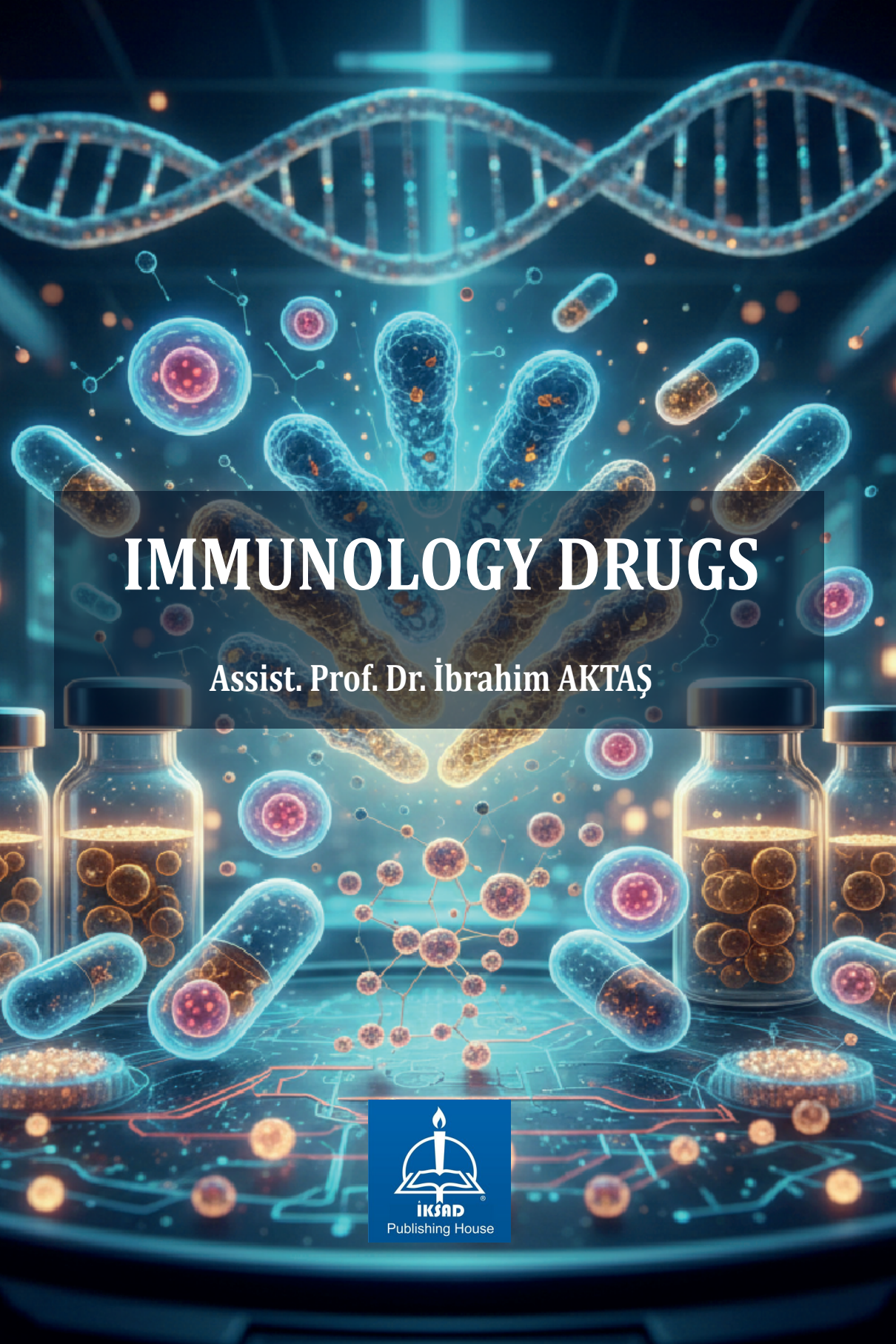

IMMUNOLOGY DRUGS

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DOI: https://www.doi.org/10.5281/zenodo.18221107

İKSAD Publishing House

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(The Licence Number of Publicator: 2014/31220)
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Iksad Publications – 2026©

ISBN: 978-625-378-569-7
Cover Design: İbrahim KAYA
January / 2026
Ankara / Türkiye
Size: 16x24cm

PREFACE

This book was written to fill the gap in the Immunology course in Midwifery-Nursing and Associate degree programs. We hope it will be a resource for instructors teaching in related units and students taking this course.

Assist. Prof. Dr. İbrahim AKTAŞ

ACKNOWLEDGEMENTS

I would also like to thank the board of directors and staff of İKSAD Publishing House who encouraged me to write a book and also contributed to the preparation of the book.

İbrahim AKTAŞ

Ankara-2026

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EPISODE 1

IMMUNE SYSTEM OVERVIEW

ENTRANCE

1. DEFINITION

Immunology: It is the identification of antigens that are foreign to the hereditary structure of living things and the reactions they give against them. The word 'immune' comes from the ancient Greek word immunitas, which was used for those who were donated from some public duties such as taxes and military service.

1.1. History: In epidemics (smallpox, measles, etc.), some people died, some did not get sick at all or had a very mild illness, and did not get sick a second time. In the writings sent to London by the wife of the British Ambassador in 1721, she mentioned the smallpox vaccine administered to healthy people with mild pox in the Ottoman Empire. Edward Jenner realized that milking women were protected from the actual smallpox disease by the cowpox sores observed on their hands. Taking advantage of this fact, he initiates smallpox vaccination. Louis Pasteur develops the anthrax and cholera vaccine for animals and the rabies vaccine for humans and animals (Aktas and Bilgic, 2025b).

In the 1900s;

■ Pfeiffer; showed complement.

■ Metchnikoff; researched phagocytosis.

■ Portier and Ricket; By observing allergy, they showed that the immune response does not always protect, and in some cases, allergic reactions that cause harm to living things may develop.

■ Tisellius; investigated the structure of the antibody.

■ In the 1950s; Studies on blood and tissue groups, immune disorders, immunology of tumors and organ transplants, and immunogenetics have begun.

2. ANTIGENS

2.1. Antigen: Substances that create an immune response (antibody) in a living thing and combine with the product that develops as a result of this response. Antigen is denoted as "Ag" (Anon, 2021a).

2.2. Properties of Antigen: What is required for a substance to be an antigen.

2.2.1. Foreignness: Substances that are foreign to the living thing they enter show antigenic properties. Because every organism synthesizes its own substances in order to survive and survive. These consist of carbohydrates, proteins, nucleic acids and fats in every organism. Their building blocks are the same in organisms. For example, protein consists of a sequence of amino acids, and lipids consist of a chain of fatty acids. However, the three-dimensional molecular structure of these structures differs in living things.

Explain This Situation With Example: Different proteins are synthesized in rabbits and guinea pigs. The rabbit protein is foreign to

the guinea pig, and when given to the guinea pig, an immune response develops to the rabbit protein. This difference is the difference in the three-dimensionality, sequence and electron charges of the amino acids that make up the proteins. The other example is; Hemoglobin has a protein structure and its function is the same in all mammals. However, due to the difference in amino acid sequence, the hemoglobin of one species is foreign to the other and thus exhibits antigenic properties. As the distance between two living things increases, the foreignness of their structural molecules increases, thus developing good antigenic properties. As kinship becomes closer, the antigenic feature may become weaker and disappear. However, if the immune system is impaired, the organism creates an immune response to itself, resulting in disease (autoimmune disease).

2.2.2. Molecular Size: For the substance to be an antigen, its molecular mass must be large. In general, those with a molecule size over 10,000 are good antigens. The ones that show the strongest antigenic properties are proteins with a molecule size over 100,000. But there are those who do not follow this rule. Although the size of the glucagon hormone molecule is 3600, it has good antigenic properties. On the other hand, dextran, whose molecule is 51,000 in size, is not a good antigen.

2.2.3. Complexity of Chemical Structure: As the complexity of the substance increases, its antigenicity also increases. For example, artificial polypeptide chains (produced from a type of amino acid) are not good antigens, even if the weight of this molecule is large. They are

more active if they consist of two or more types of amino acids. The natural protein structure is very complicated.

2.2.4. Rigidity of the Molecular Structure: In order for the structure to be recognized as an antigen by lymphocytes, it must show an unchanging structure. For this reason, substances that do not have a certain hardness, such as gelatin and lipid, do not create a good antigenicity.

2.2.5. Dissolution and Metabolization: The dissolution and metabolism of the antigenic structure affects its antigenic potency. For example, structures that cannot be broken down and metabolized by keratin-like hydrolytic enzymes are not antigenic. Similar structure; Although structures such as teflon, nylon, polyacrylamide and polystyrene have large molecules, they cannot show antigenicity because they cannot be metabolized. An immune response to these structures does not develop. The majority of prostheses placed in tissue are produced from these structures.

2.2.6. Excretion and Absorption Rate: The fact that the antigenic structure remains in the organism for a period of time that stimulates immunity is effective in its antigenicity. Since the structures that are generally absorbed and excreted slowly interact well with the immune structure, their antigenic properties are also strong. Those that are rapidly absorbed and excreted are not good antigens.

2.2.7. Electric Charge: Antigen structures must be electrically charged. The electrical charge in the microenvironment of the epitope is important compared to the entire structure Electrically charged

structures give the molecule a hydrophilic structure that allows it to penetrate the immune cell (as it gives it the ability to dissolve in aqueous media). However, those with very strong (+) or (-) charges are not good antigens as they are quickly captured and covered by other compounds.

2.2.8. Other Characteristics: Species, age and genetic structure; The characteristics of the organism to which it is applied are effective in the antigenicity of this structure. For example, while pure polysaccharide is antigenic in mice and humans, it is not antigenic in guinea pigs and rabbits. On the contrary, the strength of the immune response to the same antigen varies even in different individuals of the same species. Whether people experience severe or mild illness during the epidemic is also related to the strength of the immune response (Aktas and Sedat, 2025c).

Antigen Dose: The dose increases in parallel with the increasing dose of antigen, affecting the strength of the immune response**.** However, if the dose is low, the immune response does not develop because immunity is not stimulated. When the amount is excessive, immunity is paralyzed and a good immune response does not occur. The place where the antigen is applied to the living thing is effective in antigenicity. Parenteral administration increases antigenicity. There are structures that show antigenicity by entering into living beings through oral, skin and mucosa. If a good immune response is desired, antigen should be administered in the appropriate dose, route and time interval. Adjuvant structures increase the immune response to the antigen it is associated

with. Mineral oils containing aluminum hydroxide and phosphate-like mineral salts and dead mycobacteria are applied in this context.

3. STRUCTURES OF ANTIGENS

An immune response occurs in the living creature it enters, and it combines with the antibody that develops as a result of this response. The combination of antibody and antigen is chemical. However, not all of the antigen can participate in the combination. On the surface of the antigen, there are chemical structures (epitopes) as simple as the protrusion of the molecule, which are involved in antibody production and combine with the specific antibody synthesized. The epitope is small compared to the whole antigen. The number of epitopes is related to the complexity and molecular size of the antigen. The antigen is multivalent and combines with many antibodies. The combination of the antigen epitope and the antigen binding point of the antibody is like a key and lock matching. Combination strength is related to the degree of conformity. The greater the compatibility, the stronger the antigen-antibody combination is. The weak bond with less energy takes part in the combination. However, depending on the structural compatibility of the binding points of the two molecules, Ab and Ag, the rapprochement increases accordingly. The strength of the intermediate bonds increases accordingly and the bond becomes stronger.

4. HAPTEN AND ANTIGEN TYPES

4.1. Antigenic Properties of Chemicals

Proteins: They are the best antigens.

Carbohydrates: Polysaccharides with larger molecular weights are considered antigenic. IgM antibodies are produced for pure polysaccharide antigens. Small structures such as mono and disaccharides are not antigenic but have hapten properties**.**

Fats: They are not purely antigenic, but they are antigenic when they form compounds with polysaccharides and proteins**.**

Nucleic Acids: They are not good antigens, but they gain antigenic properties when they are broken down and combined with proteins (Aktaş and Sevimli, 2020).

Chemicals and Drugs: Although they have a simple structure and small molecular weight, an immune response may develop against many drugs and chemicals. Because they adhere to the proteins of the organism they enter or to the surface of some blood cells and become antigens (Aktaş et al., 2024a).

Cross Reactivity: There are many epitopes in the antigen. Some of these antibodies formed against an antigen similar to the epitope on the other antigen face may also bind to other antigen epitopes. But this binding is not as strong as the binding of the antibody with its own antigen. These combinations are called "Cross Reaction". Cross-reactions may occur between similar antigens of related species.

4.2. Antigens According to the Closeness of Living Things

■ **Heteroantigen:** Unrelated organisms exhibit mutual antigenic properties. For example, germ antigens are teroantigens for humans (Anon, 2018a).

■ **Isoantigen:** These are antigens that are individually different in the same or similar species of organisms. For example, it is the human blood group antigen. Some people have group A antigens and some people have group B antigens.

■ **Autoantigen:** In some diseases, the antigenic structure of the organism changes. Defense cells perceive their own cells as antigens and an immune response can occur against their own cells. These are called autoantigens (Anonymous, 2018a).

■ **Heterophile Antigen:** These are antigens with common epitopes in unrelated species. For example; Very similar antigens have been observed in the heart of mammals with streptococcus bacteria. The antibody developed against one of them also cross-reacts with the similar antigen. The types of antigens defined according to the proximity of the organism are also defined by the same name as the antibodies developed in the living creature. Respectively; hetero, heterophile, iso and auto antibody (Aktas and Ozgocmen, 2020)**.**

4.3. Hapten: They are pure lipid or polysaccharide structures that cannot form antibodies but specifically combine with the existing antibody. Since chemicals with low molecular weight are not actually antigens, they gain antigenic properties when bound to a carrier protein.

They have antibodies synthesized for themselves and specifically combine with this antibody. These are called haptens. These act like epitopes on antigens**.** Here, the stimulator is the hapten molecule and the antibody is formed for the hapten. In the absence of a carrier, the specific antibody that develops only combines with the hapten. Some simple drugs and chemicals also exhibit haptentic properties when they enter living things. These attach to the carrier molecule and cause antigenic stimulation (Aydın, 2004).

5. ADJUVANTS

They strengthen the immune response against the antigens to which they are applied together and ensure that it lasts for a long time. Adjuvants are used to obtain a stronger immune response in vaccination. There are many substances with adjuvant effects. For example; Such as Freund's adjuvant (dead tuberculosis bacilli + paraffin + lanolin), aluminum compounds, mineral oils, bacteria (pertussis and tuberculosis), bacterial products (endotoxin and nucleic acid degradation products). Adjuvant shows its effect when applied by mixing with antigen. It will not help if applied before or after.

6. DIFFERENT ANTIGEN EXAMPLES

6.1. Microbe Antigens: There are many antigenic structures in microbes. When it enters a living thing, an immune response occurs against this antigenic structure. As a result of the immune response, it neutralizes the living microbe and protects it from disease. In addition, microbe antigens and antibodies developed for them are used in

laboratories to recognize microbes or to diagnose the disease caused by microbes. Germ antigen must be recognized in vaccine preparation.

Some Antigenic Structures

■ **Viruses;** sheath and envelope antigens.

■ **Bacteria;** capsule, cell wall, cilia antigen, secreted toxin and enzymes.

6.2. Blood Group Antigens: They are antigens on the surface of human erythrocytes and vary among individuals. Antigens according to blood group are ABO and Rh system. In the ABO blood group, there are two types of antigens on the erythrocyte surface, A and B, and antibodies to this antigen in the serum, called anti-A and B.

Blood Groups for ABO

Blood Group (A, B, AB and O)

Antigen type on the erythrocyte surface (A, B, AB, -)

Type of antibodies in serum (Anti-A, B, -, A and B).

