

Immune Response to Microorganisms. Sepsis and Septic Shock

Immunity Against Infections

- ◆ **Main Role of the Immune System**

The primary physiological function of the immune system is **protection against infections**.

Immune responses are mostly studied in the context of **defense against microorganisms**.

- ◆ **Purpose of This Topic**

We connect knowledge from previous chapters (cells, organs, and mechanisms of immunity) with **real infections**.

We analyze **different types of pathogens** and the **ways in which the immune system responds**.



Infection: Interaction Between Host and Microorganism

Key Events During Infection:

- Entry of the microorganism into the body
- Colonization of tissues
- Evasion of the immune response
- Tissue damage and functional impairment

How Do Microbes Cause Disease?

- By destroying host cells
- Through toxins that damage tissues
- Sometimes the immune response itself may cause the damage

Pathogenicity:

- Depends on properties of the microorganism (e.g., ability to spread, evade immunity, etc.)
- Mechanisms of pathogenesis are diverse and complex

General Characteristics of the Immune Response to Microbes

- Immunity is based on two main systems – innate and adaptive
- Specificity of the response depends on the type of microorganism
- Microorganisms often evade immune responses
- Many microorganisms cause latent or persistent infections
- The immune system's own response can cause tissue damage

TABLE 15–1 Examples of Pathogenic Microbes		
Microbe	Examples of Human Diseases	Mechanisms of Pathogenicity
Extracellular bacteria		
<i>Staphylococcus aureus</i>	Skin and soft tissue infections, lung abscess Systemic: toxic shock syndrome, food poisoning	Skin infections: acute inflammation induced by toxins; cell death caused by pore-forming toxins Systemic: enterotoxin (“superantigen”)-induced cytokine production by T cells causing skin necrosis, shock, diarrhea
<i>Streptococcus pyogenes</i> (group A)	Pharyngitis Skin infections: impetigo, erysipelas; cellulitis Systemic: scarlet fever	Acute inflammation induced by various toxins, e.g., streptolysin O damages cell membranes
<i>Streptococcus pyogenes</i> (pneumococcus)	Pneumonia, meningitis	Acute inflammation induced by cell wall constituents; pneumolysin is similar to streptolysin O
<i>Escherichia coli</i>	Urinary tract infections, gastroenteritis, septic shock	Toxins act on intestinal epithelium chloride and water secretion; endotoxin (LPS) stimulates cytokine secretion by macrophages
<i>Vibrio cholerae</i>	Diarrhea (cholera)	Cholera toxin ADP ribosylates G protein subunit, which leads to increased cyclic AMP in intestinal epithelial cells and results in chloride secretion and water loss
<i>Clostridium tetani</i>	Tetanus	Tetanus toxin binds to the motor end plate at neuromuscular junctions and causes irreversible muscle contraction
<i>Neisseria meningitidis</i> (meningococcus)	Meningitis	Acute inflammation and systemic disease caused by potent endotoxin
<i>Corynebacterium diphtheriae</i>	Diphtheria	Diphtheria toxin ADP ribosylates elongation factor 2 and inhibits protein synthesis
Intracellular Bacteria		
Mycobacteria	Tuberculosis, leprosy	Macrophage activation resulting in granulomatous inflammation and tissue destruction
<i>Listeria monocytogenes</i>	Listeriosis	Listeriolysin damages cell membranes
<i>Legionella pneumophila</i>	Legionnaires’ disease	Cytotoxin lyses cells and causes lung injury and inflammation
Fungi		
<i>Candida albicans</i>	Candidiasis	Unknown; binds complement proteins
<i>Aspergillus fumigatus</i>	Aspergillosis	Invasion and thrombosis of blood vessels causing ischemic necrosis and cell injury
<i>Histoplasma capsulatum</i>	Histoplasmosis	Lung infection caused by granulomatous inflammation
Viruses		
Polio	Poliomyelitis	Inhibits host cell protein synthesis (tropism for motor neurons in the anterior horn of the spinal cord)
Influenza	Influenza pneumonia	Inhibits host cell protein synthesis (tropism for peripheral nerves)
Rabies	Rabies encephalitis	Inhibits host cell protein synthesis (tropism for ciliated peripheral nerves)
Herpes simplex	Various herpes infections (skin, systemic)	Inhibits host cell protein synthesis; functional impairment of immune cells
Hepatitis B	Viral hepatitis	Host CTL response to infected hepatocytes
Epstein-Barr virus	Infectious mononucleosis; B cell proliferation, lymphomas	Acute infection: cell lysis (tropism for B lymphocytes) Latent infection: stimulates B cell proliferation
Human immunodeficiency virus (HIV)	Acquired immunodeficiency syndrome (AIDS)	Multiple: killing of CD4 ⁺ T cells, functional impairment of immune cells (see Chapter 20)
Examples of pathogenic microbes of different classes are listed, with brief summaries of known or postulated mechanisms of tissue injury and disease. Examples of parasites are listed in Table 15-4. ADP, adenosine diphosphate; AMP, adenosine monophosphate; CTL, cytotoxic T lymphocyte; LPS, lipopolysaccharide. This table was compiled with the assistance of Dr. Arlene Sharpe, Department of Pathology, Harvard Medical School and Brigham and Women’s Hospital, Boston, Massachusetts.		

Extracellular Bacteria – Mechanisms of Disease Induction

Extracellular bacteria are a type of pathogenic microorganisms capable of reproducing outside the host cells. This means they do not need to enter cells in order to survive and spread. They are most commonly found and proliferate in:

- blood,
- connective tissue,
- intercellular spaces,
- body cavities such as airways and intestines.
- Although they differ in lifestyle, many extracellular bacteria possess pathogenic traits, meaning they can cause disease. They do so through two main mechanisms:

Extracellular Bacteria – Mechanisms of Disease Induction

1. Induction of Inflammation

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

- Redness, swelling, pain, and heat,
- Activation of immune cells that destroy the bacteria,
- But also damage to host tissues due to strong inflammation.
- Thus, in some cases, it is not the bacteria themselves that directly cause disease, but the tissue damage resulting from the inflammatory response.

