**TEACHING UNIT 13**

**Immune Response to Microorganisms**

The immune system serves many functions, but its primary physiological role is to protect the host from pathogens. All types of immune responses described thus far (immune cells, molecules, organs, and mechanisms) are most commonly studied in the context of reactions to microbes—bacteria, viruses, fungi, and parasites.

The development of infection in humans represents a complex interaction between the microorganism and the host organism. During an infection, the following key events occur:

1. **Entry of the microorganism into the host** – through the skin, mucosal membranes, or other routes.
2. **Dissemination and colonization of tissues** – the pathogen finds favorable sites for replication.
3. **Evasion of the immune response** – many microbes possess mechanisms to hide from or inhibit immune cells.
4. **Tissue damage and functional disturbances** – caused either directly by the pathogen or as a consequence of the immune response.

Microorganisms cause disease in various ways. Some kill host cells, while others secrete toxins that lead to damage and dysfunction of organs, even if the pathogen does not spread extensively. In certain cases, it is an excessive or misdirected immune response itself that causes tissue damage and clinical symptoms of the disease.

The degree of pathogenicity of a microorganism depends on multiple factors, including its ability to evade the immune system and replicate in tissues. Although there are numerous mechanisms that lead to infection and disease, this discussion focuses solely on immune system responses.

**General Characteristics of the Immune Response to Microbes**

Despite the diversity of defensive reactions that occur in response to infection, several universal features of the immune response to pathogenic microorganisms can be identified:

1. **The immune system operates through two main branches—innate and adaptive immunity.**

Innate immunity is the first to respond immediately after pathogen entry, serving as the "first line of defense." However, many pathogens have evolved strategies to evade innate immunity. In such cases, the host requires a more specific and potent response provided by adaptive immunity. Adaptive immunity not only targets the pathogen more precisely but also generates memory cells, enabling long-term protection against reinfection.

1. **Specificity of the Response According to the Type of Microorganism**

The host does not respond the same way to all types of pathogens. Because viruses, bacteria, fungi, and parasites differ in their modes of dissemination and tissue colonization, the immune system has evolved specialized mechanisms to combat each type of pathogen. A prime example includes the distinct subsets of effector CD4+ T lymphocytes (Th1, Th2, and Th17), as well as different antibody isotypes, each of which plays a critical role in the immune defense against specific groups of pathogens.

1. **Microorganisms Often Evade the Immune Response**

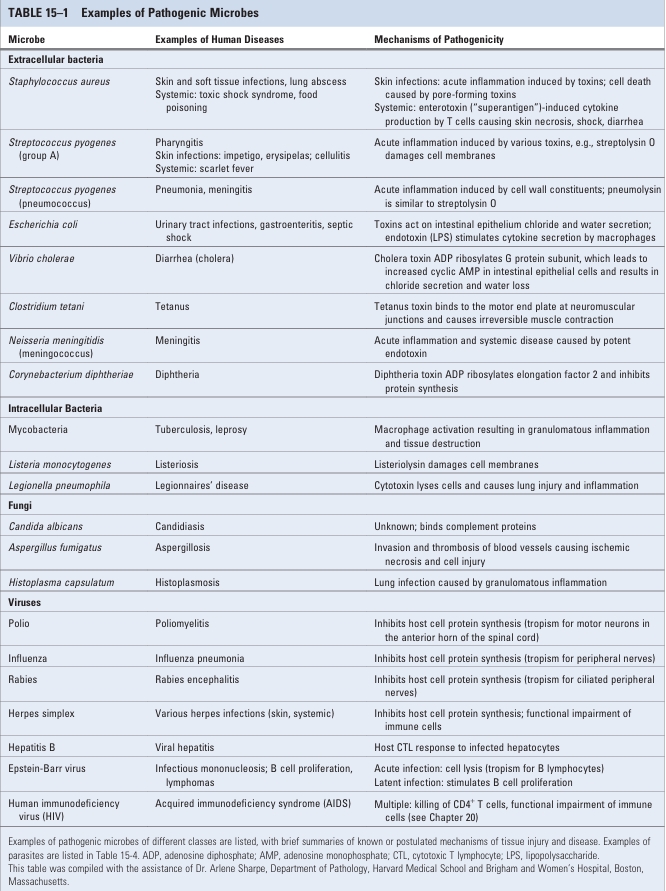
The survival and pathogenic potential of microorganisms within the host largely depend on their ability to evade or neutralize components of the immune system. This represents a continuous "arms race" between host defenses and pathogen evasion strategies. The outcome of infection frequently hinges on which side proves more effective—the host's immune system or the pathogen’s survival mechanisms.

1. **Many Microorganisms Cause Latent or Persistent Infections**

In some cases, the immune system manages to control but not completely eliminate the pathogen, resulting in a latent infection. In such a state, the microorganism remains present in the body without causing active disease. This is characteristic of certain viruses, such as herpesviruses and poxviruses, as well as intracellular bacteria like *Mycobacterium tuberculosis*. If the immune system becomes compromised—due to HIV infection, cancer, immunosuppressive therapy, etc.—a latent infection may become reactivated and lead to severe health complications.

1. **The Immune Response Itself Can Cause Tissue Damage**

Although the immune response is crucial for survival, it also carries the risk of harming the body’s own tissues. In many infections, it is the immune response—rather than the pathogen itself—that serves as the principal cause of inflammation, tissue injury, and disease symptoms.



**Extracellular Bacteria – Mechanisms of Disease Induction**

Extracellular bacteria are a type of pathogenic microorganisms capable of replicating outside host cells. This means they do not need to enter human cells in order to survive and propagate. They are most commonly found and replicate within:

* the bloodstream,
* connective tissue,
* interstitial spaces,
* body cavities such as the respiratory tract and intestines.

Although their mode of existence differs, many extracellular bacteria possess pathogenic properties—namely, the ability to cause disease. They do so through two main mechanisms:

**1. Induction of Inflammation**

When bacteria enter the body, the immune system recognizes them as foreign and initiates an inflammatory response. This leads to:

* redness, swelling, pain, and warmth,
* activation of immune cells that destroy bacteria,
* but also to tissue damage in the host as a result of intense inflammation.

Thus, in some cases, it is not the bacteria directly that cause the disease, but the tissue damage resulting from inflammation.

**2. Toxin Production**

Numerous extracellular bacteria produce toxins that exert various harmful effects on the host organism:

* **Endotoxins** are structural components of the bacterial cell wall, most commonly found in Gram-negative bacteria.
  + The most well-known example is **lipopolysaccharide (LPS)**.
  + LPS strongly activates immune cells such as macrophages and dendritic cells, leading to increased cytokine production and inflammation.
* **Exotoxins** are substances actively secreted by bacteria into the surrounding environment. Their effects can be:
  + **cytotoxic** – directly killing host cells,
  + **dysfunctional** – disrupting normal cell functions without killing them,
  + **immunological** – excessive activation of the immune system and cytokine-mediated disease induction.