Blood group in humans; It is classified as A, B, AB, O according to ABO antigens and antibodies in its serum. In Rh, the presence of Rh antigens in the erythrocytes is checked. If a person has Rh antigen, he is Rh (+) positive, otherwise he is Rh (-) negative. When stating a person's blood type, ABO and Rh systems are mentioned together. For example; Like O, Rh (+) and A, Rh (-). This is important in identifying blood groups and blood transfusions. Additionally, it is applied in

paternity determination, forensic medicine, and tissue and organ transplants**.**

6.3. Histocompatibility Antigens: The antigen that causes rejection of transplanted organs and tissues is called organ-tissue transplantation or histocompatibility antigen. Tissue antigen is present in every cell of the body. It does not only occur in fat tissue and erythrocyte cells. The formation of these antigens is under the control of genetics. The gene area on human chromosome 6 is called "major histocompatibility complex = MHC". The histocompatibility antigen is called MHC antigen or "human leucocyte antigens = HLA" since it was first shown on leukocytes. In humans; It consists of seven classes: HLA-A, HLA-B, HLA-C, HLA-D, HLA-DR, HLA-DP and HLA-DQ. In organ and tissue transplantation, HLA antigens are checked and the same or similar ones are used. These antigens are passed on from generation to generation. The closer the degree of kinship, the more similar the HLA antigen becomes. HLA antigens are the same in identical twins (Aktas et al., 2024b).

CHAPTER 2

STRUCTURE OF THE IMMUNE SYSTEM

Introductıon

It has the ability to recognize and cope with foreign microbes and antigens. The cells and organs responsible for immunity are called the immune system. The immune response is cellular. Immune cells are formed from the differentiation of stem cells in the bone marrow. The primary event for the bone marrow stem cell to be immunologically effective is its maturation in the central lymphoid organ. After mature B and T lymphocytes complete their development, they settle in the lymphoid organ in the periphery. Then, they wait for the antigen and create an immune response when they encounter it**.**

1. IMMUNE SYSTEM ORGANS

1. Central Lymphoids

A) Bone marrow (KI)

B) Thymus

C) Pouch of Fabricius and equivalents

2. Peripheral Lymphoids

A) Lymph node

B) Spleen

Mucosa Related Lymphoid Tissues1.1. Santral Lenfoidler

1.1. Bone Marrow: All blood cells are produced here. In KI, immune cells that differentiate from the main (stem) cell pass into the blood and go to the relevant organs. THAT; It is found in the spongy structure at the ends of round, long and flat bones. KI is about 6% of body weight. This is approximately 2.6 kg in adult individuals. There are two types. Red and yellow KI. The red one (myeloid) is in the spongy bone. Thrombocytes, white blood cells and red blood cells are produced here. It is rich in myeloid tissue. In yellow CI, some white blood cells are produced. It is yellow in color because it contains a lot of fat cells (Anonim, 2021b).

1.2. Thymus: It is one of the primary lymph organs. It is the organ where the lymphocyte cell, which differentiates from the parent cell in pre- and postnatal CI, matures and becomes a mature T-lymphocyte. It is located in the upper part of the human mediastinal cavity, behind the sternum bone. Development begins at birth, is at its most developed in adolescence, and becomes smaller in later periods. Anatomically, it has two parts and is surrounded by a capsule. The cellular density is high in the shell, and these are clusters of lymphocytes that have immaturely come from CI. They reproduce quickly, but most of them die in a short time. There are fewer mature lymphocytes in the medulla. Because they mature in the thymus, they are called T-lymphocytes. In addition, there are macrophages and epithelial cells in the thymus. Macrophages, epithelial cells and some thymus hormones (thymopoietin, thymosin

and thymulin) are effective in the development of T-lymphocytes.

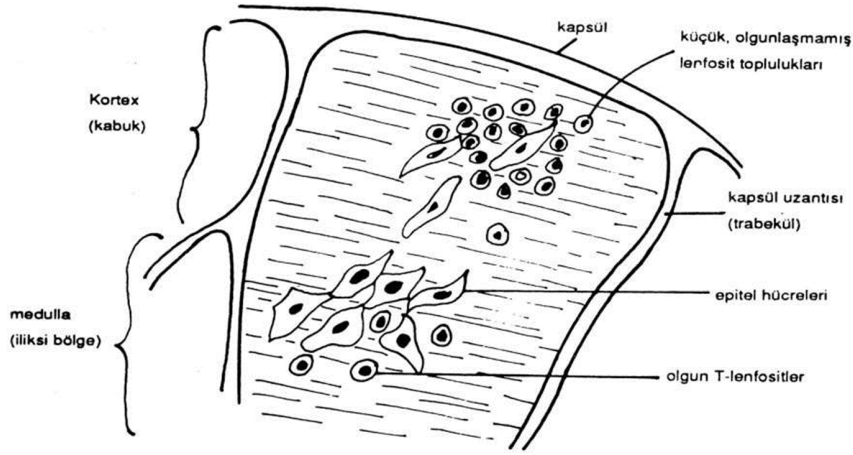


Figure 1: Schematic Picture of CI.

Thymus is active in the cellular immune response. When the thymus is removed, the function of the T-lymphocyte is impaired. In other words, disruptions occur in the production of antibodies. The T cell that passes into the thymus first settles in the cortex. Thymus is the place where the T cell is finally differentiated and selected. Cells that do not respond to antigen or respond to self-antigens are destroyed by apoptosis. When these lymphocytes are not destroyed, autoimmune disorders occur. Lymphocytes produced in the thymus are T lymphocytes, which are the basic element of acquired immunity. The paracortex of the mammalian lymph node, some parts of the Peyer's plate, and the periarterial lymphatic sheath in the spleen are areas rich in T cells. Thymus is the organ that shrinks as we age. Additionally, it is open to the stimulation of corticosteroid hormone. Corticosteroid causes the number of lymphocytes to decrease, the mitosis rate to decrease, and the cortex to deteriorate. ACTH secreted from the pituitary has a similar effect.

Excessive stress and excitement cause the thymus to atrophy, making it unable to function and the immune response declines. In disorders that develop due to the lack or absence of the thymus (DiGeorge syndrome), people become vulnerable to infection due to immunodeficiency (Anonim. 2023a).

1.3. Peripheral Lymphoids: These are the places where mature B and T lymphocytes, which differentiate into central lymphoids and are ready for immunological reactions, cluster. When the stimulation of antigens develops, the immune response occurs in the second order lymph organs.

1.3.1. Lymph Node: The lymph node is bean-shaped and is surrounded by a capsule from the outside. They are scattered or in small sections in different parts of the body. The 1-25 mm lymph node is on the lymphatic vessel and its primary duty is to filter the lymph and create an immune response to the incoming antigen. The penetrating extensions of the capsule divide the lymph node into sections. The fluid entering from outside enters from outside the organ and exits the hilus following filtration. Blood vessels also enter and exit from the hilus region. The internal structure is divided into three in the lymph node. The area around the capsule (shell), the area in the center is called the marrow area (medulla), and the area between the shell and the marrow area is called the paracortical area. In the shell area, there are structures called follicles, which are composed of clusters of B-lymphocytes that

mature in a state of rest.

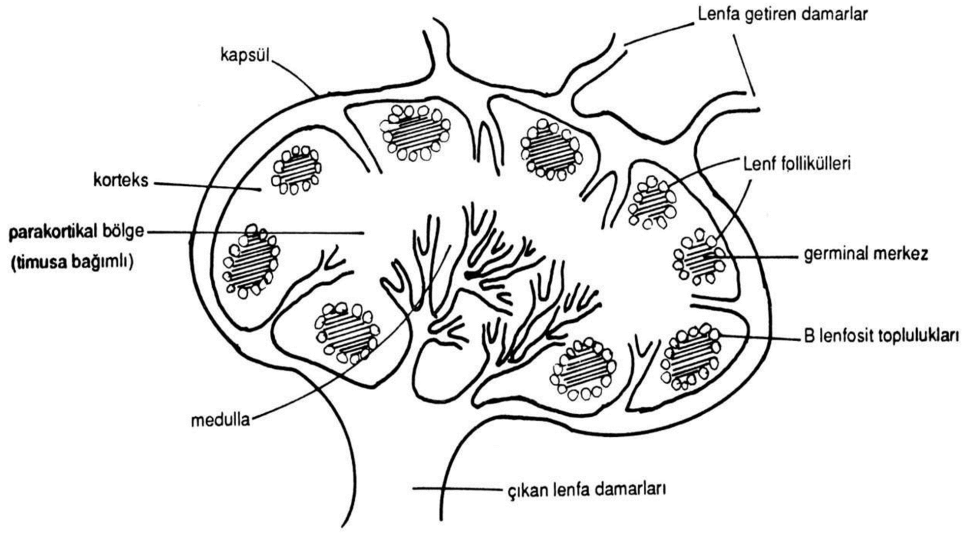


Figure 2: Schematic Picture of Thymus.

In case of antigenic stimulation, it reproduces and differentiates into mature B-lymphocytes. In the germinal center, there are differentiated B-lymphocytes (plasma cells) and macrophages. marrow area; It is the area where the vessels enter and exit the lymph node, branch out and turn into arterio-venous sinusoids, and the lymph fluid circulates. In this section there are plasma cells, B and T lymphocytes and many phagocytic macrophages. The paracortical area is where antigen presenting cells and T-lymphocytes are located. The lymph node acts as a filter for foreign structures (including cancer cells) (Gur and Aktas, 2022). This structure becomes swollen and inflamed in various diseases (diseases ranging from minor throat disorders such as pharyngitis to cancer) (Aktas and Bilgic, 2025; Anon, 2023b).

1.3.2. Spleen: It is an organ weighing 100-200 grams in the upper left corner of the abdomen. It is surrounded by a capsule and there are inward extensions in the capsule. The dark areas in the cross-section of the spleen are called red pulp. This structure consists of venous sinusoids and contains many destroyed erythrocytes. The areas that appear dull in color in the cross-section of the spleen are called white pulp. This structure is the lymphoid tissue surrounding the arteria centralis, the last part of the artery passing to the spleen. Here, T-lymphocytes are clustered around the arteriole. Additionally, there is a follicle formed by B-lymphocyte in the white pulp. Phagocytic macrophages and antigen-presenting cells (ASH) are found in the zona marginalis, which are parts of the white pulp.

Duties

■ Participates in defense by creating humoral and cellular immunity. It purifies the blood from pathogens with its strong phagoseptic properties.

■ It regulates portal blood flow through its vascular structure.

■ It acts like bone marrow in the fetus and participates in the production of blood cells.

■ It destroys abnormal blood cells that have completed their lifespan.

■ Stores blood reserves for hemorrhagic shock.

■ Recycles iron. In this context, as part of the mononuclear phagocyte, it converts hemoglobin taken from aged erythrocytes. The globin in

hemoglobin is reduced to amino acid and the heme part turns into bilirubin produced in the liver (Anonymous, 2022a).

1.3.3. Lymphoid Tissues Related to Mucosa: Places where microorganisms and foreign antigens enter the living organism; respiratory system, genitourinary system and digestive system. Under the digestive mucosa, there is a widespread lymphoid tissue without a capsule. Lymphoid cells in these areas can be found dispersed or follicular. For example, there is lymphoid tissue containing many follicles in the appendix, tonsils and Peyer's plate. The lymphoid tissue beneath the mucosa is generally responsible for the production of immunoglobulin-A. It is very important in disease prevention and local immunity.

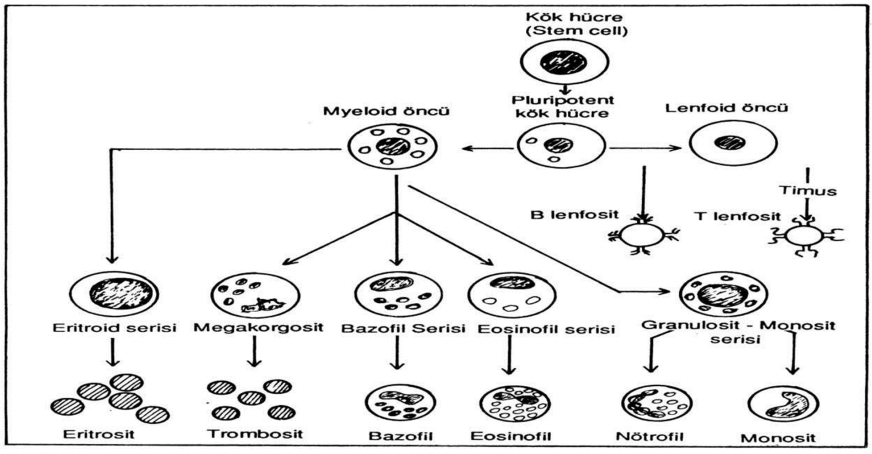


Figure 3: Blood Cell Formation "Hemopoietic Tree "

2. STRUCTURES INVOLVED IN THE IMMUNE RESPONSE

I- Macrophage

II- Lymphocyte

a) B-lymphocyte →Plasma Cell

b) T-lymphocyte

b1) Helper / Stimulator (T helper Lymphocyte (Th))

b2) Cytotoxic/Suppressive (T cytotoxic/suppressor lymphocyte (Tcy/s))

III- Natural Killer (NK)

IV- Other Cells

- Neutrophil

- Eosinophil

- Basophil and Mast Cell

- Platelet

2.1. Macrophages

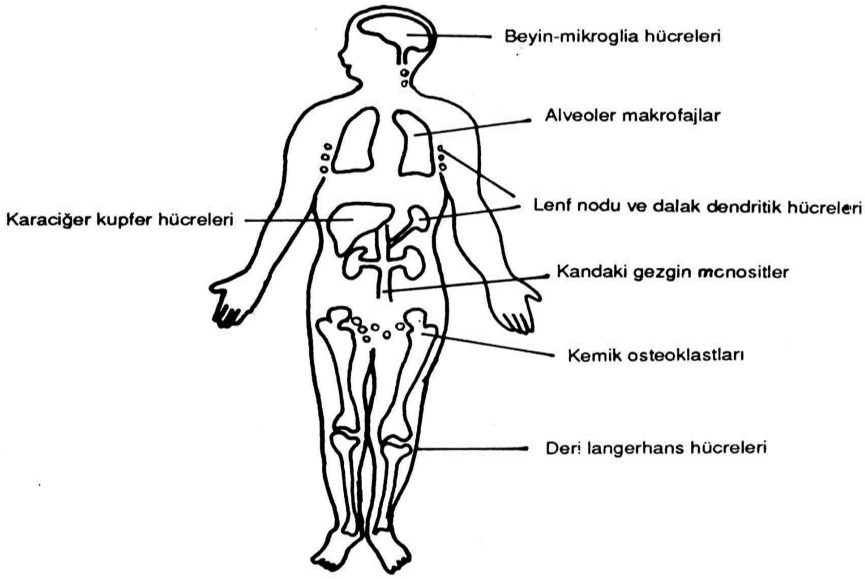


Figure 4: Mononuclear Phagocytic System Cells

Macrophage; They are cells with a size of 10-15 microns, a single nucleus, a large cytoplasm, a cytoplasm filled with digestive enzymes, many lysosomes, and wavy cytoplasm membranes. They proliferate from monocytes. Monocytes grow in CI and enter the bloodstream. These monocytes respond to the chemical mediator of inflammation. When activated by these mediators, monocytes pass through the endothelium and become macrophages. They are single core. Its primary function is to destroy dead tissue and pathogens. They are common in organs and tissues. These cells are named according to their area.

■ Monocytes floating in the blood

■ Alveolar macrophage in the lung

■ Macrophage in the serous cavity

■ Osteoclast in bone tissue

■ Microglia cell in nervous tissue

■ Macrophage in lymph node and spleen

■ Connective tissue histiocytes

■ Kupffer cell in the liver

■ Mesangial macrophages in the kidney (Anonim, 2023d).

Their Functions in the Immune Response Are Two Types

2.1.1. Phagocytic Macrophage: They phagocytose substances that need to be destroyed in living things, microorganisms and tumor cells. When microorganisms adhere to macrophages with their own special receptors or coated with complement and antibodies, phagocytosis occurs strongly and rapidly. In phagocytosis, the phagocytosed structures must bind to the receptor on the macrophage surface. For this reason, there are many different receptors on macrophages.

2.1.2. Antigen Presenting Cell: Immune cells; It captures the antigen with macrophage, dendritic and other cell types, identifies them with the T-cell and presents it to the lymphocyte. Antigens spend a preparation period in host cells and then present this antigen to the lymphocyte, initiating the immune response. The macrophage that serves to present the antigen has superficial receptors, unlike

phagocytosing macrophages. In addition, vascular endothelial cells, B-lymphocytes and skin Langerhangs cells also serve as antigen presenters**.** In short, they eliminate the structures that need to be cleared by phagocytosis in living beings and initiate the immune response by presenting antigens (Anon, 2022ı).