2. Toxin Production

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

- **Endotoxins** are components of the bacterial cell wall, most commonly found in Gram-negative bacteria.
 - The best-known example is **lipopolysaccharide (LPS)**.
 - LPS strongly activates immune cells such as macrophages and dendritic cells, leading to increased cytokine secretion.
- **Exotoxins** are substances actively secreted by bacteria into the environment. Their effects may include:
 - **Cytotoxic** – directly killing host cells,
 - **Dysfunctional** – disrupting normal cell function without causing cell death,
 - **Immunological** – excessive immune system activation and disease induction via cytokines.

Innate Immunity and Extracellular Bacteria

1. Complement Activation

The complement system is a set of plasma proteins that become activated in the presence of microorganisms and aid in their elimination. Activation can occur via multiple pathways:

- The **alternative pathway** is triggered in the absence of antibodies.
 - In Gram-positive bacteria, the activator is **peptidoglycan** from the cell wall.
 - In Gram-negative bacteria, it is **lipopolysaccharide (LPS)**.
- The **lectin pathway** is activated when bacteria express **mannose** on their surface, which allows binding of **mannose-binding lectin (MBL)**.

Outcomes of complement activation include:

- **Opsonization** – marking bacteria for easier recognition and phagocytosis,
- **Lysis of bacteria** – via the membrane attack complex (MAC), especially effective against bacteria like *Neisseria* (due to their thin cell walls),
- **Inflammation** – complement fragments act as chemotactic signals, recruiting leukocytes to the site of infection.

Innate Immunity and Extracellular Bacteria

2. Activation of Phagocytes and Inflammation Development

Phagocytes (macrophages and neutrophils) recognize extracellular bacteria using various receptors:

- **Mannose and scavenger receptors** – detect carbohydrates on the bacterial surface,
- **Fc receptors** – bind antibodies that have opsonized bacteria,
- **Complement receptors** – recognize bacteria coated with complement components,
- **Toll-like receptors (TLRs)** – recognize bacterial molecules and initiate intracellular signaling to activate the cell.

These receptors have different roles:

- Some facilitate easier phagocytosis of bacteria,
- Others activate mechanisms to kill microorganisms within the phagocyte,
- Some do both simultaneously (e.g., Fc and complement receptors).

Additionally, dendritic cells and phagocytes activated by bacteria begin to secrete cytokines, which lead to:

- **Infiltration of leukocytes** into the infected tissue (inflammatory response),
- **Engulfment and destruction** of bacteria by newly recruited immune cells.

Adaptive Immunity and Extracellular Bacteria

In the case of extracellular bacteria, the main protective mechanism of the host is **humoral immunity**, i.e., the immune response mediated by **antibodies**. This type of immunity:

- **Prevents infection**
- **Eliminates existing bacteria**
- **Neutralizes bacterial toxins**

Adaptive Immunity and Extracellular Bacteria

Antibodies are produced against:

- bacterial cell wall antigens,
- toxins that may be free or present on the bacterial surface,
- which are chemically either polysaccharides or proteins.

Adaptive Immunity and Extracellular Bacteria

Polysaccharides as Antigens

- Polysaccharides are thymus-independent antigens — meaning they do not require T cell help for B cell activation.
- The antibody response to bacteria with polysaccharide-rich capsules (e.g., *Streptococcus pneumoniae*) represents a primary defense mechanism.

Mechanisms of Antibody Action

Antibodies contribute to host protection through several mechanisms:

- **Neutralization** of toxins and bacteria (preventing their binding to host cells):
 - IgG, IgM, and IgA isotypes
 - IgA acts primarily at mucosal surfaces.
- **Opsonization and phagocytosis** – antibodies (especially IgG) label bacteria for easier recognition and destruction by phagocytes.
- **Complement activation** (classical pathway):
 - IgM and certain IgG subclasses activate complement → leading to bacterial lysis and enhancement of inflammation.

The Role of Helper T Lymphocytes (CD4⁺)

Protein antigens of extracellular bacteria also activate CD4⁺ T lymphocytes, which:

- Secrete cytokines and thereby:
 - Promote inflammation,
 - Activate phagocytes (macrophages and neutrophils),
 - Stimulate B lymphocytes to produce antibodies.

Role of Th17 Lymphocytes

Th17 Lymphocytes Play an Important Role in Fighting Bacteria and Fungi:

- Stimulate the recruitment of neutrophils and monocytes to the site of infection
- Promote local inflammation in infected tissues

Deficiency in Th17 response leads to increased susceptibility to infections, especially:

- Purulent skin infections (abscesses)
- Frequent fungal infections

One genetic cause of this disorder is a mutation in the STAT3 gene, a transcription factor required for Th17 cell development.

This condition is known as:

- **Job's syndrome** (due to similarity with the biblical description of boils)
- or **Hyper-IgE syndrome** (due to high serum IgE levels of unknown origin)

Role of Th1 Cells

Bacteria can also induce a Th1 response:

- Th1 lymphocytes secrete interferon-gamma (IFN- γ),
- IFN- γ activates macrophages, which then destroy phagocytosed bacteria,
- It also promotes the production of antibodies that bind complement and act as opsonins.