**Innate Immunity and Extracellular Bacteria**  
Innate immunity represents the first and rapid line of defense of the organism against infections, including those caused by extracellular bacteria. Extracellular bacteria are pathogens that replicate outside the host’s cells, most commonly in the bloodstream, tissues, or cavities such as the respiratory and digestive tracts. The main innate immune mechanisms against these bacteria are:

**1. Complement Activation**

The complement system consists of a group of plasma proteins that become activated in the presence of microorganisms and lead to their destruction. In extracellular bacterial infections, complement can be activated in several ways:

* **Alternative pathway:**
  + Triggered by peptidoglycan, a component of the cell wall of Gram-positive bacteria.
  + Lipopolysaccharide (LPS), found in the wall of Gram-negative bacteria, also activates complement via this pathway.
* **Lectin pathway:**
  + Bacteria that have mannose on their surface can bind mannose-binding lectin (MBL), which initiates complement activation.

**Consequences of complement activation include:**

* **Opsonization** – labeling bacteria for easier recognition and phagocytosis,
* **Lysis of bacteria** – via the membrane attack complex (MAC), particularly effective against bacteria such as *Neisseria* (due to thin cell walls),
* **Inflammation** – complement fragments act as chemoattractants, drawing leukocytes to the site of infection.

**2. Phagocyte Activation and Inflammation**

Phagocytes (macrophages and neutrophils) are innate immune cells that recognize, engulf, and destroy bacteria. They use various types of receptors:

* **Pattern recognition molecules** such as mannose receptors and scavenger receptors that recognize bacterial carbohydrates,
* **Fc receptors** – recognize antibody-coated bacteria,
* **Complement receptors** – bind bacteria opsonized with complement components,
* **Toll-like receptors (TLRs)** – detect conserved bacterial molecules (e.g., LPS, flagellin) and activate intracellular signaling in phagocytes.

**Functions of these receptors include:**

* Some enhance phagocytosis,
* Others activate the production of reactive molecules that kill bacteria,
* Some (e.g., Fc and complement receptors) act both as recognition and activation receptors.

Activated phagocytes and dendritic cells release cytokines that:

* Promote leukocyte infiltration into infected tissue,
* Induce inflammation that limits infection spread,
* Eliminate bacteria in synergy with other immune cells and molecules.

**Adaptive Immunity and Extracellular Bacteria**  
In extracellular bacterial infections, the key defense mechanism is humoral immunity, i.e., the antibody-mediated response. This immune response has several functions:

* **Prevents infection**,
* **Aids in the elimination** of already present bacteria,
* **Neutralizes toxins** secreted by bacteria.

Antibodies are generated against:

* Components of the bacterial cell wall,
* Free or cell-associated toxins,
* Antigens that may be polysaccharides or proteins.

**Immune Response to Polysaccharides**  
Polysaccharides are considered thymus-independent antigens, meaning they can activate B lymphocytes without the help of T cells. Therefore, humoral immunity is crucial for defending against encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*.

**Mechanisms of Antibody Action**  
Antibodies participate in host defense via multiple mechanisms:

* **Neutralization** – IgG, IgM, and IgA bind to toxins or bacterial structures and block their effects; IgA mainly functions in mucosal tissues,
* **Opsonization and phagocytosis** – some IgG subclasses bind bacteria and “tag” them for destruction by phagocytes,
* **Complement activation** – IgM and certain IgG subclasses activate the classical complement pathway, resulting in bacterial lysis and inflammatory response.

**Response of T-helper (CD4⁺) Lymphocytes**  
Protein antigens of extracellular bacteria activate CD4⁺ T lymphocytes, which:

* Secrete cytokines,
* Promote local inflammation,
* Enhance macrophage and neutrophil function,
* Stimulate B lymphocytes to produce specific antibodies.

**Role of Th17 Lymphocytes**  
Th17 lymphocytes are particularly important in defense against bacteria and fungi because they:

* Recruit neutrophils and monocytes to infected tissues,
* Maintain local inflammation needed to control infection.

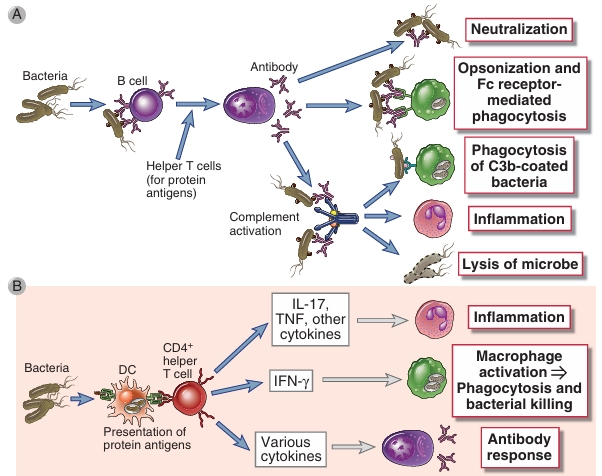
A deficiency in Th17 response is associated with increased susceptibility to infections, especially skin abscesses and fungal infections. One genetic cause is a mutation in the transcription factor **STAT3**, leading to defective Th17 cell differentiation. This condition is known as:

* **Job’s syndrome** – named for the biblical character Job, due to the appearance of boils,
* or **Hyper-IgE syndrome** – since patients have elevated serum IgE levels, although the precise mechanism is not fully understood.

**Role of Th1 Lymphocytes**

Extracellular bacteria can also induce a **Th1-type immune response**, in which:

* **Interferon-gamma (IFN-γ)**, secreted by Th1 cells,
* **Activates macrophages** to destroy phagocytosed bacteria,
* **Stimulates the production of antibodies** that have enhanced ability to bind complement and act as opsonins.



**Adaptive immunity plays a key role in the defense against extracellular microorganisms**, such as bacteria and their toxins. The two main forms of adaptive immune responses are:

**A) Antibody production**  
Antibodies (immunoglobulins), produced by B lymphocytes, function by:

* **Neutralizing bacteria and their toxins**,
* **Facilitating their elimination** through opsonization, phagocytosis, and complement activation.

**B) Activation of CD4⁺ T lymphocytes**  
Helper T cells are activated upon contact with antigens presented by dendritic cells (DCs). Their roles include:

* **Cytokine secretion**,
* **Stimulation of inflammation**,
* **Activation of macrophages**,
* **Promoting B lymphocyte antibody production**.

**Harmful Effects of the Immune Response to Extracellular Bacteria**

Although immune responses to extracellular bacteria are crucial for protection, **they can sometimes cause tissue damage and systemic complications**. The most significant adverse outcomes include **local inflammation**, **septic shock**, and **post-infectious autoimmune complications**.