2.2. Lymphocytes: Develop from stem cells in CI. CI and thymus also mature. They travel to peripheral organs and lymphoid tissues via blood and settle in their own areas. There are ~1 trillion lymphocytes in humans, and ~1 billion lymphocytes are produced and released into the bloodstream daily. 20-30% of blood leukocytes consist of lymphocytes. Lymphocyte; They are cells with a large nucleus, 8-12 microns in diameter and narrow cytoplasm. The functions, antigenic structures and maturation of T and B lymphocytes are different. But there is close cooperation between them.

2.2.1. B Lymphocytes: They are responsible for antibody-based immunity. It matures in the bone marrow in mammals and in the fabricius sac in birds. It is 25% of what is in the blood and 50% of what is in the spleen. They carry the immunoglobulin molecule they create on the cell membrane, and this structure is the specific receptor for the antigen. The immunoglobulins on this surface are from the IgD and IgM classes. The B lymphocyte carries a surface immunoglobulin receptor that binds to a type of antigen (epitope). For this reason, in the immune structure, the same amount of B-lymphocytes carrying the specific receptor are ready for thousands of antigens that may be encountered over time. When the antigenic structure is ingested into the living thing,

it finds and stimulates the B-lymphocyte loaded with this antigen-specific receptor on its surface**.**

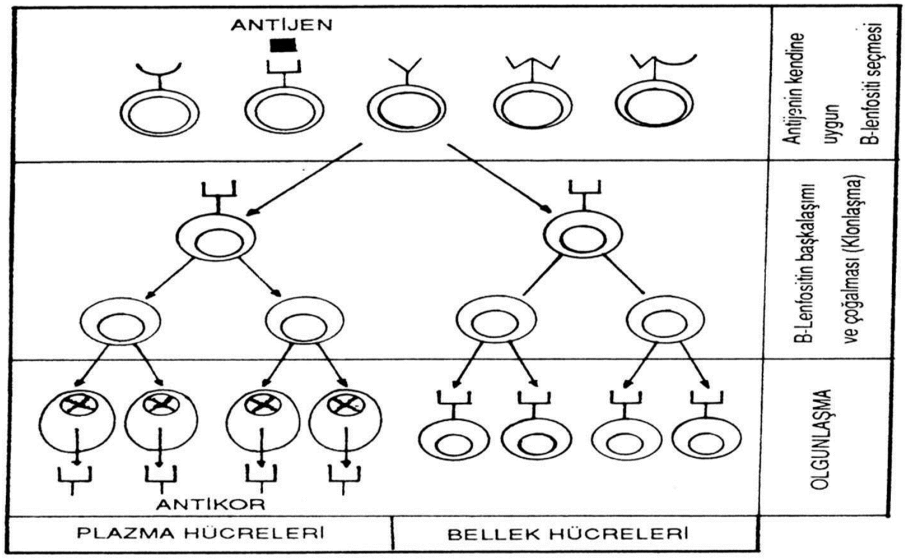


Figure 5: Developments in the Encounter of B-lymphocytes with Ag

The motivated B-lymphocyte differentiates into a plasma cell. This structure produces abundant antibodies to the stimulating antigen. This structure does not have the ability to reproduce and is short-lived, ~ 2-3 days. However, it was observed that it produced twenty thousand antibodies in 60 seconds. Some of the motivated B-lymphocytes turn into memory cells. Memory B-lymphocyte is long-lived and multiplies rapidly when it encounters the same antigen, creating a strong antibody response (Beyaz, 2004).

2.2.2. T-lymphocyte: Responsible for the cellular immune response. The T precursor cell produced in CI matures in the thymus and becomes a T lymphocyte. During this maturation, many receptors take their place

on the surface of the T lymphocyte**.** The blood cell surface receptor is numbered and identified by CD (such as CD2, CD4, and CD8). There is no immunoglobulin on the surface area of the T-cell, but instead there is an antigen-specific "T cell receptor = TCR". T lymphocyte carries TCR for every antigen, and there are thousands of T lymphocytes that can respond to all kinds of antigens that may be encountered in the immune system over time. When antigen is taken into the living being, it finds and stimulates the T-lymphocyte, which is the receptor for this antigen. The motivated T lymphocyte differentiates and develops into a T-lymphocyte that is sensitive to that antigen. They are important cells of immunity and constitute the immune structure directed by the cell that is not dependent on antibodies. In terms of its functions in the immune response, the T-cell community is not homogeneous and consists of different subgroups in terms of function and structure. The common surface molecule in T lymphocytes (CD2, CD3, CD5) and the different surface molecules in this subgroup are used to distinguish them.

Divided into Two Subgroups

■ TH lymphocyte (T helper) CD4 surface molecule carrier.

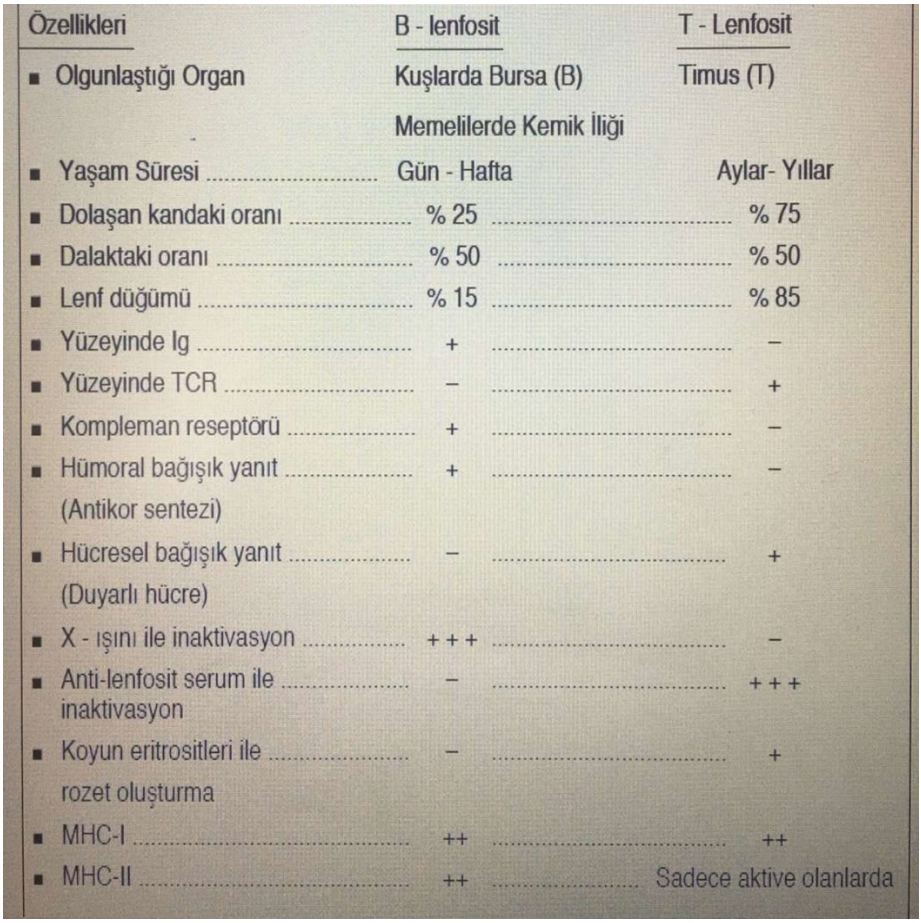
■ Tc/s lymphocyte (T cytotoxic / suppressor) CD8 surface molecule carrier.

T helper Lymphocyte (T helper (Th)): It has stimulating and helping roles. There are CD4 surface molecules. (CD4+, CD8-). Th lymphocytes; They increase the functions of Tc/s and B lymphocytes. In Th cell deficiency, the response of T and B cells to antigen is reduced

and impaired. In addition, it secretes different cytokines and ensures that monocyte-macrophage, T cells and other cells are strengthened in number and function. With these characteristics, Th lymphocyte is the command of the immune structure. The CD4 structure on the Th lymphocyte is also the entry point for HIV, the causative agent of AIDS.

T Cytotoxic / Suppressive Lymphocyte: They are suppressive and destructive lymphocytes. There are CD8 (CD4- and CD8+) surface molecules. T cytotoxics. They are cells that harm living things (such as cells infected with parasites, bacteria and viruses, tumor cells, organ transplants and tissue cells) or attack and destroy foreign cells. If they are T suppressors; They suppress cell toxicity and helper T-cell activity and balance immunity without overdoing it (Aktas et al., 2020). T lymphocytes have a long lifespan. Memory T lymphocytes recognize the antigen and create a rapid and strong immune response in the second and subsequent encounters with the antigen. In a regular study of the immune response in vivo, the TH/Tc/s lymphocyte ratio is around 1.7. When the TH/Tc/s coefficient increases and deteriorates the number of TH lymphocytes, an immune response occurs more than necessary (Allergy). If this coefficient is disrupted by increasing the amount of Tc/s lymphocytes, there will be excessive suppression in the immune

response, resulting in insufficiency in the immune response.



Özellikleri	B - lenfosit	T - Lenfosit
■ Olgunlaştığı Organ	Kuşlarda Bursa (B) Memelilerde Kemik İliği	Timus (T)
■ Yaşam Süresi	Gün - Hafta	Aylar- Yıllar
■ Dolaşan kandaki oranı	% 25	% 75
■ Dalaktaki oranı	% 50	% 50
■ Lenf düğümü	% 15	% 85
■ Yüzeyinde Ig	+	–
■ Yüzeyinde TCR	–	+
■ Kompleman reseptörü	+	–
■ Hümoral bağışık yanıt (Antikor sentezi)	+	–
■ Hücresel bağışık yanıt (Duyarlı hücre)	–	+
■ X - ışını ile inaktivasyon	+ + +	–
■ Anti-lenfosit serum ile inaktivasyon	–	+ + +
■ Koyun eritrositleri ile rozet oluşturma	–	+
■ MHC-I	++	++
■ MHC-II	++	Sadece aktive olanlarda

Figure 6: Lymphoid Organs.

2.3. Natural Killer (NK) Cells: BAK Lymphoid cells are cells called "large granulated lymphocytes" that do not have TCR or surface immunoglobulin. NK cells can destroy the cells they target (parasites, fungi, bacteria, tumors, virus-infected cells and transplanted tissue cells) without prior recognition or sensitivity.

2.4. Other Cells

■ **Polymorphous Nucleated Leukocyte (granulocyte):** 60-70% of blood leukocytes. Their cytoplasm is abundantly granulated and their nuclei are multi-lobed. They are of three types: basophil, neutrophil and eosinophil, with different functions and different staining of their granules (Anonymous, 2021d).

■ **Neutrophil:** Nearly half of CI is from these. It occurs from the maturation of the main cell (myeloblast) in the CI, and the excess is stored there. Its strong phagocytosis property increases with complement and antibody presence. It quickly removes foreign matter, microorganisms and tissue destruction products. They are short-lived (2-3 days) and are formed rapidly in KI by 80 million. 90% in bone marrow, 7% in tissue, 2-3% in blood circulation (Anonim, 2022i).

■ **Eosinophil:** Controls asthma and allergies together with mast cells and basophils. They are granulocytes that develop during hematopoiesis in CI before entering the blood. It is 2% of the leukocyte family. Its number increases in cases of allergy and parasites. Their phagocytosis ability is limited and they release granules outside the cell as a result of stimulation (Anonymous, 2023m).

■ **Mast Cell and Basophil:** Basophil is 0.2% of the leukocyte in the blood. It resembles a mast cell in tissue. It takes histamine and heparin in the granule out of the cell as a result of stimulation. These two structures are important in anaphylactic allergy (Anonymous, 2022b; Carlı et al., 2019)**.**

■ **Thrombocyte:** In CI, it is the cell particle that develops from the disintegration of the megakaryocyte during its passage into the blood following maturation. Apart from their blood clotting properties, they are also responsible for the formation of immune response and inflammation (Anonim, 2022c).

CHAPTER 3

IMMUNOGLOBULIN (ANTIBODY)

Introduction

Immunoglobulin; It is a glycoprotein that functions as an antibody and specifically combines with antigens, causing reactions. It is 20% of total plasma proteins. It is found in small amounts in intercellular fluid and tissues. It is found in serum in case of blood or plasma clotting. Serum containing antibodies to a particular antigen is called "antiserum". In the electrophoresis of serum proteins, it is in the gamma globulin part. In addition, some beta globulin and a small amount are collected in the alpha globulin section. For this reason, these structures that function as antibodies and are found in the globulins section of proteins and have immunological activity are called immunoglobulin (Ig).

Structure of immunoglobulins: Immunoglobulins (antibodies) are produced by plasma cells formed by the transformation of B-lymphocytes as a result of antigenic stimulation. Antibodies; There are significant differences between them when examined immunologically, chemically and physically. There are five separate immunoglobulin groups and they are called immunoglobulin D, G, M, A and E (IgD, IgG, IgM, IgA and IgE). They develop in response to various epitopes of different antigens. Multiple Myeloma disease develops when the plasma cell responsible for the production of antibodies becomes a tumor. In myeloma, plasma cell colonies consisting of plasma cells with

the same genetic structure are formed. The immunoglobulins produced by these structures also have the same chemical structure.

1. EXAMINATION OF IMMUNOGLOBULINS INDIVIDUALLY

1.1. Immunoglobulin G (IgG): 75% of the immunoglobulins in the serum. Adults contain 1000 mg of IgG in 100 ml of serum. 2 antigens bind to 2 Fabs in IgG. For this reason, IgG has a value of 2 and the density of IgG in tissue and blood is equal. It is the only Ig that passes from the mother to the fetus through the placenta. IgGs pass from the mother to the fetus in the 3rd month of pregnancy and continue to increase until birth. The newborn's blood contains IgGs from the mother. IgG type antibodies, which come from the mother to the fetus intrauterinely, protect the baby against infections to which the mother is resistant in the days following birth. The puppy's IgG production begins at birth and peaks around the age of two. After the age of 40, IgG level begins to decrease. IgG in blood can also leak into non-blood fluids. IgGs in the colostrum that the newborn first absorbs pass through the intestine and strengthen its immunity. Classically, one of the two Igs that activate complement is IgG and the other is IgM. IgG is a long-lived antibody and reaches very high levels in the secondary immune response. They strengthen phagocytosis by IgG opsonization on phagocytosis cells (there is a surface receptor that holds IgG from the Fc section) (Aktas and Satımıs, 2025a).

1.2. Immunoglobulin M (IgM): It is 10% of human immunoglobulin (it is the largest of the Igs and is also called macroglobulin).

Approximately 80% of IgM is in the blood and its density in the tissues is low. If IgM is observed in the newborn's serum (since IgM cannot pass through the placenta), it is thought that this baby encountered the antigen intrauterine and had an infection. For this reason, IgM determinations are routinely performed in the blood of the cord to investigate infection. IgM begins to be produced following birth in the 6-9th month. It reaches its peak (100 mg in 100 ml of serum) in months. Ig is the first to be produced in antigenic stimulation (vaccination and infection). An increase in IgM serum level is observed in the acute phase of infectious diseases. But IgM is a short-term antibody and its serum level decreases after a short time. It is replaced by IgG, which has long-term protection. For this reason, a high level of IgM compared to IgG in the serum sample is considered an infection. IgM is the Ig with the highest complement binding strength as well as antigen binding and facilitates phagocytosis. Isoantibodies belonging to blood groups in human serum are anti-A and B IgM classes. In addition, the Ig receptor on the B lymphocyte surface also has a monomer IgM structure**.**

1.3. Immunoglobulin-A (IgA): 15% of human serum Ig. Adults have 200 mg in 100 ml. 80% of IgA in serum is monomer. IgA is the main Ig in secretions. It is also present in genital, respiratory and digestive secretions, saliva, tears, milk and colostrum. Secretory IgA molecules are denoted sIgA. sIgA is different from serum IgA. sIgA is generally produced in plasma cells and secretory tissues under the mucosa. While passing through the epithelial cells, it combines with the secretory part and is secreted. Local infections and antigenic stimuli are effective in

the formation of sIgAs. sIgA prevents external microorganisms from binding to mucosal cells, settling and causing infection. In addition, it combines with potentially harmful macromolecules that enter the intestine from food, preventing their absorption and facilitating their destruction. It also neutralizes toxic or lytic enzymes created by various microorganisms. There are two subgroups with antigenic diversity: IgA1 (90% in serum, 50% in secretion) and IgA2 (10% in serum, 50% in secretion). It begins to be produced in the 2nd month following birth, gradually increases and reaches its peak level in adolescence.