Adaptive Immunity in Defense Against Extracellular Microorganisms

Adaptive immunity plays a key role in defending against extracellular microorganisms such as bacteria and their toxins. The two main types of responses are:

A) Antibody Production

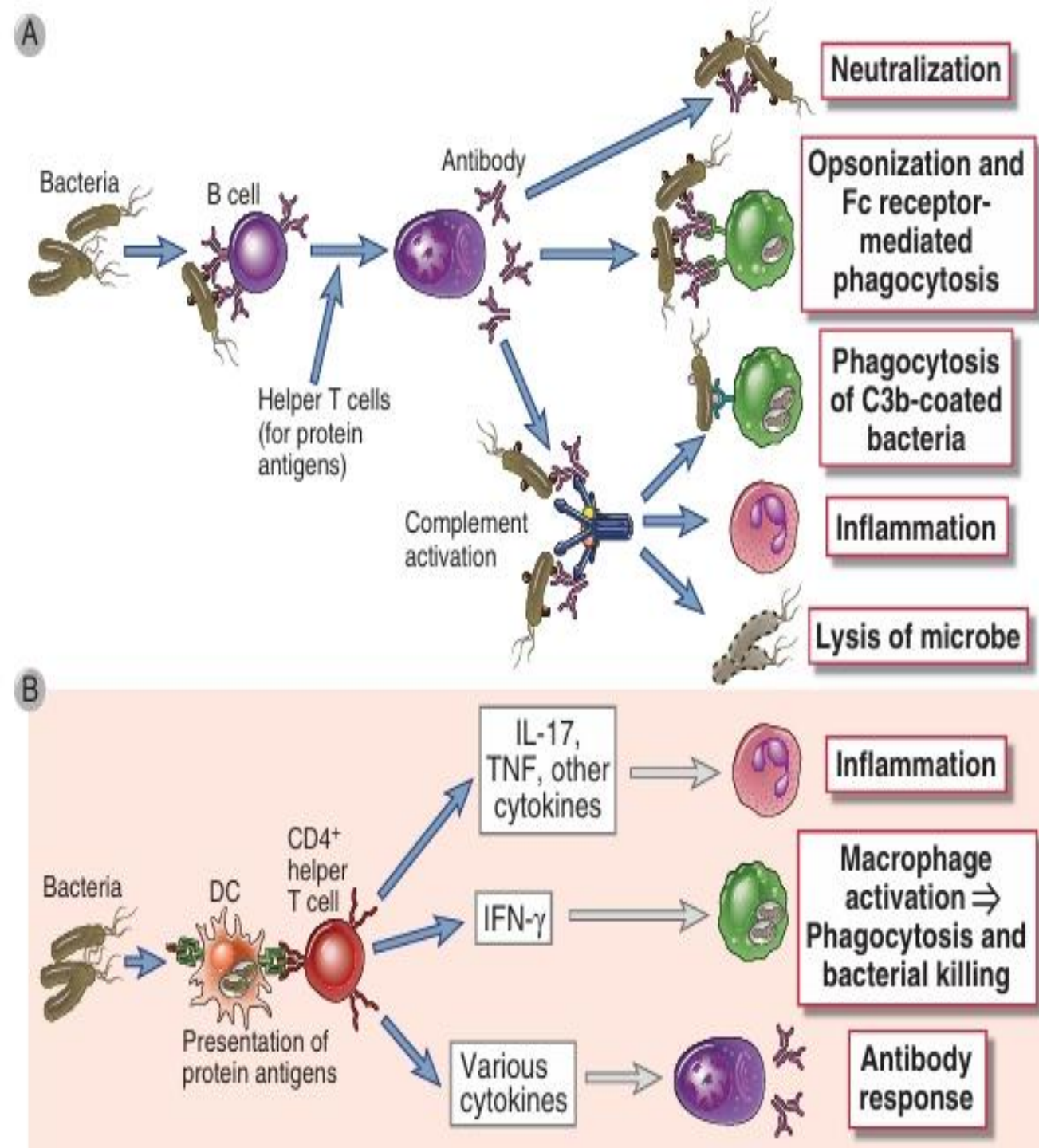
Antibodies (immunoglobulins), produced by B lymphocytes, act by:

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

B) Activation of CD4⁺ T Lymphocytes

Helper T lymphocytes are activated upon encountering antigens presented by dendritic cells (DCs). Their role includes:

- Secretion of cytokines
- Stimulation of inflammation
- Activation of macrophages
- Promotion of antibody production by B lymphocytes



Harmful Effects of the Immune System in Response to Extracellular Bacteria

1. Inflammation and Tissue Damage

Activated neutrophils and macrophages, which are involved in bacterial destruction, also release reactive oxygen species and lysosomal enzymes, which can lead to:

- Local tissue damage
- Inflammatory changes at the site of infection
- In most cases, this inflammation is self-limiting and under control.

Harmful Effects of the Immune System in Response to Extracellular Bacteria

2. Systemic Effects and Septic Shock

Cytokines secreted by leukocytes in response to bacterial products lead to:

- the appearance of systemic symptoms of infection (e.g., fever, fatigue),
- synthesis of acute-phase proteins in the liver.

In more severe cases, particularly with disseminated infection by Gram-negative or Gram-positive bacteria, septic shock may develop—a serious, potentially fatal condition.

Septic shock is characterized by:

- circulatory collapse,
- disseminated intravascular coagulation (DIC).

Harmful effects of the immune system in response to extracellular bacteria

У почетној фази, сепсу покрећу **цитокини** које **луче макрофаги** **активирани микробним молекулима** као што су LPS (липополисахарид) и пептидогликан. Главни медијатори сепсе су:

- TNF,
- IL-1 и IL-6,
- а могу допринети и IFN- γ и IL-12.

Ова масивна продукција цитокина се често назива **цитокинска олуја**.

У каснијим фазама септичког шока, јавља се **имуносупресија**, која може укључити:

- дефектну функцију Т ћелија,
- неконтролисано ширење микроорганизама.

Harmful effects of the immune system in response to extracellular bacteria

3. Улога суперантигена

Неке бактерије производе токсине који делују као **суперантигени**.

Суперантигени:

- неспецифично активирају све Т лимфоците који експримирају одређене $V\beta$ домене Т ћелијског рецептора,
- везују се и за TCR и за МНС класе II, али изван пептид-везујућег места,
- активирају много више Т ћелија него класични антигени,
- доводе до масовног лучења цитокина → **системски инфламаторни синдром**.