1. **Inflammation and tissue damage**  
   Activated **neutrophils and macrophages**, which are essential for bacterial elimination, also release:

* **Reactive oxygen species (ROS)**,
* **Lysosomal enzymes**.

These substances destroy pathogens, but can also damage **host tissues**, especially at the site of infection. While these inflammatory reactions are usually **localized and self-limiting**, in some cases they can escalate into more **severe forms of inflammation**.

1. **Systemic Manifestations and Septic Shock**  
   Cytokines secreted by immune cells in response to bacterial components promote:

* **Synthesis of acute-phase proteins in the liver**,
* **Systemic symptoms** such as fever, fatigue, and loss of appetite.

In severe and disseminated infections—particularly those caused by gram-negative or gram-positive bacteria—**septic shock** can develop.

**Septic shock** is a severe, potentially fatal condition characterized by:

* **Circulatory collapse**,
* **Disseminated intravascular coagulation (DIC)**.

In its early phase, sepsis is a consequence of a **cytokine storm**—a massive release of cytokines such as:

* **TNF (tumor necrosis factor)**,
* **IL-1**,
* **IL-6**,
* with contributions from **IFN-γ** and **IL-12**.

In later stages, **immunosuppression** may occur due to reduced activity or loss of T lymphocytes, leading to uncontrolled infection spread.

1. **Effect of Superantigens**  
   Some bacterial toxins act as **superantigens**, meaning they:

* **Activate large populations of T lymphocytes**,
* **Bind to the T cell receptor (TCR) and MHC class II molecules**,
* Without entering the peptide-binding groove, they **stimulate uncontrolled T cell activation**.

The result is **excessive cytokine release** and a **systemic inflammatory syndrome**, which can lead to **toxic shock**.

1. **Autoimmune and Post-Infectious Complications**  
   In later stages of the immune response to infection, **pathogenic antibodies** may develop, leading to autoimmune processes. Two classical examples after streptococcal infections are:

**a) Rheumatic Fever**

* Occurs after a **pharyngeal infection** with β-hemolytic streptococci.
* The body produces antibodies against **streptococcal M protein**.
* Some of these antibodies **cross-react with cardiac muscle proteins**.
* This results in **inflammation of the heart** (*rheumatic carditis*).

**b) Poststreptococcal Glomerulonephritis**

* Arises after **skin or throat infection** with other streptococcal serotypes.
* Antibodies form **immune complexes** with bacterial antigens.
* These complexes are **deposited in the renal glomeruli**, causing **nephritis**.



**Polyclonal Activation of T Lymphocytes by Bacterial Superantigens**  
Superantigens are bacterial or viral proteins that can cause massive, non-specific activation of T lymphocytes—a process known as **polyclonal activation**. Their mechanism of action significantly differs from classical T cell activation.

**A) Conventional Activation of T Lymphocytes**

* In typical infections, an **antigen-presenting cell (APC)** presents a **peptide antigen** (a fragment of a microbe) via **MHC class II** molecules.
* The peptide is **inserted into the peptide-binding groove** of the MHC molecule.
* Only a **small fraction of T cells** in the body possess a **T cell receptor (TCR)** capable of recognizing this specific peptide-MHC complex.
* **Only those T cells are activated**, proliferate, and become effector cells contributing to the immune response.

**B) Activation by Superantigens**

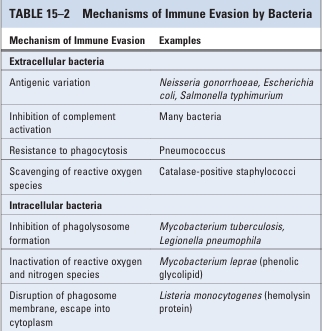
* Superantigens do **not bind within the peptide-binding groove**, but rather attach to the **outer surface** of MHC class II molecules.
* Simultaneously, they bind to the **variable (Vβ) region of the β-chain** of the TCR, **regardless of the TCR’s antigen specificity**.
* This leads to **activation of large numbers of T cells** that share the same Vβ family of receptors.
* As a result, **thousands of T cell clones** can be activated at once.

**Consequences of Superantigen Activation**

* **Massive cytokine production** — referred to as a **cytokine storm**, which can lead to **systemic inflammatory syndrome**, **septic shock**, or **toxic shock**.
* **T cell apoptosis** — in response to hyperactivation, many T cells undergo **programmed cell death**, resulting in **immunosuppression**.
* **Different superantigens** recognize **different Vβ families**, thereby determining which T cell clones are activated.

**Example: Staphylococcal Enterotoxin B (SEB)**

* One of the best-known superantigens is **Staphylococcal enterotoxin B (SEB)**.
* SEB binds to **HLA-DR molecules** (a type of MHC class II) and to **Vβ3 family** of TCRs.
* The outcome is **widespread T cell activation**, leading to systemic effects such as **fever**, **hypotension**, and **multi-organ dysfunction**.



**Immune Evasion by Extracellular Bacteria**  
Extracellular bacteria, which replicate outside host cells, possess numerous mechanisms that allow them to evade immune responses. These strategies enable the bacteria to survive within the host, establish infection, and increase their pathogenic potential.

**1. Resistance to Innate Immunity**

**a) Resistance to Phagocytosis**

* Many bacteria have a **polysaccharide capsule** that protects them from being recognized and ingested by phagocytes (macrophages and neutrophils).
* **Encapsulated bacteria**, such as *Streptococcus pneumoniae*, are significantly more virulent than their non-encapsulated counterparts.

**b) Complement Inhibition**

* Some bacteria inhibit complement activation, especially the **alternative pathway**.
* The capsules of many pathogenic Gram-positive and Gram-negative bacteria contain **sialic acid residues**, which interfere with complement activation and **reduce opsonization**.

**2. Evasion of Humoral Immunity (Antibodies)**

**a) Antigenic Variation**

* Certain bacteria, such as *Neisseria gonorrhoeae* and *Escherichia coli*, possess surface structures known as **pili (fimbriae)**, which are used for adherence to host cells.
* The **main antigenic component** of these structures is the **pilin protein**.
* The genes encoding pilin undergo frequent genetic rearrangements (e.g., **gene conversion**), leading to a vast array of antigenic variants.

**As a result**:

* The progeny of a single bacterium can express up to **1,000,000 different antigenic forms of pilin**.
* This extensive variability enables the bacteria to **evade recognition** by pre-existing specific antibodies.

**Furthermore**, these antigenic modifications may enhance bacterial adhesion to host cells, thereby further increasing **bacterial virulence**.

**b) Chemical Modification of Surface Molecules**

* Certain bacteria, such as *Haemophilus influenzae*, produce **glycosidase enzymes** that alter the structure of surface molecules, including **lipopolysaccharide (LPS)** and other polysaccharides.
* These chemical modifications:
  + Reduce **antibody recognition**,
  + Enable **evasion of humoral immunity**.