1.4. Immunoglobulin D (IgD): It is 0.2% of the immunoglobulin in the serum. It is around 3 mg in 100 ml of adult serum. It is short-lived and easily degraded by proteolytic enzymes and heat. Along with IgM and IgD, it is on the surfaces of B lymphocytes. IgD is involved in the differentiation of B-lymphocytes**.**

1.5. Immunoglobulin E (IgE): It is low in serum, being 0.004% of Ig. In adults, it is around 0.05 mg in 100 ml of serum. Sensitize the cells to which IgE binds to basophil leukocytes and mast cells with its Fc fragment. IgE is important in active immunity from parasites to helminths, in rapid type hypersensitivity such as allergic rhinitis (hay fever), asthma and urticaria. IgE bound to the cell has a longer lifespan than free IgE and is resistant to proteolytic enzymes. Compared to other Igs, it is sensitive to heat. Plasma cells that produce IgE are present in the digestive and respiratory systems, which are highly secretory surfaces. Allergy and helminth infection increase the amount of IgE in the secretion of these mucosa. If basophils and mast cells combine IgEs

bound at the Fc end with their specific antigens, these cells are stimulated and discharge the granules in their cytoplasm. The resulting substances cause an anaphylactic type allergic reaction (Aktas and Satılmıs, 2025b).

2. SYNTHESIS OF ANTIBODIES

Lymphocytes are the main cell of the immune system. It can genetically produce material related to the immune response. When stimulated by an antigenic structure, they produce antibodies and other immune response products. They are produced by the developing plasma cell by the transformation of the B-lymphocyte motivated by Ig antigen.

2.1. Genetic Basis of Antibody Types: Advances in genetics have shown that many vital developments are under gene control**.**

3. FUNCTIONS OF ANTIBODIES

■ The main function of the antibody is to bind to antigen. Antigen-Antibody combination = They form an immune complex and remove it from circulation by phagocytosis.

■ Antibodies bind to infectious agents, immobilize them, and aggregate them, facilitating their phagocytosis (opsonization).

■ Antibodies neutralize and neutralize the toxins and viruses to which they bind**.**

■ IgM and IgG antibodies activate complement.

■ The antibody prevents the microbe from attaching to the mucosa and settling.

■ It prevents the absorption of harmful macromolecules from the intestinal mucosa.

■ The cell bound to the antibody takes part in its cytotoxicity (Gur and Aktas, 2020).

■ It acts as an immunoglobulin antigen receptor on B lymphocyte.

■ IgA antibody; It fights pathogens that enter the respiratory, digestive and genitourinary mucosa.

■ IgG antibody is the only immunoglobulin that passes through the placenta and protects the baby from infections following birth. IgG in the mother's milk continues the same job.

4. MONOCLONAL ANTIBODY

It produces B-lymphocyte-specific antibodies. Separate groups of B-lymphocytes are motivated for different epitopes on an antigen. As a result, even for one antigen, B-lymphocyte antibodies and clones with different specificity and structure to many epitopes emerge. These structures are called "polyclonal antibodies". Antibodies produced by a B-lymphocyte clone against an epitope are called "monoclonal antibodies".

5. ANTIGEN - ANTIBODY COMBINATION

■ Antibody - antigen combination is specific and the antigen combines with the antibody that caused its development. Due to specificity, if one antigen or antibody is present, it may be possible to detect the other. Using this, microbial diseases can be diagnosed with serological tests.

■ Antibody-antigen combination develops between the antigen surface epitope and the tip V domain of the antibody's Fab.

■ The Ab - Ag combination is chemical and a weak, low-energy bond takes part in this combination and is alternating. As a result of the combination, no fragmentation or change in the antibody and antigen structure occurs.

■ Ag - Ab association can be loose or tight depending on the proximity of the two molecules and the suitability of their binding sites. In the key-lock model, the closeness of two molecules to each other and the compatibility of their bonding groups are important in the strength of the bond.

CHAPTER 4

FORMATION OF THE IMMUNE RESPONSE

1. DEVELOPMENT OF THE IMMUNE RESPONSE

All reactions that occur when living things interact with antigens are called immune responses. In order for an immune response to occur, the antigen must be recognized by immune cells. Cells of immunity; These are events in which T and B lymphocytes and macrophages participate as antigen presenters. They communicate with each other directly or through cytokines (a molecule that carries biological messages). Antigens that enter the living being are presented to lymphocytes after being processed by antigen-presenting cells. The function of the helper T lymphocyte is important in this process. B and T lymphocytes, which recognize and are motivated by the antigen, differentiate and create immune response products.

1.1. Entry Site and Distribution of Antigen: It enters from three places.

■ **Mucosa:** Antigen entering from the genitourinary, digestive and respiratory system mucosa reaches the regional lymphoid tissue related to the mucosa.

■ **Skin:** Antigen; It enters the organism by being applied to the skin or injected under, into and into the tissue, and these come to the nearest regional lymph node via lymph**.**

■ **Blood:** Antigens enter the bloodstream directly through insect bites and injections, and these antigens are retained in the spleen. There are abundant immune system cells, B and T lymphocytes and macrophages, in the spleen, mucosal lymphoid tissues and lymph nodes. The distribution of antigens in the body differs depending on the site of entry. But over time, it spreads to different tissues and organs through lymph and blood. For example; Antigen is detected extensively in the spleen, liver, kidney, digestive system lymphoid tissue and lymph nodes. In the formation of an immune response against the antigen, the antigen must be recognized by B and T lymphocytes. The majority of antigens (protein ones) are activated primarily after being received and prepared by some special cells called ASH. Cells with ASH feature; dendritic, macrophage, monocyte, glial cell and skin Langerhans cell, which present antigens in special cases in B lymphocytes. The common feature of ASH is that it has a tissue antigen called MHC-class 2 on its surface. The antigen (in protein structure) that enters the living organism externally is first captured by ASH and processed in these cells and separated into its epitope. Peptide particles in the form of antigen epitopes combine with MHC-II molecules produced in the cell, form a complex, and are sent together to the surface of the cell. The antigen presented on the MHC-II molecule on the surface of the cell is recognized by Th lymphocytes in this form. In this recognition event, interaction between MHC-II, Th cell CD4 surface molecule, Antigen and TCR occurs. In addition, interaction between two cells at different points and motivation through cytokines also occur. Th lymphocytes are activated following stimulation and stimulate other immune system

cells, creating a humoral and cellular immune response. In living things, foreign antigens produced in cells (cells that contain viruses and tumors) are also found (endogenous Ag). In this case, tumor and virus Ags are combined with MHC-1 ((MHC-1 are histocompatibility antigens and are present in all nucleated cells) molecules on the cell and are delivered to the surface. These antigens presented on the MHC-1 molecule on the cell surface are recognized by TC lymphocytes. Because the CD8 molecule on the TC surface and MHC-1 Antigen interacts with TCR. Stimulated TC lymphocytes lyse and destroy the cells to which they specifically bind. This is very important in the defense of virus infections and tumors. B lymphocytes detect the antigen with specific immunoglobulin receptors on their surfaces. It is presented to the Th lymphocyte along with the MHC-II molecule, stimulating and activating it. Since the B lymphocyte acts as the ASH by the cytokine secreted by the Th lymphocyte, there is no need for additional B-lymphocytes. Some of them also recognize glycolipid and polysaccharide-like antigens.

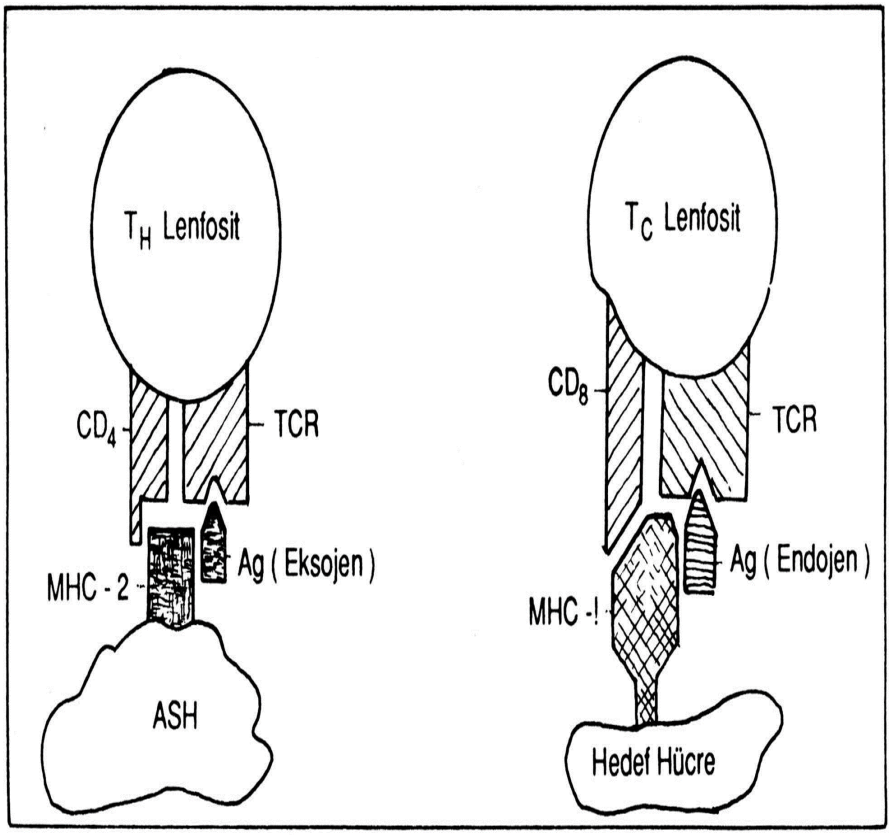


Figure 7: Lymphocytes

This antigen is large and carries a large amount of the same type of epitope. They are polymeric structures that only cause weak IgM antibody production. B and T lymphocytes that recognize the antigen differentiate and reproduce, creating an immune response. The immune response is protective and results in the benefit of the living being. However, it sometimes results in harm to the living being and causes tissue damage. This type of immune response is called an allergic reaction.

Terms and Explanations Related to Immunity

Normergy: Normal immune response

Allergy: A different, excessive and damaging immune response.

Anergy: Loss of response to antigen in allergy controlled by skin tests.

Hyperergia: Strength of the allergic reaction

Idiosyncrasy: A state of hyperactivity that develops with medication and has no immunological basis.

Atopy: Development of allergy as a result of genetic tendency**.**

2. CONSEQUENCE OF THE IMMUNE RESPONSE

Three different immune responses occur to antigenic stimulation.

2.1. Humoral Immune Response: This response is the responsibility of B lymphocytes. Specific antibodies that develop as a result of the humoral immune response are found in tissues and blood fluids and play a role in body defense. Antibodies can be transferred between individuals via blood serum. The antigen is first recognized by the appropriate Ig receptor B lymphocytes within the living being. Stimulated B lymphocytes differentiate in the germinal compartment of the lymph follicle in the lymph node to generate the primary humoral immune response. They reproduce by expanding their cytoplasm and increasing the number of ribosomes. As a result, a B lymphocyte colony that is sensitive to the motivating antigen is formed. Two types of cells are formed from this colony.

■ Plasma Cell (Plasmocyte): It is the origin of B lymphocyte. They are abundant in the lymph nodes and spleen. The function of this cell is to produce antibodies, which is the basis of the humoral response. The life of this cell is short, around 2-3 days, and they cannot reproduce. They synthesize 20,000 mol/min antibodies and disappear (Anonim, 2023).

Memory B Lymphocyte: It is a special type of B lymphocyte. It turns into a memory cell that is programmed for the antigen that caused its formation and preserves this information for a long time. When they encounter the same antigen, they rapidly differentiate and reproduce. Developing plasmocyte produces rapid and abundant antibodies (Anonim, 2023s).

■ **Primary Humilar Immune Response:** It is the response that develops to Ag, which first enters the organism and is recognized by B-lymphocytes and motivates them. Antibodies can be observed in the blood 7-10 days after the first introduction of Ag. The first antibody to develop is the IgM class. Afterwards, IgG antibody is produced. The total antibody level is low and begins to decrease after a short time**.**

■ **Secondary Humoral Immune Response:** A secondary humoral immune response occurs when the memory B-lymphocyte stores the information about Ag and then enters the same Ag into the living thing. Following the second introduction of the same Ag, the current antibody level (Abs remaining from the primary response) rapidly decreases. Afterwards, rapid, large and long-term antibody production is observed after the initial response. In the secondary response, there is 10-50 times the production of antibodies compared to the primary response. IgM as

in the first, but many IgG antibodies develop. In the formation of the secondary response, a smaller amount of antigen is sufficient than **the** primary one**.**

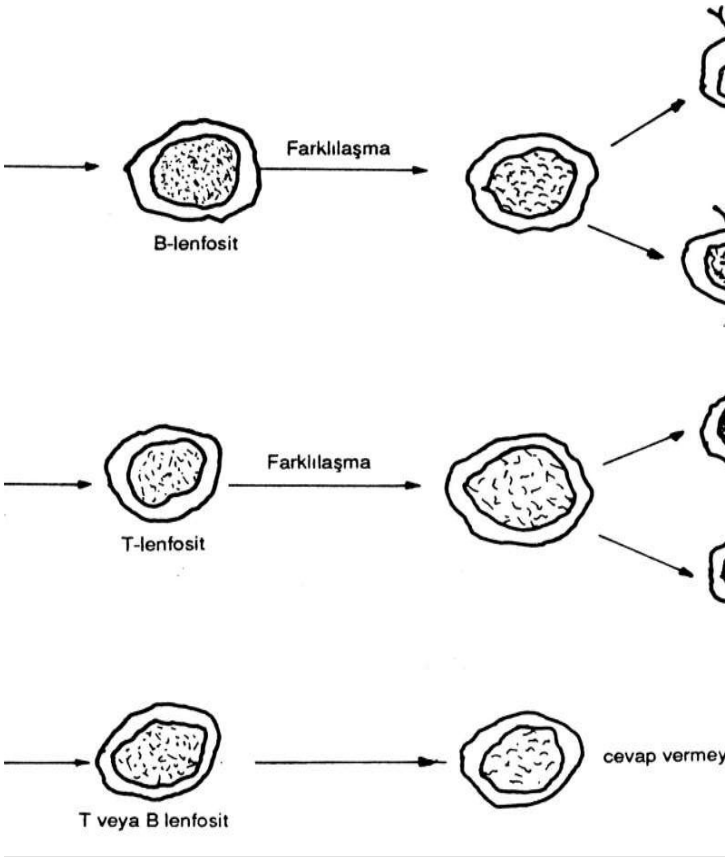


Figure 8: Results of the Immune Response

2.2. Cellular Immune Response: T lymphocytes are responsible for this immune response. In living beings, phagocytic cells (granulocytes and macrophages) and NK cells, which are natural killer cells, along with T lymphocytes, participate in the cellular immune response in the destruction of foreign antigens. Additionally, antibodies occasionally

contribute to cellular immunity. In cellular immune response events, a strong defense develops in living beings against many bacterial, virus, parasite and fungal-like antigens. In immunity, where only antibodies are involved, it protects against some toxic diseases and a small number of bacterial and viral infections. Cellular immunity is important in preventing and healing infections. T lymphocytes only recognize antigen that is in protein form and only if it is prepared and presented by an ASH (within MHC-1 or MHC-2 surface structures). T lymphocytes do not recognize free antigen. After ASH, the antigen that enters the living thing for the first time is recognized by the T lymphocyte carrying the matching TCR. Motivated T lymphocytes differentiate and reproduce rapidly in the paracortical area of the lymph node. As a result, a large number of lymphocyte communities that know this antigen are formed. Antigen-sensitive T lymphocytes (TH and TC) secrete the message molecule called cytokine. NK and macrophage cells are also activated under the influence of cytokinin.

Under the influence of cytokinin, granulocytes and macrophages gather at the event site. The phagocytic function of these cells is accelerated. Additionally, if there is antibody in the environment, this activation is strengthened.

