation.
- An exaggerated neuroendocrine response is triggered causing further damage.

MODS
24 Hours After Resuscitation

- Low grade fever
- Tachycardia
- Dyspnea
- Altered mental status
- General hypermetabolic, hyperdynamic state

MODS
Within 24 to 72 Hours

- Pulmonary failure begins

MODS
Within 7 to 10 Days

- Hepatic failure begins
- Intestinal failure begins
- Renal failure begins

MODS
Within 14 to 21 Days

- Renal and hepatic failure intensify
- Gastrointestinal collapse
- Immune system collapse

MODS
After 21 Days

- Hematologic failure begins
- Myocardial failure begins
- Altered mental status resulting from encephalopathy
- Death

Summary

- The cell
- Types of tissue
- Disease causes
- Disease pathophysiology