Polyclonal activation of T lymphocytes by bacterial superantigens

Superantigen activation

The superantigen binds to the outer side of the MHC class II molecule.

At the same time, it binds to the variable ($V\beta$) region of the β -chain of the T-cell receptor (TCR), regardless of peptide specificity.

As a result, a large number of T lymphocytes belonging to a specific $V\beta$ receptor family become activated.

This mechanism leads to the activation of thousands of T cell clones simultaneously.

Consequences of superantigen activation

- Massive cytokine production** – so-called cytokine storm, which can lead to systemic inflammatory syndrome, and even septic or toxic shock.

- Apoptosis of T lymphocytes** – as a response to hyperactivation, many T cells are eliminated through programmed cell death, leading to immunosuppression.

- Different superantigens recognize different $V\beta$ families, determining which clones will be activated.

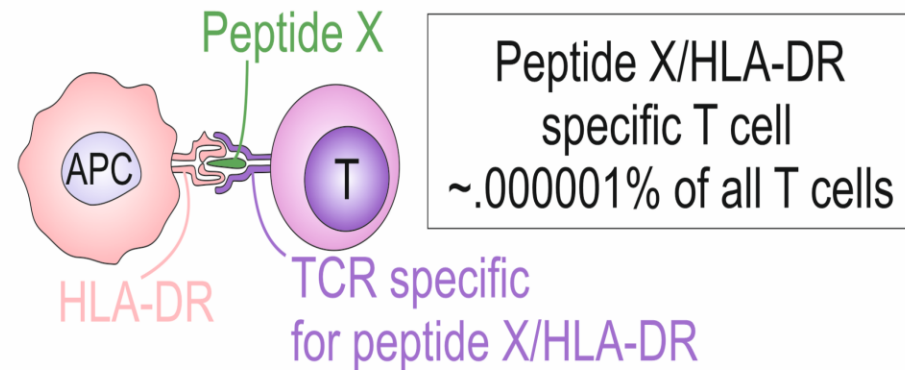
Example: Staphylococcal Enterotoxin B (SEB)

One of the best-known superantigens is staphylococcal enterotoxin B (SEB).

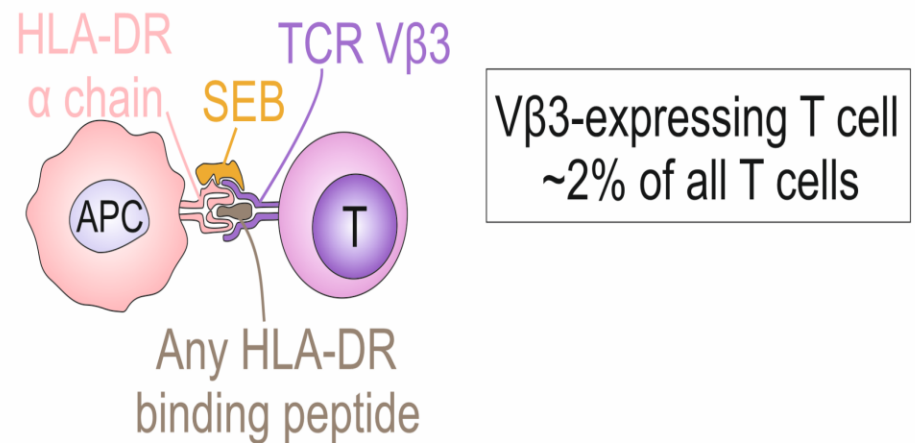
It binds to HLA-DR molecules (a type of MHC class II) and the $V\beta 3$ family of TCRs.

The result is broad T cell activation, leading to systemic effects such as fever, hypotension, and multiorgan dysfunction.

Conventional
TCR recognition
of peptide-MHC



Superantigen
binding to
class II MHC
and TCR $V\beta 3$



Harmful effects of the immune system in response to extracellular bacteria

4. Autoimmune and post-infectious complications

As a late consequence of bacterial infection, the immune system may develop pathogenic antibodies. Two well-known examples following streptococcal infections are:

- **a) Rheumatic fever**

Occurs after pharyngitis caused by group A β -hemolytic streptococcus.

The body produces antibodies against the M protein of the streptococcus.

Some of these antibodies cross-react with proteins of the heart muscle

→ leading to heart inflammation (carditis).

Harmful effects of the immune system in response to extracellular bacteria

b) Post-streptococcal glomerulonephritis

Occurs after a skin or throat infection caused by other serotypes of streptococci.

Antibodies form immune complexes with bacterial antigens,

→ these complexes deposit in the kidney glomeruli,

→ causing nephritis.

TABLE 15–2 Mechanisms of Immune Evasion by Bacteria

Mechanism of Immune Evasion	Examples
Extracellular bacteria	
Antigenic variation	<i>Neisseria gonorrhoeae</i> , <i>Escherichia coli</i> , <i>Salmonella typhimurium</i>
Inhibition of complement activation	Many bacteria
Resistance to phagocytosis	Pneumococcus
Scavenging of reactive oxygen species	Catalase-positive staphylococci
Intracellular bacteria	
Inhibition of phagolysosome formation	<i>Mycobacterium tuberculosis</i> , <i>Legionella pneumophila</i>
Inactivation of reactive oxygen and nitrogen species	<i>Mycobacterium leprae</i> (phenolic glycolipid)
Disruption of phagosome membrane, escape into cytoplasm	<i>Listeria monocytogenes</i> (hemolysin protein)

Evasion of Immune Response by Extracellular Bacteria

Pathogenicity (virulence) depends on the bacteria's ability to evade innate and adaptive immune mechanisms.