■ TC lymphocytes direct themselves to the target cell carrying the antigen and kill them by lysis.

■ With the help of TH lymphocyte, B lymphocyte is activated and specific antibody appears. In this way, the antibody is also involved in the process.

■ Cytokine-activated NK cell also destroys the target cell.

Cytokine: Produced in macrophages and lymphocytes. They are peptide-structured substances that transmit messages between cells involved in inflammation and immunity. The difference between cytokines and hormones is that they are not systemic and affect the cells in the immediate vicinity. They bind to receptors in the cell and stimulate cell reproduction. In the immune system's fight against the pathogen, these cells signal immune system cells such as macrophages and T cells and enable them to go to the site of infection (Anonim, 2023n).

Formation of Immune Response: Cytokines; It regulates the host's reactions to damaging factors and foreign antigens by affecting the development, movement, proliferation and differentiation of all cells responsible for body defense.

There are different types of cytokines: Group 1: They are secreted by monocyte-macrophages and are effective in natural immunity. Type 1 interferon (Type 1 IFN); tumor necrosis factor (TNF); interleukin-1 (IL-1); IL-6 and IL-8.Group: They act on lymphocytes. IL-2, IL-4.

Group 2: Those that activate the inflammatory cell. Type-2 IFN; Lymphotoxin (LT); IL-5; migration inhibition factor (MIF).

Group 3: Those that stimulate hematopoiesis. IL-3; granulocyte-macrophage colony-stimulating factor (GM-CSF); monocyte-macrophage colony-stimulating factor (M-CSF); granulocyte colony-stimulating factor (G-CSF). With every Ag stimulation, sensitive T-

lephocytes and antibodies are seen together. In addition, there is cooperation and interaction within B and T lymphocytes in the development of both types of immune responses. For example, the developing TS and TH lymphocytes recognize Ag and are active in the differentiation and antibody production of the B-lymphocyte. On the other hand, antibodies that develop as a result of B-lymphocyte stimulation are effective in cellular cytotoxicity (Aktas and Bayram, 2020). While an Ag may stimulate only T- and B-lephocytes, it often stimulates both together.

2.3. Immune Non-Response: The failure of the organism (which has reached immunological competence) to mount an immune response to a particular Ag to which it is in a state of immune response is called tolerance.

For example

■ It may be a congenital, genetic trait. ■ The applied Ag rate is insufficient. ■ The applied Ag rate is high. ■ Ag; If it is applied frequently and in large numbers, tolerance to that Ag occurs, especially in B-lymphocytes. ■ If the number or function of the regulatory TH-lymphocyte, which plays an auxiliary role in the development of the immune response, is inadequate or dysfunctional, a good immune response will not develop. ■ If TS-lymphocyte function and number increases, the immune response is suppressed.

3. IMMUNO SUPPRESSION

It is tolerance to certain Ag. For other Ags, the immune response operates normally. In immunosuppression, the immune response is generally suppressed as a result of different elements affecting the living thing. For all antigenic structures, there is a decrease in immune response power or immune response**.**

Conditions Seen in Immunosuppression

■ X – ray ■ Removal of thymus

■ Viral infection disorders ■ Antilymphocytic serum

■ Inherited immune disorder ■ Desensitization

■ Some medications ■Use of specific antiserum.

■ **Malnutrition:** The immune response power is inadequate in children with nutritional deficiency due to protein deficiency. This is the reason for frequent and long-lasting infections in such children.

■ **Age:** The immune response is not sufficient in newborns and the elderly. The immune response becomes stronger until adolescence. It is highest in adolescence. Afterwards, it gradually decreases.

Infectious Diseases: The immune response is suppressed in the main viral diseases such as measles and AIDS and in various infections related to lymphoid tissue.

■ **Congenital Immune Response Disorder:** There are many disorders that have a genetic basis.

■ **Drug:** Drugs administered following tumor treatment and organ transplantation cause immunosuppression. These drugs have a cytostatic effect and prevent the cell from multiplying by disrupting the reproduction of cell DNA. In this context, since the bone marrow is suppressed (the lymphocytes that need to differentiate and reproduce with Ag stimulation cannot reproduce), the immune response is suppressed. For example; methotrexate, cyclophosphamide, cyclosporine, chlorambucil, azathioprine and corticosteroids can be given.

■ X-Ray: Since it stops lymphocyte reproduction in the lymphoid tissue, immune suppression occurs. Lymphoid tissue normalizes after 3-4 weeks following irradiation.

■ Removal of the Thymus: When the thymus is removed, the immune response is suppressed.

■ Antilymphocytic Serum: Lymphocyte is applied to the experimental animal and specific antibodies are produced in response. When serum containing this antibody is administered to a human for treatment, the functions of lymphocytes are blocked. As a result, the immune response is suppressed. It is necessary to suppress the immune system to prevent rejection, especially after tissue-organ transplants. In these cases, antilymphocytic serum is preferred as immunosuppressive. Because it does not affect other cells, it has few side effects.

■ Desensitization: Immune serum (serum containing specific antibodies, for example, tetanus antiserum) is widely used in the medical field. When immune serum is applied again to someone who

has previously received immune serum, the possibility of allergy is high. In such cases, it is used to suppress and prevent allergic reactions (immune responses that harm living things). Immune serum is started to be administered in a light dose and continued by increasing the dose. It is first injected intradermally and then subcutaneously (sc) to block the allergic reaction in the living organism. As a result, the allergic immune response will be suppressed, and then a full dose of immune serum can be used.

■ **Application of Specific Antiserum:** Application of specific antiserum for a certain antigen suppresses the immune response for that Ag. For example; In Rh incompatibility, the immune response to the Rh antigen is suppressed by applying anti-Rh antibodies (Rh antiserum) to the mother.

Hypersensitivity in Allergic Reactions

Definition: The immune response that causes discomfort is called hypersensitivity or allergy.

4. HYPERSENSITIVITY MEDIATED BY ANTIBODIES

■ **Type - I:** Anaphylactic (Rapid) → Antibody mediated

■ **Type - II:** Antibody-dependent cytotoxic → Antibody-mediated

■ **Type-III:** Developed by immune complex → Antibody-mediated

■ **Type - IV:** Cellular (late)→ Developed by sensitive T-lymphocyte

4.1. Type-I: Anaphylactic Hypersensitivity

4.1.1. Anaphylaxis: It is an allergic reaction that starts suddenly and causes death. It develops within 5-30 minutes following the shock dose. Some of it is due to protein release from white blood cells. These protein structures are structures that can initiate serious allergic reactions. Anaphylaxis may occur due to animal immune serum application, medication (penicillin), insect bites (bee types) and some foods. Severe facial redness, edema that starts behind the ear and spreads to the whole body, itching, urticaria, intense coughing fit, laryngeal edema, breathing difficulties and vomiting may be observed. (Anonim, 2021c).

■ **Phases of Anaphylaxis**

A) Sensitization: The dose of the first antigen that sensitizes the living being is low (Guinea pig is 0.1 microgram and given to the skin).

B) Waiting Phase: At least 2-3 weeks should pass after the application of the first sensitizing Ag. (Required for the production of appropriate antibodies that cause anaphylaxis.)

C) After Waiting: Anaphylaxis occurs when the same Ag maximum dose of 1-10 milligrams is given IV. The second Ag that causes anaphylaxis is called the shock dose. The organ that is most affected by anaphylaxis and causes clinical symptoms is called the shock organ. For example; cardiovascular and internal organs for the rabbit; for the dog, digestive organs; in mice, it is the small vasculature and in guinea pigs it is the bronchi.

■ **Mechanism of Anaphylaxis:** Ags involved in anaphylactic type sensitivity are called Allergens and antibodies are called Reagins. IgE antibodies develop in response to allergenic Ags. These antibodies are sensitizing and can bind to basophil leukocytes and mast cells in organs and tissues. These two have receptors to which the Fc of IgE binds. Basophil leukocytes and mast cells are abundantly granulated and multinucleated cells and contain vasoactive amine in their granules. These cells are common around small blood vessels and in connective tissue. They are especially abundant in the liver capsule, pleura, peritoneum, nipple, nostrils, heart tissue, and the smooth muscle organs of the uterus and intestine. IgE antibodies, which develop with the first introduction of allergenic Ags, bind to the receptors on the surface of basophil leukocytes and mast cells with their Fc ends and sensitize them. The Fab portions of the antibodies that bind to Ag are free. The same Ag that enters the living thing after a while reaches the bound antibody in that cell and combines with them, forming a bridge on the cell and between the antibodies. This combination stimulates the cells and discharges the granules in their cytoplasm, causing the release of vasoactive amine and the formation of an anaphylactic condition**.**

■ **Mediators Involved in Anaphylaxis:** They are released from the stimulated mast cell and basophil leukocyte granule.

Histamine: Creates a local immune response. It regulates physiological functions in the intestine. It is a nitrogen compound released as a neurotransmitter. Its effect occurs when it adheres to the histaminergic receptor. Local permeability increases as a result of capillary expansion.

It contracts the intestine and bronchi. It increases saliva, stomach and adrenal gland secretion. It reduces blood pressure by dilating the vessels. The effect of histamine begins in 1-2 minutes, the effect lasts around 10 minutes, and then it is rapidly destroyed (Anonim, 2022d).

Slow-Reacting Substance in Anaphylaxis (SRS-A): This structure contracts smooth muscles for hours. This structure causes the long-term bronchial spasm observed in allergic asthma. But even antihistamine medication cannot solve the contraction. SRS-A is inactivated by arylsulfatase produced by eosinophil leukocyte.

Other Structures: Secondary structures in the development of anaphylaxis; acetylcholine, serotonin, prostaglandin, heparin, kinin (bradykinin), anaflatoxins and eosinophil chemotactic factor.

4.1.2. Atopy Allergy: It is a local anaphylactic hypersensitivity reaction. It is observed in 10% of the population. Hypersensitivity affects one or several organs and local clinical symptoms are observed. However, locally developing atopy can progress and cause systemic anaphylaxis or even anaphylactic shock. It can develop against fungal spores, flower pollen, house dust, animal dander, insect stings, foods (nuts, eggs and seafood), chemicals (food additives and dyes) and medicines. Atopic allergy is genetically based and shows familial predisposition (Kırmaz, 2016).

4.1.3. Atopi ve Anaflaksi Esaslı Allerjik Rahatsızlıklar

■ **Allerjik Astma:** Alerjik bronşit diye adlandırılan alerjen nedenli akciğerde bronşların daralımıyla oluşan, nefesin daralması ve hırıltılı

öksürük atağıyla seyreden, ilaçla tedavi veya kendi kendine düzelen, tekrarlayıcı hava yolu rahatsızlığıdır. Allerjenin (Hayvan tüyü, ev tozları, polen ve ot) havayla alınmasını müteakipAllergic Disorders Based on Atopy and Anaphylaxis

■ Allergic Disorders Based on Atopy and Anaphylaxis

■ Allergic Asthma (allergic bronchitis): It is a recurrent airway disease caused by allergen-induced narrowing of the bronchi in the lungs, accompanied by shortness of breath and wheezing cough attacks, and can be treated with medication or resolved on its own. Following the ingestion of allergens (animal dander, house dust, pollen and grass) into the air, the bronchi, which are the shock organs, are affected and severe breathing difficulties occur (Asthma attack). Long-term increased mucus secretion and bronchospasm make breathing difficult (Ünser, 2016).

■ **Allergic Flu:** Generally, the causative agent is pollen. This is how it spreads to the environment from flowers and trees in spring and autumn. The affected organ here is the eye and nasal mucosa. Airborne allergen; house mites, pollen and animal dander. As a symptom; It causes itching, sudden watery eyes, redness, nasal congestion and discharge due to edema **(Anonymous, 2022).**

■ **Urticaria:** It is a common skin allergy in children. Although it usually resolves within 24-48 hours, it sometimes becomes chronic, lasting longer than 6 weeks. Following oral ingestion of the allergen, redness, severe itching, swelling and edema develop on the mucosa and skin. Medicines and foods cause urticaria (Akçay, 2023).

■ **Food Allergy:** It begins with the immune system perceiving the protein in the food as a threat and producing IgE type antibodies. When sensitive ones encounter the same food again, they bind to the previous IgE antibody and cause the release of histamine from the mast cell. The main ones are; Allergy may develop to foods such as eggs, cow's milk, peanuts, fish, walnuts, hazelnuts, pistachios, shellfish, wheat, soy, sesame and legumes. Protein-based allergens in foods are similar to other allergens. For example; In patients who are allergic to pollen, edema and itching in the mouth and throat develop with the consumption of bananas, peaches and apples. As a symptom; Fatigue, urticaria, migraine, widespread edema and anaphylaxis-like symptoms are observed (Anonim, 2023p).

■ **Atopic Dermatitis:** It is around 1-3% in children. It develops due to oral allergen exposure in genetically related children under the age of 2. It usually disappears after the age of 2. It is characterized by vesicles and redness on the neck, hands, head, knees and elbows (Kırmaz, 2016).

■ **Drug Allergy:** It is a drug and antibody-related (Type I, II and III) and cellular (Type IV) hypersensitivity reaction**.**

■ **Anaphylactic Style Drug Allergy:** It may occur in a short time after taking a small dose of the drug. Ingestion of the same causes the same symptoms to repeat and these people have high IgE.

■ **Anaphylactic Shock and Anaphylaxis:** It may develop with insect stings, animal-derived immune serum and some medications**.**

4.1.4. Diagnosis and Treatment of Atopy and Anaphylaxis

■ **Diagnosis:** In determining type-I hypersensitivity reactions, skin tests are used to determine which allergen the patient is sensitive to. The structure to be tested is applied to 0.1 ml of skin. Irregular swelling and itching develop in a few minutes, grow in 10-15 minutes and disappear in 1 hour; It is a sign of a positive skin test**.**

■ **Treatment:** Desensitization is performed. First, sensitization may occur when the immune serum is administered to a person for the first time. When immune serum is applied to a sensitized person for the second time, there is a risk of anaphylaxis. However, when the Ag to be applied is first applied at 15-minute intervals and in small doses, the IgE antibodies on the surface of the basophil leukocytes and mast cells will gradually be saturated, so an anaphylactic reaction will not develop when high doses of Ag are applied later. However, since desensitization is temporary, the person becomes sensitive again over time. The second method for desensitization is to obtain long-term results. In this method, the person is diagnosed with skin tests to which of the allergens he/she is sensitive to, and then the same Ag is given as a small dose of vaccine at one week intervals and IgG antibodies are created. As a result, when a person encounters an allergen, the IgG antibody captures and neutralizes the Ag. Since the allergen cannot reach IgE on the basophil and mast cell surfaces, the allergic reaction is prevented.

4.2. Type-II: (Antibody-Dependent Cytotoxic Hypersensitivity): When antibodies develop for Ags on the surface of the cell and when this antibody combines with Ag, the cell melts and the tissue is

destroyed. Complement, IgM and IgG antibodies take part in this picture. The antibody here binds to Ags on the cell with Fab parts. The Fc portions of the antibody are exposed. This situation stimulates the killer or phagocytic cell carrying the Fc receptor and the complement, resulting in the death of the cell. If the target cell is a neutrophil, granulocytopenia will develop, if it is an erythrocyte, hemolytic anemia will develop, and if it is a platelet, thrombocytopenia will develop. In addition, newborn Rh disease, erythroblastosis fetalis, incorrect blood transfusions and some autoimmune disorders develop with this system. Medicines can also cause this type of allergy.

4.3. Type-III: (Hypersensitivity Developing with Immune Complex): As a result of antigenic stimulation, specific antibodies are produced. If the developing antibody and antigen are in particle form, they combine with it and form an Ab-Ag compound = immune complex. With the development of the immune complex, the destruction of Ag becomes easier. However, in some cases, immune complexes are difficult to destroy. They are also stored in the tissue when the immune complex increases. The complexes accumulating in the tissue affect complement and platelets, which in turn attract the inflammatory cell to the scene, resulting in inflammatory tissue destruction. Events that occur with this system.