**Immunity to Intracellular Bacteria**

**Intracellular bacteria**, particularly **facultative intracellular species**, possess the ability to **survive and even replicate within phagocytic cells**. By residing inside host cells, they are shielded from circulating antibodies and require a specialized **cell-mediated immune response**. While these immune responses can control infection, they frequently cause **inflammatory tissue damage** as well.

**Innate Immunity**

The **innate response** to intracellular bacteria primarily involves:

**Phagocytes**

* **Neutrophils and macrophages** ingest bacteria, but many intracellular bacteria survive within the **phagolysosomes**.
* Recognition of microbial molecules via **TLRs (Toll-like receptors)** and **NOD-like receptors** activates phagocytes to produce inflammatory cytokines and antimicrobial agents.

**Natural Killer (NK) Cells**

* Infected host cells express **activation ligands** that are recognized by **NK cells**.
* **Dendritic cells and macrophages** secrete **IL-12** and **IL-15**, which stimulate NK cell activation.
* **Activated NK cells secrete IFN-γ**, a key cytokine that enhances macrophage ability to kill intracellular bacteria.

Although this innate response provides **temporary control** of infection, **complete eradication** of intracellular bacteria typically **requires adaptive immunity**.

**Adaptive Immunity**

**Primary Protective Mechanism: Cell-Mediated Immunity**

* Individuals with **T cell deficiencies** (e.g., patients with AIDS) are **highly susceptible** to infections with intracellular bacteria.
* The response can be divided into **two main types**:

**1. CD4⁺ T Lymphocytes (Th1 Subtype)**

* Are activated by **bacterial antigens** presented on **MHC class II** molecules.
* Under the influence of **IL-12**, naive CD4⁺ cells differentiate into **Th1 cells**.
* Th1 cells:
  + Secrete **IFN-γ** and express **CD40L**, which:
    - **Activate macrophages**,
    - Stimulate production of **reactive oxygen species (ROS)**, **nitric oxide (NO)**, and **lysosomal enzymes**,
    - Assist in **isotype switching** of antibodies (e.g., to IgG2a in mice).

**2. CD8⁺ Cytotoxic T Lymphocytes (CTLs)**

* Become activated when bacterial antigens **gain access to the cytosol** of infected cells.
* These antigens are presented on **MHC class I** molecules.
* CTLs **recognize and kill infected cells directly**.

**Cooperative Action of CD4⁺ and CD8⁺ T Cells**

* **CD4⁺ T cells** activate macrophages for microbial killing,
* **CD8⁺ T cells** eliminate infected cells directly,
* **Together**, they provide a **potent and coordinated immune defense** against intracellular bacteria.

**Pathological Effects of the Immune Response**

* **Chronic activation** of macrophages and T lymphocytes may lead to **tissue damage**.
* A typical outcome is **granulomatous inflammation**, which:
  + **Contains the infection**,
  + But may also cause **necrosis**, **fibrosis**, and **functional impairment** of affected tissues.

**Example: Tuberculosis (M. tuberculosis)**

* In **90% of cases**, the infection is **controlled but not eliminated**.
* **IFN-γ** activates macrophages, while **TNF** enhances local inflammation.
* The bacterium avoids destruction by **inhibiting phagosome-lysosome fusion**.
* **Granulomas** with **caseous necrosis** form, leading to **tissue damage**.

**Diagnostic Test for Infection: PPD (Purified Protein Derivative Test)**

* In **previously infected individuals**, the test elicits a **delayed-type hypersensitivity reaction (type IV DTH)**.

**Immune Response and Disease Outcome: Example of Leprosy**

* **Causative agent**: *Mycobacterium leprae*.
* Two **polar forms** of disease:

1. **Lepromatous Leprosy**
   * **Weak cellular immune response**, strong antibody production.
   * **Numerous bacteria** in lesions, **poor macrophage activation**.
   * Presence of **IL-4 and IL-10**, low **IFN-γ** (indicative of a **Th2-type response**).
2. **Tuberculoid Leprosy**
   * **Strong Th1 response**: high **IFN-γ** and **IL-2**, low antibody levels.
   * **Granulomas** form around nerves → **peripheral nerve damage**, but **few bacteria** in tissues.

**Mechanisms of Immune Evasion by Intracellular Bacteria**

Intracellular bacteria employ various strategies to escape immune destruction:

* **Inhibition of phagosome-lysosome fusion** (e.g., *M. tuberculosis*, *Legionella*),
* **Escape into the cytoplasm** (e.g., *Listeria monocytogenes*),
* **Inactivation of reactive oxygen and nitrogen species** (e.g., *M. leprae*).

**Summary**

Intracellular bacteria pose a significant challenge to the immune system due to their ability to **survive within phagocytes**.

* Their **elimination depends on effective cell-mediated immunity**, particularly **Th1 cells** and **cytotoxic T lymphocytes**.
* However, **prolonged immune activation** can lead to **tissue damage**, as seen in **tuberculosis** and **leprosy**.
* The **balance between immune defense and immunopathology** is critical in determining the **clinical outcome** of the disease.

**Immune System and Fungi**  
Fungal infections (mycoses) represent a significant cause of morbidity and mortality, particularly in individuals with compromised immune systems.

* Some forms of mycoses are **endemic**, arising from **inhalation of environmental spores**.
* Others are **opportunistic**, causing mild or no disease in healthy individuals but potentially leading to **severe infections in immunosuppressed persons**.

The **most important risk factor** for severe fungal infections is **immunosuppression**:

* For example, **neutropenia** due to chemotherapy or bone marrow suppression significantly increases the risk.
* The incidence of opportunistic mycoses is increasing due to the rise in **HIV infections**, **cancer treatments**, and **post-transplant immunosuppressive therapy**.

One of the **most severe fungal infections** in AIDS patients is pneumonia caused by *Pneumocystis jiroveci*, though many other fungi contribute to morbidity and mortality in these patients.

**Immune Response to Fungi**

Fungi may be **extracellular** or survive **within phagocytes**, meaning the immune response often includes elements of both extracellular and intracellular defense — similar to responses against bacteria.

However, the **immune response to fungi is less well understood** than to bacteria or viruses, partly due to a lack of suitable animal models and because infections often occur in patients incapable of developing adequate immunity.

**Innate Immunity to Fungi**

The main mediators of innate immunity are:

* **Neutrophils**
* **Macrophages**

**Key roles include**:

* Recognition of fungi via **TLRs** and **C-type lectin receptors** (e.g., **dectin-1**),
* Phagocytosis and secretion of fungicidal substances such as:
  + **Reactive oxygen species (ROS)**,
  + **Lysosomal enzymes**.

**Example**:  
*Cryptococcus neoformans* can **inhibit TNF and IL-12 production** and **stimulate IL-10**, preventing macrophage activation.

**Adaptive Immunity to Fungi**

The most important defense mechanism is **cellular immunity**.