The most important mechanisms include:

1. Resistance to phagocytosis and complement

Many bacteria possess antiphagocytic features that allow them to survive despite the presence of phagocytes (neutrophils and macrophages). A major factor in this resistance is the:

- **Polysaccharide capsule**, which makes bacteria more resistant to phagocytosis. Capsule-bearing bacteria are significantly more virulent than capsule-deficient strains.

Additionally, some capsules contain **sialic acid residues**, which:

- inhibit activation of the alternative complement pathway,
→ thereby reducing opsonization and bacterial lysis.

Evasion of Immune Response by Extracellular Bacteria

2. Antigenic Variation of Surface Antigens

Bacteria can evade the humoral immune response (antibodies) by altering the genes encoding their surface structures.

Examples: Gonococci (*Neisseria gonorrhoeae*) and *Escherichia coli*

These bacteria possess pili (fimbriae) – structures used to adhere to host cells.

The main antigen of pili is the protein **pilin**.

The genes encoding pilin undergo frequent genetic changes (gene conversion), resulting in:

- Progeny of a single bacterium being able to produce up to **1,000,000 antigenically distinct pilin variants**,
- Which helps them **evade antibody-mediated recognition** developed against earlier forms of pilin.
- Although this strategy helps bacteria avoid immune detection, it also enhances **adhesion to host cells**, increasing their **virulence**.

Evasion of Immune Response by Extracellular Bacteria

Chemical Modifications of Surface Molecules

Some bacteria, such as *Haemophilus influenzae*, can escape immune detection by:

- **Altering the expression of glycosidases,**
- **Leading to chemical modifications of lipopolysaccharides (LPS) and other surface polysaccharides.**

These changes:

- **Reduce recognition by specific antibodies,**
- **Enabling the bacteria to evade the humoral immune response.**

This is one of several strategies used by extracellular bacteria to resist immune clearance and maintain infection.

Immune System and Intracellular Bacteria

Intracellular Bacteria and the Immune Response

Intracellular bacteria, especially **facultative intracellular species**, have the ability to:

- **Survive and even replicate inside phagocytic cells,**
- **Evade antibodies** by hiding within host cells,
- Therefore requiring a **cell-mediated immune response** for their elimination.

Although these immune responses can effectively **control the infection**, they frequently lead to:

- **Tissue damage,**
- Due to **intense inflammatory reactions.**

Innate Immunity

Innate response to intracellular bacteria mainly involves:

Phagocytes

Neutrophils and macrophages ingest bacteria, but they often survive inside phagolysosomes.

Recognition of microbial molecules through TLR and NOD receptors activates phagocytes.

NK cells

Infected cells express activating ligands for NK cells.

Dendritic cells and macrophages secrete IL-12 and IL-15, which activate NK cells.

NK cells produce IFN- γ , which activates macrophages and aids in killing intracellular bacteria.

- Although this response can temporarily control the infection, complete elimination of bacteria usually requires adaptive immunity.

Adaptive Immunity

Main mode of protection: Cell-mediated immunity

Individuals with T cell deficiencies (e.g., AIDS) are highly susceptible to intracellular bacteria.

The response is divided into two types:

1. CD4⁺ T-helper cells (Th1 subtype)

- Activated via antigens presented on MHC II molecules.
- Under the influence of IL-12, they differentiate into Th1 cells.
- Secrete IFN- γ and express CD40L, which:
 - Activates macrophages,
 - Stimulates production of reactive oxygen species, NO, and lysosomal enzymes,
 - Assists in antibody class switching (e.g., to IgG2a in mice).

Adaptive Immunity

2. CD8⁺ Cytotoxic T Cells (CTLs)

- Activated when bacterial antigens enter the cytoplasm,
- Recognized via MHC class I molecules,
- Directly kill infected cells.

Cooperative Action of CD4⁺ and CD8⁺ Cells

- CD4⁺ cells activate macrophages,
- CD8⁺ cells eliminate infected cells,
- Together they provide effective immunity against intracellular bacteria.

Pathological Effects of the Immune Response

Prolonged activation of macrophages and T lymphocytes can lead to tissue damage.

Typically, granulomatous inflammation occurs:

- It contains the infection,
- But can cause necrosis, fibrosis, and functional tissue impairment.

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 elimination by inhibiting phagosome-lysosome fusion.
- Granulomas with caseous necrosis form, leading to tissue damage.

Testing for infection: PPD (purified protein derivative test)

- In previously infected individuals, it elicits delayed-type hypersensitivity (DTH, type IV).

Immune response and disease outcome: Example of leprosy

Cause: *Mycobacterium leprae*

Two polar forms of the disease:

1. Lepromatous leprosy

1. Weak cellular immune response, strong antibody production.
2. Numerous bacteria in lesions, poor macrophage activation.
3. IL-4 and IL-10 present, little IFN- γ (Th2-type response).

2. Tuberculoid leprosy

1. Strong Th1 response: abundant IFN- γ and IL-2, weak antibody production.
2. Granulomas form around nerves \rightarrow peripheral nerve damage, but few bacteria in tissue.

Mechanisms of immune evasion.

Intracellular bacteria use various strategies to evade destruction:

- Inhibit phagosome-lysosome fusion (*M. tuberculosis*, *Legionella*),
- Escape into the cytoplasm (*Listeria monocytogenes*),
- Inactivate reactive oxygen and nitrogen species (*M. leprae*).

Immune response and fungi

- **Fungal infections (mycoses)** represent a significant cause of morbidity and mortality, especially in individuals with weakened immune systems. Some forms of mycoses are endemic and occur after **inhalation of spores from the environment**. Other forms are **opportunistic** – they cause mild or no illness in healthy individuals but can lead 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 damage significantly increases the risk.
The incidence of opportunistic mycoses is rising due to the increase in **HIV infections, cancer treatments, or immunosuppressive therapy after transplantation**.
One of the most severe mycoses in patients with **AIDS** is **pneumonia caused by the fungus *Pneumocystis jiroveci***, but many others contribute to morbidity and mortality in these patients.