4.3.1. Arthus Reaction: When Ag is applied to the skin 3-4 times with a week interval, tissue damage such as redness and swelling develops in the injection area 3-6 hours after the last Ag application. Because the antibody that develops at a high rate upon Ag stimulation forms an

immune complex. It is activated in complement; Inflammation, leading to bleeding and tissue necrosis, develops in that area. This condition is inflammation of local vessels (vasculitis) (Anonim, 2023c).

4.3.2. Serum Discomfort: When a high amount of tetanus serum (prepared from sheep and horse-like animals) is applied to a person, fever, skin rash, joint swelling and pain, and lymph and spleen node enlargement are observed after 8-10 days. In this case, while the applied Ag begins to decrease, antibody production also increases. In 8-10 days, antibodies and Ag reach a certain level in the blood, and while the amount of immune complex Ag decreases, the amount of antibodies increases. The discomfort will heal on its own in approximately 1-2 weeks (Anonim, 2023c).

4.3.3. Immune Complex Disorders: Ag is not external, it is the body's own Ag. For this reason, some autoimmune disorders are in this group. For example; Such as Systemic Lupus, Rheumatoid Arthritis, Acute Glomerulonephritis and other Collagen tissue disorders. These structures accumulate in the kidney glomeruli and small vessel walls and initiate tissue damage.

4.4. Type-IV: (Cellular Hypersensitivity): The mechanism of formation in cellular hypersensitivity and immunity is the same. Sensitive T-lymphocyte takes part in this mechanism. With the stimulation of Ags on the sensitive T- lymphocyte, the lymphokine is released. As a result, tissue damage develops as a result of tissue inflammation, with the accumulation of first leukocytes, then lymphocytes and monocytes in the area where Ag enters. Cellular

hypersensitivity and cellular immunity develop together. However, although hypersensitivity and desensitization are eliminated, immunity continues. This is the difference between the two events. Clinical examples of this mechanism.

4.4.1. Tuberculin (PPD) Skin Test: Some antigenic structures (Tuberculin) of the bacillus that causes tuberculosis cause a delayed hypersensitivity reaction in infected people. The reaction begins 24 hours after intradermal application of Ag and occurs in 48-72 hours. The development of redness, swelling and hardness in the test area is considered positive. This finding indicates that the individual has previously encountered the same Ag and developed cellular immunity for that Ag (Anonim, 2020a).

4.4.2. Contact Dermatitis (Eczema): It is a skin disorder with mostly psychosomatic origin that occurs with skin redness, vesicles and itching symptoms as a result of contact with cosmetics, metals and drugs (Anonim, 2022f).

Defense Against Infections: Large-bodied organisms such as plants, humans and animals always interact with pathogens commonly found in nature. The interaction with the microbe may be ineffective for both parties, but it may also be mutually beneficial. However, what is important for medical microbiology is that microbes interact with living things to cause disease. A clinical phenomenon emerges as a result of microbes causing harm to the living organism they are in contact with and counter reactions occurring in the host in response to this effect. This situation is called infectious disease. The ability of microbes to

cause discomfort is called pathogenicity. The measure of pathogenicity is defined by virulence. Virulent microbes have a high power to cause discomfort. Strains that do not have the ability to cause discomfort are called avirulants (viruses administered as live vaccines).

Ways Microbes Cause Discomfort

■ Those that settle, multiply and spread after entering the body (anthrax and pneumococcus).

■ Those that stay where they enter the host and do not spread. However, those that release exotoxins and cause discomfort (diphtheria and tetanus).

■ Those that spread in the host and have a toxin effect due to their structure (creating an endotoxin effect on the cell wall of Gram (-) intestinal bacteria).

■ Those that cause disease and damage by causing an allergic reaction (Tuberculosis).

■ When factors that disrupt the immune system and cause disease (HIV-AIDS) come into contact with a living thing, they encounter resistance from the living thing. The living creature tries to protect itself by resisting the infection agent and to destroy the microorganism if discomfort occurs.

■ **Protective Mechanisms:** They are divided into two: acquired (acquired) and congenital (natural).

5. NATURAL IMMUNITY

They occur naturally in the organism. They do not discriminate between pathogens and constantly protect the organism from diseases by performing preventive and protective functions. This defense is determined by the genetic and structural characteristics of the living thing. As a result, a person can remain healthy without being disturbed, even though he lives in a dense world of microbes.

5.1. Acquired Immunity: These are specific immune response events that develop against microbes or their products that enter the living organism. These events develop as a humoral and cellular immune response and create resistance specific to that antigen. Acquired immunity is resistance acquired later. It can be earned in two ways: passively and actively.

5.1.1. Active Immunity: It is a humoral and cellular immune response that appears in the organism after a certain time by establishing a relationship with microbes or their products and protects it from these pathogens. This immunity is acquired naturally by experiencing microbial disorders or artificially by administering vaccines prepared from pathogens.

5.1.2. Passive Immunity: Acquired immunity is called acquired immunity by taking specific antibodies from a living creature that has gained active immunity by encountering microbes or their products and applying them to another person whom they want to protect. Since antibodies are mostly found in serum, the transfer of antibodies from

one living thing to another occurs through blood serum. Passive immunity formed in this way is short-lived and ends after 3-5 weeks. However, protection begins following the application of antibody-containing serum. Passive immunity saves lives, especially in diseases such as tetanus and diphtheria.

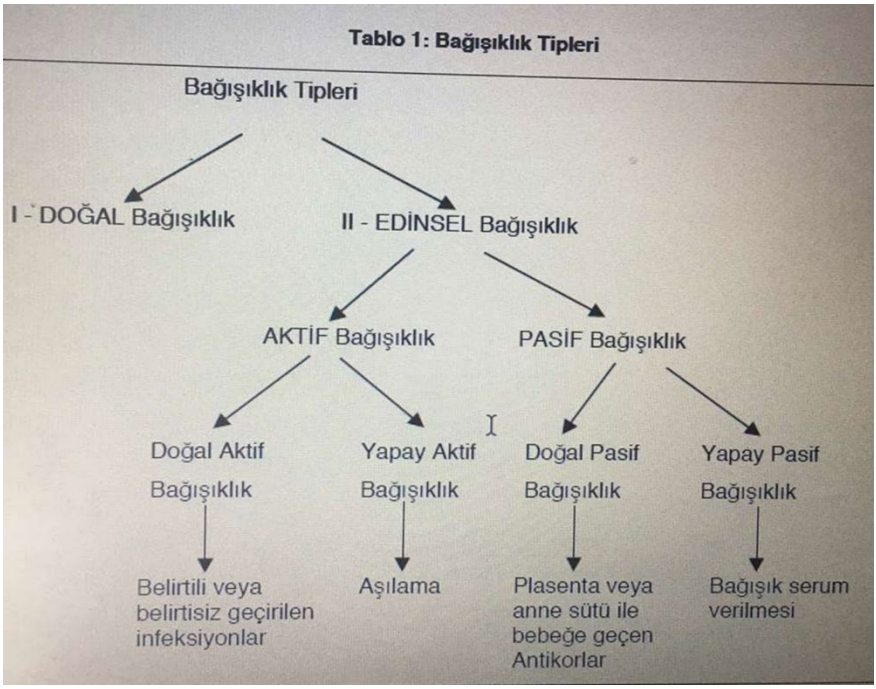


Figure 1: Immunity Types

An example of passive immunity is the pregnant woman's IgG class antibodies passing through the placenta to the offspring and protecting **it.** In this way, the baby is also immunized against the diseases to which the pregnant woman is immunized, with the antibodies she receives from the mother. In addition, antibodies in colostrum and breast milk at birth also create passive immunity to protect the baby from infections.

6. MECHANISM OF NATURAL RESISTANCE

6.1. Heredity: Living species show different sensitivity and resistance to disease elements. For example; The polio virus only causes discomfort in humans. No disturbance to animals such as rats and rabbits has been observed. Additionally, resistance differences may occur between races and within individuals of the same species. It has been observed that Indians and American blacks are more susceptible to tuberculosis.

6.2. Anatomical Barriers: Preventing microorganisms from entering the body. In natural resistance, the obstacles created by the anatomical structure (the first line of defense is skin and mucosa) prevent the entry of microbes.

■ **Skin:** Mechanically prevents the entry of most pathogens. However, when the integrity of the skin is disrupted (scratching, scratches, abrasions, cuts, trauma, surgical incisions, burns and wounds), it facilitates the entry of microbes and increases the rate of infection. In addition, external microbes cannot survive on the skin for a long time due to the oil and sweat gland secretion in the skin and the antimicrobial effect of fatty acid. Again, the lysozyme enzyme in these secretions is capable of breaking down the cell wall structure of the bacteria. In addition, the normal flora of the skin prevents bacteria and irritating microbes from settling and multiplying.

■ **Mucosa:** Digestive, eye, genito-urinary system and respiratory mucosa are entry points for factors that cause discomfort. There is a barrier in the mucosa that creates resistance to pathogens.

■ **Eye:** Tear; It is important in protecting against pathogens with the lysozyme enzyme it contains and its washing properties**.**

■ **Respiratory System:** Upper respiratory system; They are frequently encountered with microbes and toxic substances. The first obstacle is the hairs of the nose, which act as a filter. The secretion of the nose adheres the particles and the lysozyme, sIgA and phagocytic cells it contains form other obstacles. Mucus secretion in the respiratory tract also sticks the particles and prevents them from falling down. The quivering hairy epithelium in the respiratory mucosa brings the microbes and particles collected in the lower respiratory tract to the pharynx with its sweeping movements from inside to outside. From there, 90% of the harmful substances inhaled pass into the stomach by swallowing. In this process; They help functionally eliminate cough reflex, swallowing and sneezing. Small particles that cannot be removed reach the alveoli and lower respiratory tract. They are phagocytosed by alveolar macrophages there. Toxic gases, cigarettes, alcohol, extremely dirty and cold air, and respiratory tract obstruction negatively affect the defenses of the respiratory mucosa. In addition, the mouth, nose, pharynx and nasopharynx flora in the upper respiratory tract mucosa prevent the settlement of pathogenic factors.

■ **Digestive System:** Mouth; It is the place most exposed to oral microbes. The majority of germs are acquired through food and drink.

The body's defenses begin in the mouth (oral flora and salivary lysozyme-like enzymes). The important resistance barrier in digestion is stomach acid, and this strong acid causes the death of pathogens. However, some pathogenic agents pass into the intestines along with the food. In the small intestine; Pancreatic enzyme, bile, and intestinal secretion have antimicrobial effects. In addition, bowel movement and stool (diarrhea rapidly removes pathogenic factors) are also a kind of defense. The normal flora of the large intestine also serves this function.

■ **Genito-Urinary System:** Mechanically removes microbes. Here, the acidity of the urine, the high amount of urea, the structure of the bladder epithelium, the antimicrobial effect of the prostate secretion and the length of the urethra in men. The structure of the female sexual organs and vaginal epithelium, pH, acidity, and its normal flora are the elements that prevent the settlement of pathogens.

The Function of Normal Flora in Body Defense: Microbes meet normal flora where they enter the body. They compete with bacteria, which are members of the flora, to adhere to the tissue and compete for nutrition. As long as the body flora is in balance, they have the upper hand in the race against pathogens. In addition, the body's own flora plays an important role in natural resistance with its stimulating effect on the production of antibodies in living things.

6.3. Protective Elements in Body Fluid

Lysozyme: It is the enzyme in urine and cerebrospinal fluid (CSF), tears, saliva, nasal secretions and body fluids. The enzyme reduces the

risk of infection by breaking down murein in the cell wall of Gram (+) bacteria and destroying them. They are synthesized by macrophages and leukocytes (Anonim, 2022k).

Properdin: It is the large structured protein in serum. Complement reacts with C3 and creates a lethal effect on bacteria and viruses. In its deficiency, neisseria gonorrhoeae and neisseria meningitidis infections are frequently observed (Anonim, 2022l).

Fibronectin: It has elastic and adhesive properties. It anchors the produced fibrils to the environment surrounding the cell. It helps stop bleeding when an injury occurs. It is a non-specific opsonin and facilitates phagocytosis (Anonim, 2023u).

C-Reactive Protein (CRP): It is one of the acute phase proteins. It is produced by fat cells and liver. Its amount in the blood increases during inflammatory reactions. CRP binds to bacteria and facilitates their phagocytosis by binding complement to this structure (Anonim, 2022m).

Interferon: It is a protein that acts against bacteria, parasites, tumors and viruses. İFN alpha - In white blood cells; IFN beta - in other cells; IFN gamma - in T lymphocytes; IFN tau - Produced in the trophoblast cell. It plays an important role in the regulation of the immune response and the fight against viruses and tumors (Anonim, 2022n).

Nitric Oxide (NO): The macrophage initiates the reaction that destroys the bacteria and tumors it surrounds with the NO it secretes. It plays a

role in eliminating dysfunction in the cell membrane in all organs (Çelik, 2018).

Complement: This protein structure is synthesized in the liver. It binds to the antigen - antibody compound and becomes active. In this way, it causes cell melting. It becomes active and takes part in the defense of the living thing. Complement structure; It covers 10% of serum globulin and is expressed as "C". Its parts are C1, C2, C3, C4, C5, C6, C7, C8 and C9. In addition, there are their subparts or intermediate products formed during the reaction (C3a, C5a, C3b and the whole are around 20, and C9 is the least and C3 is the most). Complement is inactive and unstable to heat unless stimulated. It loses its activity in 30 minutes and 56°C. Its effect is an enzymatic reaction in which the proteins that make it up are activated in a chain manner (Anonim, 2023t).

■ **Classical Pathway:** It is the chain activation of complement particles, starting with C1. This pathway is mostly initiated by immune structures. The antigenic structure is generally in cell (bacteria and erythrocyte) format, and antibodies are capable of binding C (IgM and IgG)**.**

■ **Alternative Pathway**: It begins with the activation of C3 instead of C1 in complement. Following events that are different from the classical ones, activation is completed with the same system starting from C5. This pathway is effective in natural resistance, especially at the beginning of diseases, and antibodies are not required for such activation. Bacteria, parasites, fungi, tumors and virus-infected cells and Ig residues activate complement via an alternative pathway.

Events that Occur as a Result of Complement Activation

■ C3a and C5a mast cell granules, which are intermediate products in C activation, are emptied and cause the release of histamine.

Histamine; It causes edema, increased vascular permeability and contraction of smooth muscle. These are necessary events in tissue repair.

■ Complement helps phagocytosis through the effect of chemotaxis (C5a).

■ **Opsonization Effect:** The C3b fragment binds to the target cell, facilitating phagocytosis of these cells.

■ It activates leukocytes and accelerates their destruction.

■ **Cytolysis:** The cell covered with specific antibodies disintegrates and dissolves with the participation of the entire complement chain. **6.4.**

Cellular Elements

Phagocytosis: Particulate matter (including microbes) is taken into the cell by phagocytes and broken down and digested. Phagocytosis has a very important place in natural resistance**.**

Cells That Perform Phagocytosis

Leukocyte: PNL circulates in the blood and, when necessary, enters the tissue space and causes phagocytosis**.**

Macrophage: They are large cells. Those that can circulate in lymph fluid, blood and tissues are called migratory macrophages. Those that persist in organs and tissues are called resident macrophages.

Occurrence of Phagocytosis: Phagocytosis is the cell's phagocytosing of a foreign particle.

■ **Chemotaxis:** Movement of the phagocytosis cell to the scene. Cellular products, various substances, degradation products and pathogens secrete chemotactic substances that attract phagocytes. Phagocytes that receive the warning move to the scene with ameboid movements. Abnormal chemotaxis of leukocytes and lymphocytes also causes inflammatory disorders such as arthritis, asthma and atherosclerosis (Anonim, 2021e).

■ **Adhesion:** It is the adhesion of the microbe to phagocytes**.**

■ **Ingestion:** Pitting occurs in the area where the microbe adheres to the phagocytosis cell. The protoplasm flows and forms extensions that surround the pathogen, and the pathogen remains in the vesicle in the cell. This formed vesicle is called phagosome. As a result, the particle is taken into the cell.