**Th1 Response** (for intracellular fungi):

* Activates macrophages via **IFN-γ**,
* Crucial in controlling infections like **histoplasmosis**,
* May cause **granulomatous inflammation** that contains but also damages tissue.

**Th17 Response** (for extracellular fungi):

* Promotes **inflammation** and **recruitment of neutrophils and monocytes**,
* Activated through **dectin-1**, which recognizes fungal glucans,
* **IL-6** and **IL-23** from dendritic cells promote Th17 differentiation.

**Example**:  
With *Candida albicans*, infection often begins at **mucosal surfaces**, and the **Th17 response is essential to prevent its dissemination**.

**CD8⁺ T Lymphocytes**:

* In some fungal infections (e.g., *C. neoformans*), **collaborate with CD4⁺ T cells** in fungal elimination, particularly in immunosuppressed patients.

**Role of Antibodies**

Fungi also stimulate production of **specific antibodies**, which:

* Provide **protective functions**,
* But their role is generally **less critical than the cellular immune response**.

**Conclusion**

* The immune response to fungi involves both **innate and adaptive components**.
* **Neutrophils and macrophages** form the first line of defense.
* **Th1 and Th17 lymphocytes** play critical roles in **fungal clearance** and in **tissue damage**.
* **Immunosuppression** remains the most significant risk factor for developing **severe fungal infections**.

**Immune System and Viruses**

Viruses are **obligate intracellular microorganisms** — to replicate, they must enter host cells and utilize their machinery for synthesizing proteins and nucleic acids. Entry is typically achieved via **binding to specific receptors** on the host cell surface.

**Mechanisms of tissue damage caused by viruses**:

* Inhibition of host cell protein synthesis and function,
* Lysis of infected cells (cytopathic effect),
* Establishment of **latent infections** without active virus production.

**Innate Immune System and Viruses**

**Main mechanisms of innate protection**:

* **Type I interferons (IFN-α and IFN-β)**: block viral replication in both infected and neighboring uninfected cells.
* **Natural Killer (NK) cells**: kill virus-infected cells, especially those lacking MHC class I (often a viral evasion strategy).

**Activation pathways**:

* Viral nucleic acids are recognized by:
  + **TLRs** in endosomes,
  + **RIG-I** and **MDA-5** receptors in the cytoplasm.
* These signaling pathways induce **interferon production**.

**Adaptive Immune System and Viruses**

**a) Humoral Immunity (Antibodies)**

* Antibodies prevent viral entry by binding to **viral envelopes** or **capsid antigens**.
* **IgA** neutralizes viruses at mucosal surfaces (e.g., oral polio vaccine).
* Antibodies can:
  + **Neutralize** the virus,
  + **Opsonize** for phagocytosis,
  + **Activate complement**, leading to lysis of enveloped viruses.

Note: Antibodies are only effective **during the extracellular phase** of the viral life cycle.

**b) Cytotoxic T Lymphocytes (CD8⁺ CTLs)**

* Eliminate infected cells **presenting viral peptides via MHC class I**.
* CTL differentiation often requires:
  + **CD4⁺ T helper cell** support,
  + **Co-stimulatory signals**.
* CTLs can:
  + Induce **apoptosis** of infected cells,
  + Secrete **IFN-γ**, which activates phagocytes and has antiviral effects.

CD8⁺ T cells are **key for eliminating intracellular viruses**.

**Latent Infections**

* Virus remains in cells but **does not replicate** actively.
* **CTLs control** the infection but **cannot eliminate it**.
* **Immunodeficiency** (e.g., HIV) → reactivation of viruses (e.g., **Epstein-Barr**, **Herpesviruses**).
* Consequences may include **cell lysis**, **uncontrolled proliferation**, or **malignant transformation**.

**Tissue Damage from Immune Responses**

In some viral diseases, the **immune response causes more damage** than the virus itself.

**Examples**:

* **LCMV in mice**:
  + CTLs destroy infected meningeal cells → **meningitis**.
  + Mice lacking T cells remain **asymptomatic carriers**.
* **Hepatitis B in humans**:
  + **CD8⁺ T cells damage hepatocytes**.
  + Immunocompromised patients remain **carriers** without symptoms but **transmit the virus**.
* **Immune complex diseases**:
  + In chronic infections (e.g., Hepatitis B), immune complexes → **vasculitis**.

**Molecular Mimicry**:

* Similarities between viral and self-antigens may trigger **autoimmune responses**.

**Mechanisms of Immune Evasion by Viruses**

**a) Antigenic Variation**

* **Mutations and recombinations** alter viral antigens.
* **Influenza virus**: antigenic drift and shift.
* **HIV**: extreme antigenic diversity → vaccine development challenges.

**b) Inhibition of MHC I Presentation**

* Viruses can block:
  + **Antigen processing**,
  + **Peptide transport into the ER**,
  + **MHC I surface expression**.

Prevents CTL recognition but **activates NK cells**.

**c) Production of Immunosuppressive Molecules**

* **Poxviruses** produce proteins that bind and neutralize cytokines (e.g., IFN-γ, TNF, IL-1).
* **Epstein-Barr Virus** synthesizes an **IL-10-like protein** → inhibits macrophages and dendritic cells.

**d) T Cell Exhaustion**

* Chronic activation leads to **PD-1 pathway activation** → T cell dysfunction.
* Observed in **chronic LCMV infection in mice** and **HIV in humans**.

**e) Infection of Immune Cells**

* Best example: **HIV**, which infects and destroys **CD4⁺ T cells**.

**Summary**

Immune defense against viruses involves:

* **Type I interferons**,
* **NK cells**,
* **Antibodies**,
* **CD8⁺ cytotoxic T cells**.

However, viruses have evolved numerous strategies to **evade immune detection** and destruction. The **balance** between **effective clearance** and **immune-mediated damage** determines the clinical outcome of viral infections.

**Immune System and Parasites**

In medicine, the term *parasites* encompasses:  
• Protozoa (unicellular parasites),  
• Helminths (worms),  
• And ectoparasites (e.g., ticks and mites).

Parasites are the cause of a large number of diseases, especially in developing countries. It is estimated that more than 30% of the world population is infected with some form of parasite. Malaria alone affects over 100 million people annually and causes 1–2 million deaths.

Parasites often have complex life cycles that include both humans and intermediate hosts (e.g., insects, snails). Infections are most commonly transmitted:  
• By the bites of infected insects (e.g., malaria, trypanosomiasis),  
• Or through contact with contaminated water environments (e.g., schistosomiasis).

Most parasitic infections are chronic due to:  
• Weak or ineffective immunity,  
• Parasites avoiding elimination,  
• Antiparasitic drugs often being ineffective.

**Innate Immunity and Parasites**

**Protozoa**  
• The primary mechanism: *phagocytosis*.  
• Many protozoa survive and replicate within macrophages.  
• Surface molecules of parasites activate TLR2 and TLR4 on phagocytes (e.g., *Plasmodium*, *Toxoplasma*, *Cryptosporidium*).