Immune response and fungi

- Fungi can be extracellular or survive inside phagocytes, meaning the immune response often includes elements of both types of responses – similar to bacteria.
- However, the immune response to fungi is less studied than that to bacteria and viruses, partly due to the lack of appropriate animal models, and partly because infections often occur in patients who are unable to develop an adequate immune response.

Innate Immunity and Fungi

Main mediators of innate immunity include:

- **Neutrophils**
- **Macrophages**

Key roles:

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

Example:

- *Cryptococcus neoformans* can inhibit the production of **TNF** and **IL-12**, and stimulate **IL-10**, thereby preventing **macrophage activation**.

Adaptive immunity and fungi

The most important defense mechanism is cell-mediated immunity.

Th1 response (intracellular fungi)

Activates macrophages via IFN- γ .

Essential in controlling infections such as histoplasmosis.
May lead to granulomatous inflammation, which limits the spread of infection but also causes tissue damage.

Adaptive immunity and fungi

- **Th17 response (extracellular fungi)**

Induces inflammation and recruitment of neutrophils and monocytes.

Activated via the dectin-1 receptor, which recognizes fungal glucans. IL-6 and IL-23 from dendritic cells stimulate the development of Th17 cells.

Example:

In *Candida albicans*, infection usually begins at mucosal surfaces, and the Th17 response is important for preventing systemic spread.

CD8⁺ T cells

In some fungal infections (*C. neoformans*), they cooperate with CD4⁺ T cells in fungal clearance, especially in immunosuppressed patients.

Role of Antibodies

Fungi also stimulate the production of specific antibodies, which:

have a protective function,
but their role is less significant compared to the cellular response.

Immune System and Viruses

Viruses are obligate intracellular microorganisms – in order to replicate, they must enter host cells and use their machinery for protein and nucleic acid synthesis.

Entry into the cell is most often achieved through receptors on the cell surface.

Viruses cause tissue damage through several mechanisms:

- Disruption of host cell protein synthesis and function
- Induction of lysis of infected cells (cytopathic effect)
- Establishment of latent infection without immediate virus production

Innate immunity and viruses

Main Mechanisms of Innate Protection:

Type I interferons (IFN- α and IFN- β) – block viral replication in infected and uninfected cells.

NK cells (natural killer cells) – kill infected cells, especially those lacking MHC class I (a common viral immune evasion strategy).

Activation Mechanism:

Viral nucleic acids activate:

- TLRs in endosomes,
 - RIG-1 and MDA-5 receptors in the cytoplasm.
- Activation of these pathways leads to interferon synthesis.

Adaptive immunity and viruses

a) Humoral immunity (antibodies)

Antibodies prevent viral entry into cells 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 and enhance phagocytosis
- Activate complement, leading to lysis of enveloped viruses

Adaptive immunity and viruses

✓ Antibodies act only during the extracellular phase of the virus.

b) Cytotoxic T cells (CD8⁺ CTLs)

Destroy infected cells that present viral peptides via MHC I molecules.

Differentiation of CTLs often requires CD4⁺ T-helper cell assistance and co-stimulation.

CTLs can:

- Induce apoptosis of infected cells,
- Secrete IFN- γ , which activates phagocytes and has antiviral effects.

✓ CD8⁺ T cells are crucial for eliminating intracellular viruses.

Latent Infections

The virus remains in the cell but does not replicate.

CTLs control the infection but do not eliminate it.

In cases of immunodeficiency → **viral reactivation** (e.g., Epstein-Barr virus, herpesviruses).

Consequences: cell lysis, uncontrolled proliferation, and even malignant transformation.

Tissue Damage Caused by the Immune Response

Some diseases result from the immune response, not direct viral action

- **Example: LCMV in mice**
CTLs kill infected meningeal cells → meningitis.
Mice without T cells do not develop disease → become carriers.
- **Example: Hepatitis B in humans**
CD8⁺ T cells damage hepatocytes.
Immunocompromised individuals become asymptomatic carriers but can still transmit the virus.
- **Example: Immune complexes**
Form in chronic infections (e.g., hepatitis B) → vasculitis.
- **Molecular mimicry**
Similarity between viral and self-proteins → possible autoimmune reaction.

Mechanisms of Immune Evasion by Viruses

a) Antigenic Variability

- Mutations and recombination → changes in viral antigens.
- Example: **Influenza virus** – antigenic drift and shift.
- **HIV** – high antigenic variability → hinders effective vaccination.

b) Inhibition of MHC I Presentation

- Viruses block:
 - antigen processing,
 - peptide transport into the endoplasmic reticulum,
 - MHC I molecule expression.
- This **prevents CD8⁺ CTL response**, but **triggers NK cell activation**.

Mechanisms of Immune Evasion by Viruses

c) Production of immunosuppressive molecules

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

d) T cell exhaustion-mediated immunosuppression

- Activation of the PD-1 pathway → reduced T cell function
- Examples: chronic *LCMV* infection in mice, *HIV* in humans

e) Infection of immune cells

- The best example is *HIV*, which infects and destroys CD4⁺ T cells

Immune System and Parasites

In medicine, the term **parasites** includes:

- **Protozoa** (unicellular parasites),
- **Helminths** (worms),
- and **Ectoparasites** (e.g., ticks and mites).
- Parasites are the cause of a large number of diseases, particularly in developing countries. It is estimated that more than **30% of the global population** is infected with some form of parasite. **Malaria alone affects over 100 million people annually** and causes **1–2 million deaths** each year.

Immune System and Parasites

Parasites often have complex life cycles

that include humans and intermediate hosts (e.g., insects, snails). Infections are most commonly transmitted:

- through the bites of infected insects (e.g., malaria, trypanosomiasis),
 - or through contact with contaminated aquatic environments (e.g., schistosomiasis).

Most parasitic infections are chronic because:

- immunity is weak or ineffective,
- parasites evade elimination,
- antiparasitic drugs are often not effective.