■ **Digestion or Intracellular Killing:** There are many granules called lysosomes, which contain hydrolytic (dissolving) enzymes in the cytoplasm of the phagocyte. Following ingestion, the lysosome adheres to the phagosome and fuses, forming phagolysosomes. As a result, lysosomal enzyme destroys pathogens by digesting and killing them. Adhesion is important for phagocytosis and is stronger when the surface

of the microbe is covered with antibody. The antibody developed for the antigen on the surface of the microbe surrounds and binds to the microbe with its Fab sections. The Fc portions of the antibody are exposed. There is an Fc receptor on the cell that performs phagocytosis (macrophage and leukocyte). As a result, they easily and tightly bind to the bacterial cell coated with antibody through the phagocyte Fc receptor and easily cause phagocytosis. This antibody, which facilitates phagocytosis of the microbe, is called opsonin, and this situation is called opsonization. In the absence of opsonization, phagocytosis occurs, but is weak.

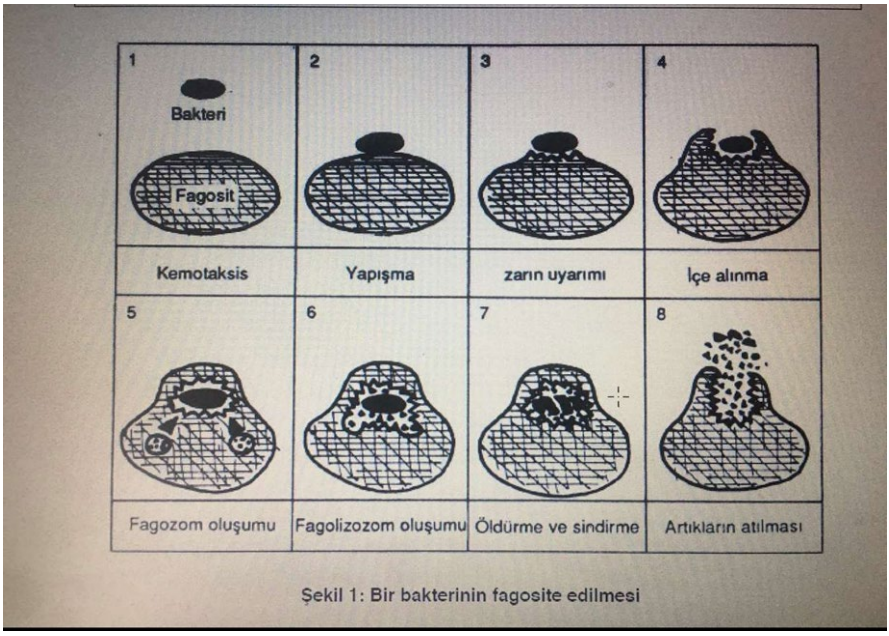


Table 10: Phagocytization of a Bacteria.

Phagocytosis is a defensive event that destroys many microbes. However, some microbes cannot be killed even though they are taken

into the cell by phagocytes (the tuberculosis agent cannot be killed by phagocytes and spreads the disease by circulating with them).

Inflammation: It is the reaction that occurs when tissue is damaged by microbes or physical, chemical or other reasons. Inflammation is the elimination of the cause (bacteria and product) that causes tissue damage, limiting it to the area where it is located, and renewing the damaged tissue by repairing it. Inflammation; It develops in two types: acute and chronic.

Akut iltihabın Gelişmi

■ As the capillary in the incident area expands, there is an increase in blood passing through (hyperemia).

■ As the permeability of the capillary wall increases, blood plasma leaks out of the vessel and causes edema.

■ Along with plasma, monocytes, lymphocytes and leukocytes cross the wall of the vessel with chemotactic stimulation and gather in the inflammation area, which is the gap in the tissue.

■ Phagocyte destroys the microbe by phagocytosing it.

■ Many resulting substances (lysosomal enzymes and coagulation factors) take part in the formation of inflammation.

■ Cells that kill microbes by phagocytosing them eventually become damaged themselves. In addition, the lytic enzyme developed during the reaction is harmful to the surrounding tissues.

■ In the area of inflammation; A fluid called pus develops from dead phagocytic cells, fragmented or dead pathogenic factors, and tissue residue.

■ In the area of inflammation, the increase in cell metabolism creates a local temperature increase.

■ During the healing phase, the inflammatory product is dissolved and dispersed by the effect of local and proteolytic enzymes. Traveling macrophages repair tissues by clearing microbes and cell debris.

■ Inflammation limits harmful elements in their area and renders them harmless. It is important in natural resistance.

Chronic Inflammation: Since the factor causing inflammation cannot be eliminated sometimes, the inflammation is prolonged. As macrophage and lymphocyte-like mononuclear cells increase in the area of inflammation, the area is surrounded by hard tissue. Five characteristic symptoms are observed in inflammation. These;

■ Local red hyperemia (rubor) ■ Local swelling edema (tumor)

■ Local temperature increase (color) ■ Local pain (dolor)

7. ELEMENTS AFFECTING NATURAL RESISTANCE

7.1. Fever: It is the most obvious symptom of inflammation and microbial disorders. Body temperature is kept balanced by the center in the brain. Stimulation of this center by physical and chemical factors increases body temperature. In microbial disorders, the thermoregulation site, which is the thermoregulatory center of the brain,

is stimulated by the endogenous pyrogens Interferon, IL-1 and TNF. As the main pathogens (bacteria and viruses), endotoxin, which is a bacterial product, Ab-Ag compounds, sensitive T - lymphocytes and steroid substances are the elements that cause endogenous pyrogen secretion.

The Effect of Increased Body Temperature on Natural Resistance

■ An increase in body temperature to 37°C creates an unsuitable breeding environment for many pathogens.

■ As human lymphocytes are stimulated in the presence of high fever, there is an increase in antibody production.

■ Different body temperature increases the resistance of some organisms to some pathogens. For example, sensitivity to anthrax increases in chickens when the temperature is lowered to 37°C.

7.2. Age of the Host: Children and the elderly are susceptible to microbial disturbances. For example, although the rubella virus causes serious damage to the fetus, it causes a mild or moderate infection in the mother.

7.3. Hormonal Balance: In case of deficiency or excess of hormones, the resistance status for microbes is affected.

■ Pyogenic bacterial and fungal infections are frequently observed in diabetics (Aktas and Gur, 2021).

■ Salmonella (typhoid) disease is more common in people with sickle cell anemia.

■ In adrenal gland disorders, sensitivity to microbial diseases increases due to the abundance or deficiency of these secreted hormones (corticosteroid-like).

7.4. Nutrition: A balanced diet in terms of protein, minerals and vitamins increases resistance to diseases. Irregular nutrition, especially protein deficiency, reduces resistance to diseases.

7.5. Decrease in Natural Resistance: Negative changes that may occur in the structure or functions of natural resistance factors and elements affecting natural resistance cause the natural resistance to decrease and break down.

This will increase infections.

■ A significant increase in pyogenic (pus-forming) microbe infections is observed in diabetics.

■ In cases where leukocyte function is impaired and complement deficiency, antimicrobial and phagocytic activity decreases, thus the defense against microbes decreases.

■ Many reasons (such as extreme fatigue, chronic alcoholism, drug addiction, pregnancy, stress, trauma, old age, vitamin C-A and some mineral deficiencies, severe burns, cytostatic, corticosteroid and immunosuppressive drug use) disrupt the natural resistance and increase the tendency to infections. When an infection develops, it has a severe course and cannot be cured easily**.**

CHAPTER 5

SERUMS AND VACCINES

İntroduction

In recent years, preventive medicine has begun to be used as a basis instead of therapeutic medicine. In this understanding, importance has been given to protecting societies through hygienic conditions (personal hygiene education, clean water supply and sewage) and nutrition, as well as active and passive immunization against infectious diseases. Transmissible microbial disorders account for 20% of clinical cases and 70% of all acute illnesses. According to epidemiology, it has been determined that 3-5 million children aged 0-5 die annually from vaccine-preventable diseases. In Turkey, 80 children a day and 22,000 a year die from vaccine-preventable diseases. These figures indicate the importance of infectious microbes for human health and the value of active and passive immunization. On the other hand, problems in the drug treatment of infectious diseases. Insufficiency of antimicrobial drugs in viral diseases and increasing resistance to this drug. There is no other option other than immune antisera in the treatment of diseases caused by microbe toxins (diphtheria and tetanus). Emphasizes the importance of immune antiserum and vaccine administration. In addition, vaccination against infections is an easy, cheap and simple method for individuals and society.

1. VACCINE

The substance that creates an immune response when applied and protects the living thing from infectious diseases is called a vaccine. The vaccine is antigenic in nature. By creating a cellular and humoral immune response in the living thing, they provide protection as if they had an infectious disease, without causing discomfort.

1.1. Vaccine Types

There are four types of vaccines.

■ Dead vaccine

■ Live vaccine

■ Vaccine prepared from germ residues

■ Biotechnological vaccine

1.1.1. Killed Vaccine: It is a virus vaccine inactivated with killed bacteria. After the virus or bacteria are produced in laboratories, they are diluted to a certain extent of pathogen in 1 cm3 of liquid and killed with heat, acetone, formaldehyde, ultraviolet and phenol-like substances. In this inactivation and killing process, the antigenic structure and microbial integrity are generally not disrupted, and dead vaccines are administered parenterally. Generally, antibodies are observed 4 days after the first application. However, the antibodies that develop after the first administration are not at a protective level. For this reason, immunity should be increased by 2, 3 or more vaccinations.

The protection period of a non-living vaccine is shorter than other vaccines. Examples of non-living vaccines.

■ **Killed Bacteria Vaccine:** Cholera, typhoid, plague, paratyphoid, typhus and whooping cough.

■ **Inactivated Virus Vaccine:** Rabies, influenza and polio (salk type).

1.1.2. Live Germ Vaccine: It is a vaccine whose pathogenicity is eliminated or reduced without losing its antigenic properties. Live vaccines are administered to living animals in different ways. This vaccine creates a mild or silent infection in the living organism and develops immunity similar to natural infection. Vaccine infection is specific to BCG in some vaccines, mild (rubella) in some vaccines, and asymptomatic (polio) in others. Live germ vaccines create a cellular immune response and have longer protection. In particular, some live virus vaccines (mumps, rubella and measles) create lifelong immunity with one dose.

■ **Live Bacterial Vaccine**: BCG vaccine.

■ **Live Virus Vaccine:** Yellow fever, Sabin polio vaccine, mumps, measles and rubella.

1.1.3. Vaccine Created from Germ Scraps

Toxoid (Anatoxin) Vaccine: The toxin of the bacteria is obtained in pure form. It changes with formalin and heat and becomes a microbe toxin, which completely loses its toxic power and completely preserves its harmless antigenic properties and creates immunity. It is used to

protect against diseases caused by the toxin of bacteria such as tetanus and diphtheria. Toxoid vaccine creates a humoral immune response and provides protection with antibodies (Anonim, 2020b).

Vaccine Prepared from a Certain Part of the Microbe: In some infections, vaccines prepared from a certain part of the microbe (HBs Ag particle, N. meningitidis cell wall polysaccharide) are good protective.

1.1.4. Biotechnological Vaccine: Molecular biotechnology is used to obtain an effective vaccine with fewer side effects.

Vaccine Prepared Using This Technique

■ **Recombinant DNA Vaccine:** The gene encoding the protein of the microbe that has an effect on immunity is identified. These genes are transferred to the carrier cell and produced abundantly in that cell. For example, the gene encoding Hepatitis B surface antigen (HBsAg) is transferred to the yeast cell and acquired in large quantities, and this gene is administered as a vaccine (recombinant HBV vaccine).

■ **Synthetic Peptide Vaccine:** The amino acid sequence of the protein that is effective in immunity is determined. This protein is produced synthetically under laboratory conditions. For example; such as streptococcal M protein vaccine and cholera toxin.

■ **Mutant Vaccine:** The virulence gene in pathogens is eliminated through biotechnology. Such as the elimination of the gene encoding the bacterial toxin of V.cholerae, an avirulent mutant strain.

■ **Anti Idiotype Vaccine:** It is a vaccine technique created through antibodies.

2. DEFINITIONS ABOUT VACCINES

■ **Primovaccination:** It is the first application of the vaccine to a person.

■ **Booster:** These are repeated vaccinations given for certain periods of time to ensure that the immunity formed by primovaccination continues at an effective level and to reinforce the immunity**.**

■ **Monovalent Vaccine:** These are vaccines that contain only one type of microbe or antigen. For example, mumps and measles vaccine.

■ **Polyvalent Vaccine:** It is obtained by mixing several toxoid or dead bacterial vaccines. The application of mixed vaccines is practical, easy and time-saving. It creates strong immunity compared to a single application. For example, diphtheria, whooping cough (DBT) and tetanus vaccine**.**

■ **Protective Value of Vaccine:** It is the best protection for the organism against the disease. It is the expression of those who are vaccinated against that infection compared to those who are not vaccinated. In order to obtain this resistance rate, it is necessary to apply it to the wider society and calculate its experimental results over time. This is also time consuming and difficult. However, in understanding the protection of the vaccine, it is useful to measure the cellular and humoral immune response it creates. For example, the antibody level in toxoid and killed vaccines can give an idea**.** For some live vaccines,

skin testing is useful in determining the cellular response that develops. For example, BCG vaccination followed by PPD test.

■ Vaccine Protection Time: It describes the duration of the vaccine's protection. This long vaccine is a good vaccine. Live vaccine is one of the vaccines with a long protection period.

3. FEATURES RELATED TO THE APPLICATION OF THE VACCINE

In order to obtain the expected result from the vaccine, it should be administered in sufficient doses and numbers, for appropriate periods of time, and in accordance with the procedure and method.

■ Vaccine Application Sites

■ Drop or spray into the nose ■ Oral administration

■ Parenteral Application: If administered as an injection (Sc or IM), it should not be administered into the vein. IV administration cannot be done due to the decrease in the immunization power of the vaccine and the high number of side effects.

■ Since this vaccine contains adjuvant and cannot be administered deep enough and is administered sc, the needle must be of sufficient length for im administration because necrosis occurs in the tissue. In this application, the thigh or deltoid and hip area is preferred. However, there is a possibility of damage to the sciatic nerve in the hip area and also the possibility of injection into the fatty tissue is high.

■ In parenteral applications, the best way is intradermally and an early and strong immune response develops with the same amount of antigen.

■ It finds easy application in large mass vaccinations of nasal and oral vaccines.

■ Age of Vaccination: It is given at the age when the disease is more frequently observed. However, another important aspect of age in vaccination is that the vaccine given has more or less side effects depending on age. For example, typhoid vaccines are not administered to people over the age of 40 due to their high side effects. Since polio, diphtheria and whooping cough are very common in infancy, their vaccines are administered immediately after birth. On the other hand, whooping cough vaccine is not given after the age of 6 because there is no danger. Rubella vaccine should be administered to girls before puberty.

Vaccination Risk: The benefit to be obtained from vaccination must be compared with the risks it will cause. Administration of live rubella vaccine to a pregnant woman causes anomaly in the fetus. In this case, the risk of vaccination is much greater than the risk of the pregnant woman in contact with the rubella patient contracting the disease.

■ **Vaccine Quality:** The quality of the vaccine should not be compromised.

■ The antigenic substance in it should not deteriorate or, if it is a live vaccine, the microbes in it should not die and its amount should not decrease.

■ It should not be contaminated with external microbes, should not contain debris and particles. It should be homogeneous, free of turbidity and stable.

The vaccine must be stored well to ensure stability. Killed vaccines and BCG are stored at +2/8°C, live virus vaccine - at 15/20°C. TT and DBT vaccines are not frozen. BCG should be kept in the dark.

■ Preservative antibiotics and substances can be added to prevent the vaccine from spoiling (Aktas, 2016).

■ Lyophilized vaccines (where water is evaporated, dried and turned into powder in a cold and vacuum environment) are vaccines that are preserved in good health and whose stability does not change over a long period of time.

■ Every vaccine must have an expiration date and lifespan. Unstable and stale vaccines should not be administered.

4. CONDITIONS TO BE CONSIDERED DURING VACCINATION

4.1. Side Effects: While it may be directly related to the vaccine substance, it may also be due to additives. Due to side effects, information about reactions to previous vaccinations should be obtained before administering the vaccine.

■ **Local Vaccine Reactions:** When the vaccine is administered as an injection, an increase in temperature, swelling, redness, pain and swelling in the regional lymph node are observed in that area.

Increasingly serious, local reactions may be observed, especially with repeated vaccinations (tetanus and diphtheria).