**Helminths**  
• Too large for phagocytosis.  
• Neutrophils and macrophages release microbicidal substances, but helminths possess thick protective outer layers.  
• They can activate the alternative complement pathway but are often resistant to lysis.

**Adaptive Immunity and Parasites**

**a) Protozoa – Cell-mediated immunity (Th1)**  
• *Leishmania major* resides in the endosomes of macrophages.  
• Th1 CD4⁺ lymphocytes → IFN-γ → activate macrophages → parasite destruction.  
• A Th2 response (e.g., IL-4) → suppresses classical macrophage activation → worsens the infection.

**Example: BALB/c mice**  
• Predisposed to a Th2 response → susceptibility to infection.  
• Resistant mouse strains → dominant Th1 response → effective defense.

**b) Malaria and Similar Infections**  
• *Plasmodium* resides in erythrocytes and hepatocytes.  
• Antibodies act in the bloodstream.  
• CD8⁺ T cells eliminate parasites in the liver.  
• IFN-γ is crucial for protection (also in toxoplasmosis and cryptosporidiosis).

**c) Helminths – Humoral Immunity (Th2)**  
• Th2 CD4⁺ T cells → IL-4 and IL-5:  
o IL-4 → promotes IgE production.  
o IL-5 → promotes the development and activation of eosinophils.  
• IgE binds to mast cells and eosinophils, which release mediators → damage and expulsion of parasites.

**Barrier defense:**  
• Enhanced peristalsis and intestinal responses contribute to the expulsion of parasites.

**Immune-Mediated Damage in Parasitic Infections**

• Some parasitic infections cause granulomatous reactions and fibrosis:

**Schistosomiasis:**  
• *Schistosoma mansoni* eggs → activate CD4⁺ T cells → inflammation and granulomas in the liver.  
• These granulomas are Th2-dependent, unlike classical Th1 granulomas.  
• IL-4 and IL-13 → “alternative macrophage activation” → fibrosis, cirrhosis, portal hypertension.

**Lymphatic filariasis:**  
• Parasites block lymphatic vessels → lymphedema.

**Immune complexes:**  
• In schistosomiasis and multiple malaria episodes → circulating immune complexes → vasculitis and glomerulonephritis.

**Immunity to parasites depends on the type of parasite:**  
• Protozoa: Th1 response and macrophages,  
• Helminths: Th2 response, IgE, eosinophils.

• Parasites often survive due to immune evasion and chronic immune activation.  
• Excessive or inappropriate immune responses may lead to severe tissue damage.

**Evasion of the Immune Response by Parasites**  
Parasites have evolved numerous mechanisms to evade and suppress the host immune system. These strategies render parasitic infections chronic, complicate treatment, and present a major challenge for vaccine development.

**1. Antigenic Variation**

Parasites frequently alter their surface antigens to avoid recognition by antibodies and T cells. There are two main forms of this phenomenon:

**a) Antigen variation depending on developmental stage**

* *Example:* In *Plasmodium* species (the causative agent of malaria), the antigens of sporozoites differ from those of merozoites, enabling the parasite to evade the immune response.

**b) Continuous antigenic switching**

* *Example:* *Trypanosoma brucei* and *T. rhodesiense*.
* These parasites cyclically express different surface glycoproteins, leading to waves of parasitemia.
* By the time the immune system mounts a response to one antigen, the next generation of parasites already expresses a different one.
* This strategy effectively prevents the development of an effective vaccine.

**2. Resistance to Effector Mechanisms of Immunity**

• Parasites develop structures that render them resistant to complement-mediated lysis and cytotoxic T lymphocytes (CTLs):

* *Example:* Schistosome larvae, during their migration through the lungs, develop a protective tegument that resists lysis.  
  • Some protozoa hide inside host cells or form cysts that are resistant to immune attack.  
  • Helminths residing in the intestinal lumen are shielded from cellular immune responses due to their location.  
  • Certain parasites release or shed their antigens, which:
* help evade immune detection,
* block effective antibody-mediated responses (e.g., *Entamoeba histolytica*).

**3. Immunosuppression Induced by Parasites**  
Parasites can actively inhibit the host immune system through various mechanisms, enabling long-term persistence within the host.

**a) T Cell Anergy**

* Observed in severe schistosomiasis and filariasis.
* The mechanisms are not fully understood, but may involve structural damage to lymphoid organs such as lymph nodes.

**b) Activation of Regulatory T Cells (Treg)**

* *Example:* *Leishmania* species stimulate the development of Treg cells, which:
  + suppress immune responses,
  + promote parasite persistence within the host.

**c) Generalized Immunosuppression**

* Seen in malaria and African trypanosomiasis.
* Associated with:
  + immunosuppressive cytokines produced by activated macrophages and T lymphocytes,
  + defects in T cell activation.

**Conclusion:**  
Parasites are highly adaptive organisms that:

* change their surface antigens,
* develop structures resistant to immune effectors,
* actively suppress the host immune system.

These features are key reasons why parasitic infections tend to be chronic and pose a significant challenge to the development of effective vaccines.

**Sepsis – Definitions and Terminology**

**Sepsis** (from the Greek *σῆψις* — decay) is a traditional medical term historically used to describe a severe infection in which microorganisms (most commonly bacteria) and/or their toxins enter the bloodstream, causing systemic symptoms and organ dysfunction.

**Modern Definition of Sepsis (Sepsis-3, 2016)**

According to the **Sepsis-3** definition from 2016, **sepsis** is defined as:

"**Life-threatening organ dysfunction caused by a dysregulated host response to infection.**"

The **key criterion** for diagnosis is the presence of **organ dysfunction**, which is **objectively assessed by an increase in the SOFA (Sequential Organ Failure Assessment) score by ≥2 points** compared to the patient’s baseline.

**Septic Shock**

Septic shock is considered the most severe form of sepsis and is defined as:

"**A subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are profound enough to substantially increase mortality.**"

**Diagnostic criteria for septic shock:**

* Sepsis **plus** persistent hypotension despite adequate fluid resuscitation,
* **Requirement for vasopressors** to maintain a **mean arterial pressure (MAP) ≥ 65 mmHg**,
* **Serum lactate level > 2 mmol/L** in the **absence of hypovolemia**.