Innate Immunity and Parasites

Protozoa

- Main mechanism: phagocytosis.
- Many protozoa survive and replicate within macrophages.
- Surface molecules of parasites activate TLR2 and TLR4 and stimulate phagocytes (e.g., *Plasmodium*, *Toxoplasma*, *Cryptosporidium*).

Helminths

- Too large for phagocytosis.
- Neutrophils and macrophages secrete microbicidal substances, but helminths have thick protective sheaths.
- They may activate the alternative complement pathway but are often resistant to lysis.

Adaptive Immunity and Parasites

a) Protozoa – Cell-Mediated Immunity (Th1)

Leishmania major resides within the endosomes of macrophages. **Th1 CD4⁺ T cells** produce **IFN- γ** , which activates macrophages to destroy the parasites.

In contrast, a **Th2 response** (e.g., IL-4 production) **suppresses macrophage activation** and worsens the infection.

Example: BALB/c mice:

- These mice are prone to a **Th2-dominant response**, making them susceptible to infection.
- In contrast, **resistant mouse strains** exhibit a **dominant Th1 response**, providing effective protection.

Adaptive Immunity and Parasites

b) Malaria and Similar Infections

Plasmodium species inhabit **erythrocytes** and **hepatocytes**.

- **Antibodies** act in the bloodstream to control the blood-stage parasites.
- **CD8⁺ T cells** eliminate infected hepatocytes during the liver stage.
- **IFN- γ** is critical for protection — not only in malaria, but also in **toxoplasmosis** and **cryptosporidiosis**.

Adaptive Immunity and Parasites

c) Helminths – Humoral Immunity (Th2)

- **Th2 CD4⁺ T cells produce:**
 - **IL-4** → stimulates **IgE production**.
 - **IL-5** → promotes **development and activation of eosinophils**.
- **IgE binds to mast cells and eosinophils, triggering the release of mediators that:**
 - **damage and help expel the parasites.**

Barrier Defense:

- **Enhanced intestinal peristalsis and mucosal responses contribute to the elimination of helminths.**

Adaptive Immunity and Parasites

Immune-Mediated Tissue Damage in Parasitic Infections

- Some parasitic infections lead to **granulomatous reactions** and **fibrosis**:

Schistosomiasis:

- **Schistosoma mansoni** eggs → activate **CD4⁺ T cells** → inflammation and **granuloma formation** in the liver.
- These granulomas are **Th2-dependent**, unlike the classic **Th1-type** granulomas.
- **IL-4** and **IL-13** promote “**alternative macrophage activation**”, leading to:
 - **Fibrosis**
 - **Cirrhosis**
 - **Portal hypertension**

Lymphatic Filariasis:

- Parasites **block lymphatic vessels** → resulting in **lymphedema**.

Immune Complex-Mediated Damage:

- In **schistosomiasis** and **multiple malaria infections**, **circulating immune complexes** may cause:
 - **Vasculitis**
 - **Glomerulonephritis**

Sepsis and Septic Shock

Sepsis and Septic Shock

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

A life-threatening organ dysfunction caused by a dysregulated host response to infection.

Septic Shock

Subgroup of sepsis in which circulatory, cellular, and metabolic abnormalities lead to a significantly increased risk of mortality.

TERM	DEFINITION
Bacteremia	Presence of bacteria in the blood without systemic response (can be transient and physiological, e.g., after dental procedures).
Septicemia	Older term, less commonly used today. Implies sepsis with confirmed bacteremia.
Toxemia	Presence of microbial toxins in the bloodstream.
Pyemia	Historical term for pus in the blood, now replaced by more precise terms like leukocytosis, purulent infection, etc.
Severe Sepsis	This term was abandoned in Sepsis-3 definitions as it implies a concept now included under "sepsis with organ dysfunction."

Clinical Criteria: qSOFA and SOFA

qSOFA (*quick Sequential Organ Failure Assessment*) — a rapid assessment tool used in both hospital and prehospital settings

qSOFA is used as a warning system to identify patients with infection who are at increased risk of poor outcomes.

•**Positive qSOFA:** $\geq 2 \geq 2$ points → suspicion of sepsis, further evaluation required.

Criterion	Threshold	Points
Respiratory rate	$\geq 22/\text{min}$	1
Systolic blood pressure (SBP)	$\leq 100 \text{ mmHg}$	1
Mental status (GCS < 15)	Yes	1

SOFA evaluates **6 organ systems**:

► **Diagnosis of sepsis**: An increase in SOFA score by **≥2 points** compared to baseline indicates **organ dysfunction**.

System/Parameter	Assessment Criteria
Respiratory	PaO ₂ /FiO ₂ ratio
CNS	Glasgow Coma Scale (GCS)
Cardiovascular	Mean arterial pressure (MAP), need for vasopressors
Hepatic	Bilirubin (μmol/L)
Coagulation	Platelet count (10 ⁹ /L)
Renal Function	Creatinine (μmol/L), urine output

Table: Old vs. New Sepsis Terminology

Old Terminology (Pre-2016)	New Terminology (Sepsis-3, 2016.)
SIRS (Systemic Inflammatory Response Syndrome)	Abandoned concept due to low specificity for sepsis.
Sepsis = Infection + ≥ 2 SIRS criteria	Now defined as infection + organ dysfunction (SOFA score ≥ 2).
Severe Sepsis = Sepsis + organ dysfunction	Term removed — now all encompassed under "sepsis."
Septic Shock = Severe Sepsis + fluid-unresponsive hypotension	Now defined as sepsis + vasopressor requirement + lactate > 2 mmol/L.
Septicemia	Historical term — no longer used in modern classifications.
Bacteremia = bacteria in blood	Still valid but not always present in sepsis.

Sepsis

The word **sepsis** originates from ancient Greek (σῆψις), meaning **putrefaction**, and has historically been used in medicine 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 **spread of bacteria** from a **primary focus**, initially via the **lymphatic system** and subsequently through the **bloodstream**.