**Other Terms (in Historical and Clinical Contexts):**

| **TERM** | **DEFINITION** |
| --- | --- |
| **Bacteremia** | Presence of bacteria in the bloodstream without systemic inflammatory response (may be transient and physiological, e.g., after dental procedures). |
| **Septicemia** | An older term, now rarely used. Refers to sepsis with confirmed bacteremia. |
| **Toxemia** | Presence of microbial toxins in the bloodstream. |
| **Pyemia** | Historical term for the presence of pus in the blood, now replaced with more precise terms such as leukocytosis, purulent infection, etc. |
| **Severe Sepsis** | This term has been abandoned in Sepsis-3 definitions, as it refers to a concept now encompassed by "sepsis with organ dysfunction." |

**Clinical Criteria: qSOFA and SOFA**

**qSOFA (quick Sequential Organ Failure Assessment)**

*A rapid bedside tool for use in both hospital and pre-hospital settings*  
qSOFA is used as an early warning score to identify patients with suspected infection who are at increased risk of poor outcomes.

| **Criterion** | **Threshold** | **Points** |
| --- | --- | --- |
| Respiratory rate | ≥ 22/min | 1 |
| Systolic arterial pressure | ≤ 100 mmHg | 1 |
| Altered mental status (GCS < 15) | Yes | 1 |

▶ **Positive qSOFA**: **≥2 points** → suspect sepsis, further evaluation required.

🔹 **SOFA (Sequential Organ Failure Assessment)** — *Comprehensive assessment of organ function in intensive care*

SOFA evaluates **6 organ systems**, assigning scores from 0 to 4 based on the degree of dysfunction:

| **System / Parameter** | **Scoring Description** |
| --- | --- |
| **Respiratory** | PaO₂/FiO₂ ratio |
| **Central Nervous System** | Glasgow Coma Scale (GCS) |
| **Cardiovascular** | Mean arterial pressure, need for vasopressors |
| **Liver** | Bilirubin level (μmol/L) |
| **Coagulation** | Platelet count (×10⁹/L) |
| **Renal Function** | Creatinine level (μmol/L), urine output |

▶ **Sepsis diagnosis**: An **increase in SOFA score ≥2 points** from baseline indicates **organ dysfunction**.

**Table: Old vs. New Sepsis Terminology**

| **Old Terminology (until 2016)** | **New Terminology (Sepsis-3, 2016)** |
| --- | --- |
| **SIRS** (Systemic Inflammatory Response Syndrome) | Abandoned concept — low specificity for sepsis |
| **Sepsis = Infection + ≥2 SIRS criteria** | **Sepsis = Infection + organ dysfunction (SOFA ≥2)** |
| **Severe sepsis = Sepsis + organ dysfunction** | **Term discontinued** — now included under the unified term “sepsis” |
| **Septic shock = Severe sepsis + hypotension unresponsive to fluids** | **Septic shock = Sepsis + need for vasopressors + lactate >2 mmol/L** |
| **Septicemia** | Historical term — **no longer used** in modern classifications |
| **Bacteremia = presence of bacteria in the blood** | Still valid term; **not always present in sepsis** |

**The Word *Sepsis***  
The word *sepsis* originates from Ancient Greek (*σῆψις*), meaning "putrefaction," and throughout the history of medicine it was used to describe conditions associated with purulent and foul-smelling infections, such as septic wounds or septic abortion.

With the discovery of microorganisms in the late 19th century, it became clear that the clinical picture of such conditions was based on the dissemination of bacteria from a primary focus, initially through the lymphatic system and later through the bloodstream. This led to the emergence of terms such as:

* **Septicemia**: presence and multiplication of microorganisms in the blood.
* **Pyemia**: presence of pus in the blood (a now obsolete term).
* **Toxemia**: presence of microbial toxins in the circulation.

However, a critical question arose: is the clinical presentation of sepsis a result of bacteria circulating in the blood or of their products? It became evident that:

* **Bacteremia** can occur without clinical symptoms.
* **Bacteremia occurs in over 50% of cases of severe sepsis**.
* But **up to 50% of confirmed bacterial sepsis cases have no detectable bacteria in the blood**.

As a result, the concept of sepsis has evolved. Today, **sepsis is more accurately considered a physiological host response to infection**, rather than a clinical diagnosis based solely on evidence of bacteria in the bloodstream.

**Modern Understanding and Definition of Sepsis (Sepsis-3, 2016)**

The development of hemodynamic monitoring in intensive care medicine has shown that patients with sepsis may present with:

* high body temperature or hypothermia,
* tachycardia,
* hypotension,
* oliguria,
* increased cardiac output,
* decreased peripheral vascular resistance.

**It is important to emphasize:**

* Sepsis can also result from infections caused by viruses, fungi, or parasites (e.g., *Candida albicans*, *Plasmodium falciparum*, *Adenovirus*).
* In a significant number of sepsis cases, **bacteremia is not present**.
* **Cytokines**, secreted by host immune cells in response to infection (primarily **TNF-α, IL-1, and IL-6**), play a central role in the development of **hemodynamic and metabolic disturbances** in sepsis.
* **Classification of Sepsis – Old vs. New**

| **Term (Old System)** | **Explanation** | **Status under Sepsis-3** |
| --- | --- | --- |
| **Sepsis** | Infection + ≥2 SIRS criteria | Abandoned approach |
| **Severe Sepsis** | Sepsis + organ dysfunction | Discontinued – now included under "sepsis" |
| **Septic Shock** | Sepsis + hypotension unresponsive to fluids | Retained under new criteria |

**Current Definition:**

* **Sepsis:** A life-threatening organ dysfunction caused by a dysregulated host response to infection.
* **Diagnosis requires an increase in the SOFA score by ≥2 points.**
* **Septic shock:** Sepsis with persistent hypotension despite fluid resuscitation, requiring vasopressor support and lactate >2 mmol/L.

**Etiopathogenesis of Sepsis**

**Modern understanding of sepsis** focuses on the dysregulation of the host’s response to infection, leading to life-threatening tissue and organ damage. Sepsis is no longer synonymous with infection accompanied by bacteremia, but rather a heterogeneous syndrome representing the interaction between the pathogen and the host’s complex immune-inflammatory response.

**Sources of Infection and Etiology**

Although endogenous sources of infection remain the most common, there is now a much broader range of causative agents. In hospital settings, sepsis is increasingly diagnosed as being caused by multidrug-resistant bacteria (e.g., ESBL-producing Enterobacteriaceae, *Pseudomonas aeruginosa*, *Acinetobacter spp.*), but also by non-bacterial pathogens such as *Candida spp.* and viruses (e.g., cytomegalovirus in immunosuppressed patients). Infections related to medical procedures (e.g., catheter-associated infections) have become increasingly dominant etiological factors.

**Pathophysiological Mechanisms**

A key feature of sepsis is excessive activation of the innate immune system via pattern-recognition receptors (PRRs), such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs). Recognition of pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS) in Gram-negative bacteria or lipoteichoic acid in Gram-positive bacteria, activates transcription factors such as NF-κB. This leads to explosive production of cytokines: TNF-α, IL-1β, IL-6, as well as anti-inflammatory mediators such as IL-10. This results in the so-called **cytokine storm**, endothelial dysfunction, intravascular coagulation, capillary leakage, and multiorgan dysfunction.

Additionally, sepsis is characterized by **profound immunosuppression** in the later stages of response, with lymphocyte apoptosis, expression of inhibitory molecules (e.g., PD-1/PD-L1), decreased HLA-DR expression on monocytes, and increased regulatory T cell (Treg) populations, all of which contribute to susceptibility to secondary infections.

**Organ Dysfunction**

* **ARDS (Acute Respiratory Distress Syndrome)** is now an integral component of the SOFA score.
* **DIC (Disseminated Intravascular Coagulation)** is increasingly associated with the concept of **immunothrombosis**—a defensive coagulation mechanism which, when dysregulated, progresses to pathological thrombosis.
* **Lactic acidosis** is recognized as a direct marker of **tissue hypoperfusion** and serves as a critical parameter in determining the intensity of therapeutic intervention.

**Clinical Symptoms, Diagnosis, and Treatment of Sepsis**

Diagnosis of sepsis in hospital settings is based on **recognized symptoms of infection**, in combination with **clinical, laboratory, and hemodynamic parameters**. Given the high mortality of sepsis and severe sepsis, **rapid identification and timely therapeutic intervention are essential**.

**The most common clinical symptoms and signs of sepsis include:**

* Generalized weakness, fatigue
* Loss of appetite
* Fever > 38°C or hypothermia < 36°C
* Tachypnea (respiratory rate > 22/min)
* Tachycardia (heart rate > 90/min)
* Hypotension (systolic blood pressure < 90 mmHg)
* Oliguria (< 0.5 ml/kg/h)
* Confusion, delirium, drowsiness
* Hypoxia, pallor
* **Laboratory findings**: leukocytosis or leukopenia, elevated CRP and/or procalcitonin, increased lactate

In addition to these symptoms, the **presence of a confirmed or suspected infection** (e.g., pneumonia, urinary tract infection, intra-abdominal infection, wound infection, etc.) is required to establish the diagnosis of **sepsis**.

**Diagnostic Tools: SIRS, qSOFA, and SOFA**

| **Criterion** | **SIRS (outdated)** | **qSOFA** | **SOFA** |
| --- | --- | --- | --- |
| **Purpose** | Screening for systemic inflammation | Screening for severe sepsis outside the ICU | Detailed assessment of organ dysfunction in the ICU |
| **Parameters** | Temperature, heart rate, respiratory rate, WBC | Respiratory rate ≥22/min, altered mental status (GCS <15), systolic BP ≤100 mmHg | Respiration (PaO₂/FiO₂), coagulation (platelets), bilirubin, MAP/vasopressors, creatinine/urine output, GCS |
| **Positive if** | ≥2 criteria | ≥2 criteria | ≥2 points increase compared to baseline SOFA score |
| **Note** | Used before 2016, now obsolete | Quick and suitable for use outside the ICU | Standard for defining sepsis and septic shock |

**Table 2. qSOFA Score (Quick SOFA)**

| **Criterion** | **Value** | **Points** |
| --- | --- | --- |
| Respiratory Rate | ≥ 22/min | 1 |
| Glasgow Coma Scale (GCS) | < 15 | 1 |
| Systolic Blood Pressure | ≤ 100 mmHg | 1 |

**qSOFA ≥ 2**: Associated with higher risk of poor outcome and indicates the need for further evaluation.

**Table 3. SOFA Score**

Evaluates six organ systems: respiratory, coagulation, hepatic, cardiovascular, renal, and neurological. Each system is scored from 0 to 4 points.  
An increase in SOFA score of ≥2 points indicates **sepsis**.

**Therapeutic Goals in the Treatment of Sepsis**

**Early Goal-Directed Therapy (EGDT):**

* Central Venous Pressure (CVP): 8–12 mmHg
* Mean Arterial Pressure (MAP): ≥ 65 mmHg
* Urine Output: ≥ 0.5 ml/kg/h
* Central Venous Oxygen Saturation (ScvO₂): > 70%
* Lactate: normalization (< 2 mmol/L)

**3-Hour Bundle (Surviving Sepsis Campaign):**

1. Measure lactate level
2. Obtain blood cultures prior to antibiotic administration
3. Administer broad-spectrum antibiotics
4. Administer 30 ml/kg of crystalloids for hypotension or lactate ≥ 4 mmol/L

**6-Hour Bundle:**

1. Administer vasopressors if MAP remains <65 mmHg after fluid resuscitation
2. Measure CVP and ScvO₂
3. Reassess lactate if it was initially elevated
4. Consider dobutamine or blood transfusion if ScvO₂ remains <70% despite fluid resuscitation

**Six Urgent Steps in the Management of Suspected Sepsis:**

1. Provide high-flow oxygen
2. Draw blood cultures before starting antibiotics
3. Administer antibiotics without delay
4. Start initial fluid resuscitation (30 ml/kg of crystalloids)
5. Determine hemoglobin and lactate values
6. Monitor hourly urine output

Although protocols establish clear targets, the response to therapy varies depending on the patient's comorbidities, the causative agent, and the individual's physiological response capacity. Monitoring the dynamics of symptoms, laboratory parameters, and response to treatment is essential for a successful outcome.

**Immunopathogenesis of Sepsis**

| **Phase / Mechanism** | **Key Mediators** | **Clinical Consequences** |
| --- | --- | --- |
| 1. Activation of innate immunity | TLR, NLR, DAMPs, PAMPs | Activation of inflammation, hemodynamic changes |
| 2. Cytokine production | TNF-α, IL-1β, IL-6, IL-8 | Cytokine storm, hypotension, fever |
| 3. Endothelial dysfunction | NO, reactive oxygen species, TNF | Vasodilation, hypotension, lactic acidosis |
| 4. Capillary permeability | TNF-α, VEGF, bradykinin | Edema, ARDS, organ dysfunction |
| 5. Coagulation activation | Tissue factor, thrombin, fibrin | DIC, microangiopathy, bleeding |
| 6. Immunosuppression | IL-10, TGF-β, PD-1, Treg, lymphocyte apoptosis | Secondary infections, poor clinical outcome |

**Phases / Components of Sepsis Pathogenesis**

| **Phase / Component** | **Key Cells / Mediators** | **Clinical Consequences** |
| --- | --- | --- |
| Initial infection and pathogen spread | Bacteria, fungi, viruses | Fever, tachycardia, bacteremia |
| Activation of innate immunity | Macrophages, neutrophils, DCs, TLR4, CD14 | Inflammation activation, cytokine burst |
| Mediator production | TNF-α, IL-1, IL-6, IFN-γ, LPS | Fever, leukocytosis, vasodilation |
| Systemic inflammation | NO, PAF, prostaglandins, cytokines | Hypotension, capillary permeability, ARDS |
| Organ dysfunction | TNF, IL-1, ROS, coagulation activation | DIC, hepatic and renal insufficiency |
| Immunosuppression | PD-1, IL-10, Treg, anergic T lymphocytes | DIC, hepatic and renal insufficiency |