Sepsis

- **Septicemia:** the presence and multiplication of microorganisms in the bloodstream.
- **Pyemia:** the presence of pus in the blood (now considered a terminologically outdated term).
- **Toxemia:** the presence of microbial toxins in the circulation.

Sepsis

Bacteremia can exist without clinical symptoms.

- In more than 50% of severe sepsis cases, bacteremia is present.
- However, up to 50% of confirmed bacterial sepsis cases have no detectable bacteria in the blood.

Therefore, the concept of sepsis has evolved. Today, sepsis is considered more as a physiological response of the body to infection rather than a clinical diagnosis based solely on the presence of bacteria in the bloodstream.

Sepsis

Sepsis can also result from infections caused by viruses, fungi, or parasites (e.g., *Candida albicans*, *Plasmodium falciparum*, *Adenovirus*).

- In a large number of sepsis cases, bacteremia is not present.
- Cytokines released by host immune cells in response to infection—particularly **TNF- α** , **IL-1**, and **IL-6**—play a central role in the development of hemodynamic and metabolic disturbances in sepsis.

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

- Although endogenous sources of infection remain the most common, there is now a much greater diversity 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.), as well as by non-bacterial pathogens such as *Candida* spp. and viruses (e.g., cytomegalovirus in immunosuppressed patients).
- Healthcare-associated infections (e.g., catheter-associated infections) are becoming increasingly dominant etiological factors.

- A key characteristic of sepsis is the excessive activation of the innate immune system through 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 like **NF- κ B**. This leads to explosive production of cytokines: **TNF- α** , **IL-1 β** , **IL-6**, and also anti-inflammatory mediators like **IL-10**.
- This cascade results in a cytokine storm, endothelial dysfunction, intravascular coagulation, increased capillary permeability, and organ dysfunction.
- Additionally, a significant degree of immunosuppression occurs during the late phase of sepsis. This includes lymphocyte apoptosis, expression of inhibitory molecules (e.g., PD-1/PD-L1), decreased HLA-DR expression on monocytes, and an increase in T regulatory (Treg) cells, all of which promote susceptibility to secondary infections.

- **ARDS** (Acute Respiratory Distress Syndrome)
- **DIC** (Disseminated Intravascular Coagulation) is increasingly associated with so-called immunothrombosis — a defense mechanism involving coagulation which, when dysregulated, progresses into pathological thrombosis.
- **Lactic acidosis** is recognized as a direct marker of tissue hypoperfusion and a critical parameter in determining the intensity of therapeutic intervention.

- General weakness, fatigue
 - Loss of appetite
 - Temperature $> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$
 - Tachypnea (respiratory rate $> 22/\text{min}$)
 - Tachycardia (heart rate $> 90/\text{min}$)
 - Hypotension (systolic blood pressure $< 90 \text{ mmHg}$)
 - Oliguria ($< 0.5 \text{ ml/kg/h}$)
 - Confusion, delirium, drowsiness
 - Hypoxia, pallor
 - Laboratory findings: leukocytosis or leukopenia, elevated CRP and/or procalcitonin, increased lactate
- In addition to the listed symptoms, diagnosis of sepsis requires a confirmed or suspected infection (e.g. pneumonia, urinary tract infection, intra-abdominal infection, wound infection, etc.).

Diagnostic Tools:SIRS, qSOFA and SOFA

Criterion	SIRS (Obsolete)	qSOFA	SOFA
Purpose	Screening for systemic inflammation	Screening for severe sepsis outside ICU	Detailed assessment of organ dysfunction in ICU
Parameters	Temperature, heart rate, respiration, leukocytes	Respiration $\geq 22/\text{min}$, altered mental status (GCS <15), systolic BP ≤ 100 mmHg	Respiration (PaO ₂ /FiO ₂), coagulation (PLT), bilirubin, MAP/vasopressors, creatinine/urine output, GCS
Positive if	≥ 2 criteria	≥ 2 criteria	≥ 2 points increase from baseline SOFA
Note	Pre-2016, now abandoned	Quick, useful outside ICU	Gold standard for defining sepsis and septic shock

Six Emergency Steps in the Management of a Patient with Suspected Sepsis:

1. Administer high-flow oxygen
2. Obtain blood cultures before starting antibiotics
3. Administer broad-spectrum antibiotics without delay
4. Initiate fluid resuscitation with crystalloids (30 ml/kg)
5. Measure hemoglobin and lactate levels
6. Monitor hourly urine output

Therapeutic Targets in Sepsis Management

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)

Three-Hour Bundle Protocol (Surviving Sepsis Campaign):

- Measure serum lactate level
- Obtain blood cultures before administering antibiotics
- Administer broad-spectrum antibiotics
- Administer 30 ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/L

Six-Hour Bundle Protocol (Surviving Sepsis Campaign):

- Add vasopressors if MAP remains <65 mmHg after fluid resuscitation
- Measure Central Venous Pressure (CVP) and Central Venous Oxygen Saturation (ScvO₂)
- Re-measure lactate if the initial value was elevated
- Consider dobutamine infusion or blood transfusion if ScvO₂ remains $<70\%$ despite adequate volume replacement

1	Activation of Innate Immunity	TLR, NLR, DAMPs, PAMPs	Activation of inflammation, hemodynamic changes
2	Cytokine Production	TNF- α , IL-1 β , IL-6, IL-8	Cytokine storm, hypotension, fever
3	Endothelial Dysfunction	NO,ROS, 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 outcome

Initial infection and pathogen spread	Bacteria, fungi, viruses	Fever, tachycardia, bacteremia
Activation of innate immunity	Macrophages, neutrophils, DCs, TLR4, CD14	Inflammation activation, cytokine explosion
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, Tregs, anergic T lymphocytes	DIC, hepatic and renal insufficiency