■ **Systemic Mild Vaccine Reactions:** Reactions caused by foreign protein in the vaccine; mild fever, feeling of malaise, vomiting and nausea are similar.

■ **Systemic Severe Vaccine Reactions:** Occurs rarely. Fever of 40°C and above, convulsion.

■ **Allergen Vaccine and Focal Organ Reactions:** Rarely, allergic reactions such as anaphylactic shock may develop following vaccine administration. Additionally, previous allergic conditions such as asthma and eczema may recur. Allergic encephalitis may develop following some vaccinations (semple type rabies). It is the exacerbation of tuberculosis foci or the recurrence of kidney diseases, especially observed following typhoid vaccinations.

Contraindications of Vaccination

■ **People with Low Resistance:** It should not be administered to people with low immunity (who cannot limit vaccine infection). Live vaccines may cause serious discomfort in these people. Those with low immunity who are at risk of vaccination.

■ **Pregnant women:** Live vaccines should not be administered. However, to prevent neonatal tetanus, tetanus toxoid vaccine can be given in the 4th month of pregnancy in risky areas.

■ **People with Chronic Organ Diseases**: The vaccine should not be given to people with heart, nervous system, liver and kidney diseases.

■ **Febrile Disorders:** Vaccination is not administered during the course and convalescence of all infectious diseases and in the presence of fever. Especially for diseases that suppress the immune system, such as measles, influenza, viral hepatitis and typhoid, vaccination should be administered after three months have passed.

■ **Age-Related Contraindications:** Diphtheria and typhoid vaccine should not be administered to people over 40 years of age, yellow fever and typhoid vaccine should not be administered to those under 2 years of age, and BCG vaccine should not be administered to premature babies.

■ **Diabetics:** People with diabetes are not vaccinated (typhoid fever is strictly prohibited). Polio can be treated after the age of 3 by controlling blood sugar.

■ **Allergic Persons:** Typhoid, smallpox and BCG vaccines are not administered to those with skin infection eczema and those in contact with eczema. When it is necessary to vaccinate allergic people, the dose of the vaccine is divided into parts. It is even given by desensitization.

■ **Interaction Between Vaccines:** A new vaccine should not be given until 5 days have passed following the application of dead vaccine. A new vaccine should not be given until 1 month has passed after live vaccine administration. Anti-serum cannot be administered together

with live virus vaccine. You must wait 3 months. Anti-serum can be applied simultaneously to the dead vaccine from separate sites.

■ Those with cancer ■ Those with malignant blood disorders ■ Those whose spleen was removed

■ Cachectics ■ People with congenital or later compromised immunity

■ Taking immunity suppressants (Radiotherapy)

– Cytostatic (Ca) drug – Immunosuppressive drug – Corticosteroid

5. CHARACTERISTICS OF VACCINES AND METHODS OF APPLICATION

5.1. Diphtheria Vaccine: It is a toxoid vaccine prepared for diphtheria disease caused by Corynebacterium diphtheriae. It is done by bringing the toxin of the diphtheria agent into toxoid form. In living organisms, it produces the antitoxin antibody that protects against diphtheria. There is a pediatric form given to children under 6 years of age and a low-dose adult form. It is generally given to children under 6 years of age in the form of DBT + mixed tetanus toxoid + diphtheria toxoid. In adults, it is given in the form of tetanus + diphtheria. In both forms, its protection is 95% and its protection period is 10 years. Since immunity cannot be formed in those who have had diphtheria, primovaccination should be applied afterwards (Anonim, 2022g).

5.2. Tetanus Vaccine: It is produced by Clostridium tetani. It is everywhere in nature, including soil, dust and manure areas. It causes strong contraction in the patient's jaw and neck muscles. It is

transmitted to a person from infected needles, nails and nail-like cuts, from wounds contaminated with soil, dust, feces or saliva, from dead tissue formed in accidents and burns, and from the umbilical cord of the newborn. It is a vaccine that produces antitoxin antibodies that protect against tetanus in living beings by rendering the toxin of the causative agent of tetanus into a toxoid state. The causative agent of tetanus is a pathogen that is abundant around us. For this reason, people should be vaccinated at all ages. Tetanus toxoid vaccine develops strong immunity. Its protection is over 95% and its protection period is 10 years. It must be repeated at 10-year intervals. It can be given to children under the age of 6 in the form of DBT, and to adults in the form of tetanus + diphtheria or as tetanus toxoid alone. To prevent the newborn from getting tetanus, a total of 2 doses should be administered to unvaccinated pregnant women in risky areas, in the 4th and 5th months of pregnancy. Since immunity is not formed in those who have recovered from tetanus, primovaccination should be applied afterwards. (Anonim, 2023d).

5.3. Whooping Cough Vaccine: It is a dead bacterial vaccine. It is given in the form of DBT. The baby can be protected by vaccinating the mother during pregnancy. Babies are given three doses, starting after six weeks. Additional doses may be given to older children and adults. It is not given after the age of 6 because whooping cough is rarely observed and vaccine reactions increase. Its protection is around 70%. Recently, a cell-free pertussis vaccine containing only the antigenic structure of the bacterium has been made. Compared to the

first vaccine, its protection is the same, but it has fewer side effects (Anonim, 2022h).

5.4. BCG Vaccine: It is a live bacterial vaccine. It is prepared from attenuated bacteria obtained by weakening bovine TB bacteria through culture passage. The vaccine prevents the spread of the bacillus through the lymphatic system and blood. It reduces the occurrence of TB, miliary TB and meningitis-like disease. Its protection value is 80% and its protection is around 5-10 years. PPD skin test must be positive to check the effectiveness of the vaccine (Anonim, 2020b).

■ **BCG Administration**: 0.05 ml following birth. It is applied intradermally, on the left arm. The second dose is given as 0.1 ml at the start of school (it should be given with an interval of 5 years until the age of 20). Afterwards, PPD skin test checks must be repeated every 10 years. The vaccine can be given to people of all ages and those with PPD (-). BCG vaccine is generally given 0.1 ml intracutaneously (ID) to the left shoulder blade and deltoid region. 2-6 weeks after the application, mild swelling develops, then swelling with fluid inside and finally swelling with pus inside. It opens to the outside and becomes ulcerated. It heals by crusting over in 2 months, leaving a scar. There is slight swelling in the lymph node under the arm. The PPD test should be positive 4-8 weeks after BCG vaccination. The younger the vaccinated child, the lower the probability of a positive PPD test. It was determined that 20% of the babies vaccinated following birth were not PPD positive at all, and most of them turned from PPD positivity to negativity within 1 year**.**

■ **PPD Skin Test:** ID of the arm and 0.1 ml is applied. After 72 hours, the size of the hardness in the injection area is measured and evaluated. This test shows the person's exposure to tuberculosis microbes and their immunity against this disease. PPD is positive if its hardness is 10 mm or more in the skin test. In those who received BCG vaccination, a hardness of 3-5 mm is positive.

■ **Complications of BCG Vaccine:** It is closely related to the dose, location, depth of the vaccine, and the immune status and age of the vaccinated person.

Observed Complications: Swelling of lymph nodes in the neck and armpit; large wound formation at the vaccination site or secondary infection by other bacteria; osteomyelitis; widespread BCG disorder (in cases of immunodeficiency).

■ **Storage of BCG Vaccine:** It is prepared in liquid and dry form. The dry form can be stored at 2-8°C for 1 year. It should be used within 24 hours after reconstitution. Once diluted, it should not be left in the sun, otherwise the bacilli will be inactivated within 5 minutes. If it is a liquid vaccine, it is stored at 2-8°C for 3 weeks**.**

5.5. Typhoid Vaccine: It is a dead mixed vaccine containing three separate bacteria: Salmonella (S)typhi, S. paratyphi-A and B. It is a bacterial disease transmitted through contaminated food and drinking water. Discomfort appears 7-15 days after the bacteria enters the body. It is observed as an epidemic in summer and autumn. If necessary, it is also given to people between the ages of 2 and 40 who are at risk. 2 doses are administered 6-8 weeks apart and a booster is administered 1

year later. Afterwards, a booster every 3-4 years is sufficient. Typhoid (TAB) vaccine is not administered to children under the age of 2 and over the age of 40 due to its side effects. Typhoid vaccine is given 1 ml and sc. Its protection is 70% (Anonim, 2022p).

5.6. Cholera Vaccine: It is a disease caused by the bacteria called Vibrio cholerae in the small intestine. Here it produces a protein-based poison called enterioxin. This enzyme increases the production of cyclosis endorozin 3,5 monophosphate, causing the passage of body fluid into the cavity. The fluid and electrolytes taken into the body are not absorbed from the small intestine and are excreted. Signs of serious discomfort appear in the first 6-48 hours after the pathogenic bacteria is ingested into the body. This vaccine; It is a dead bacteria vaccine and is administered im or sc as 0.5 ml to children aged 6-24 months and 1 ml to adults. When necessary, 2 doses are administered 4-6 weeks apart. Its protection (50%) is 6 months and its protection can be continued with a booster every 6 months if desired (Anonim, 2023ü).

5.7. Mumps Vaccine: It is a contagious childhood disease caused by viruses. The virus causes swelling and inflammation in the large salivary gland called the parotid gland. The vaccine is a live, virus vaccine and is administered alone or as a single dose of MMR sc. It is given from 12 months onwards and its protection is 95% and its protection period is at least 10 years **(Anonymous, 2023ü).**

5.8. Polio Vaccine: It is seen in children under the age of 15 and is rarely observed in individuals over the age of 15. It is an infectious disease that causes permanent paralysis in the legs and arms. The only

way to protect yourself from this disease is vaccination. This two-way vaccination also prevents people from transmitting the virus to each other.

■ **Salk:** It is a dead virus vaccine and is administered parenterally. It ensures the formation of protective structures for the virus in the blood.

■ **Sabin:** It is a live virus vaccine and is administered as two drops in the mouth. It prevents the virus from passing from the intestine to the blood in the digestive tract and causing disease. Nowadays, Sabin type Polio vaccine is more commonly used. Its protection is up to 95% and it has no side effects. There are all three types of Polio virus in the vaccine. (Type I, II, III (Polyvalent or Trivalent) vaccine). Recently, the use of killed polio vaccine has increased and cases of paralytic polio caused by live vaccine have been observed (Anonim, 2023e).

5.9. Measles Vaccine: The causative agent is the measles virus. It is an infectious disease that is observed in all ages, especially in childhood. It is transmitted through breathing and is accompanied by rash and fever. Children under one year of age are more susceptible to discomfort. It is a live, virus vaccine and is given as a single dose SC alone or together with mumps and rubella vaccines. This vaccine is administered to healthy children when they are 15 months old. However, it can also be applied between 6-15 months in communities where the risk of measles is high. However, after 15 months, a plus dose should be applied. Its protection is close to 100% and is lifelong (Anonim, 2023f).

5.10. Rubella Vaccine: It is a mild disease caused by the rubella virus in children. The vaccine is live and is given as a single dose or sc in MMR form. It is applied to those over 12 years of age. Its protection is 95% and provides lifelong protection **(Anonymous, 2023g).**

5.11. Rabies Vaccine: It is generally administered against the rabies virus caused by bat or dog bites. Post-bite vaccine is administered together with rabies immunoglobulin. It is recommended that those at high risk of potential exposure be vaccinated before exposure. Vaccinating dogs is effective in preventing the spread of the disease to humans **(Anonymous, 2023h).**

■ **Semple Type Rabies Vaccine:** It is a vaccine made by producing the virus in the brain of the sheep and then killing it. It is given in a program of 14 or 21 doses, depending on the nature of the person to be vaccinated, the biting animal and the wound. It is applied to the sc and abdominal area as one dose every day. Its protective value is high, its protection period is 6 months and its side effects are high.

■ **HDCV Rabies Vaccine:** It is made by growing and killing the virus in human cell culture. It is preferred because it has high antigenicity and low side effects. HDCV vaccine after contact with a rabid or suspected rabid animal 0./3.7./14./28. and on the 90th day, 1 ml and 6 doses are administered im**.**

5.12. Hepatitis-B Vaccine: Transmission; It can be transmitted through the application of uncontrolled blood or blood product, dental or medical intervention with unsterilized instruments, sharing of used syringes, sharing of personal items such as toothbrushes and razors,

body jewelry or tattoo application with unsterilized materials, and sexual intercourse with unsafe persons. HBs Ag, which is the particle of the virus, is the vaccine**.** It should be given to those who are at risk after birth. Its protection is 95%. The protection period is up to 5 years. It is administered as 0.5 ml for children up to 10 years of age, and 1 ml for adults and administered intramuscularly. 2 doses are given one month apart and 3 doses are given as a reinforcement dose after 6 months. Those who are vaccinated should be tested for anti-HBs antibodies and their immunity should be checked. Patients and healthcare personnel who receive blood products should be vaccinated because they are at risk (Anonim, 2023ı).

Hepatitis B prophylaxis after Suspicious Exposure: 0.5 ml antiserum and 0.5 ml (10 mg) vaccine are administered intravenously in the first 12 hours to the baby of HBsAg(+) mother. In case of skin contamination, 5 ml of antiserum is applied in the first 24 hours and 1 ml (20 mg) of vaccine is applied within 7 days.

5.13. Meningococcal Vaccine: It is a gram (-) diplococcus type bacteria called Neisseria meningitidis. It is the most common type of factors that cause meningitis in children and adults. It reaches the nasal cavity and sinuses through the air, settles there and multiplies. It then reaches the brain membrane and causes inflammation. This condition is called meningitis (inflammation of the brain membrane). In addition, the pathogen passes into the blood, causing meningococcemia throughout the body.

Conjugate Vaccine: This vaccine is administered to people over the age of 55, military personnel, dormitory students, people traveling to risky countries and those with immune deficiency**.**

Polysaccharide Vaccine: It is produced from the building blocks of the bacterial cell wall. Although it has many side effects, it is also applied to people under the age of 55 and pregnant women. It is given to one arm, the deltoid muscle. When given before the age of 16, another booster dose should be administered afterwards **(Yeşil, 2023).**

5.14. Pneumococcal Vaccine: It is prepared from the polysaccharide in the capsule of Streptococcus pneumonia. It is the cause of meningitis in children under 5 years of age. Additionally, it causes blood poisoning, otitis, pneumonia and sinusitis. It is given as a single dose of 0.5 ml im and sc. It generally lasts 5 years and provides 80% protection. It is recommended to be applied to those who are over 60 years of age and those with low immunity, in childhood when the disease is frequently observed (Anonim, 2023i).

5.15. Haemophilus Influenza Vaccine: Haemophilus influenzae type b bacteria causes diseases that can be fatal (sepsis, meningitis, pneumonia, inflammation of the pericardium, joints, skin and soft tissue and bones, sinusitis and otitis). The vaccine is prepared from the polysaccharide in the bacterial capsule. The vaccine with the maximum capsule b (Hib) is given. It is recommended for use in children at risk. A single dose is administered and provides protection for 3 years **(Anonymous, 2023k).**

5.16. Flu Vaccine: It is a non-living vaccine and is prepared from influenza virus. Since the antigenicity of this virus changes frequently, the vaccine should be prepared from the new type in the last epidemic. In the vaccine, there are two subtypes of influenza A and one subtype of influenza B**.** If there is antigenic similarity between the vaccine and the disease-causing virus, the vaccine provides 50-80% protection. It is given annually in the autumn to high-risk individuals (Anonim, 2023l).

6. PASSIVE IMMUNEMENT

Serum used for human protection and treatment purposes is produced as heterologous (sheep, horse and cattle) or homologous (in humans).

6.1. Heterologous Serum: Sera containing high titers of antibodies belonging to the immunized animal. The microbes that cause the disease or their residues or antigens such as scorpion or snake venom are given to the experimental animal after special preparation and high levels of specific antibodies are produced for these antigens. Serum obtained from animals immunized with this method is used to prevent disease or treat some diseases. In immune serum, horses, sheep and cattle are used to produce a lot of serum. Since immune serum of animal origin contains high amounts of foreign proteins, it very often causes hypersensitivity reactions and therefore loses its importance. On the contrary, the use and importance of human-origin immune serum is increasing.

Homologous (Immune Serum of Human Origin)

6.2. Gammaglobulin or Immunoglobulin: They are obtained from human placenta or plasma. It has application areas in many disorders. It has few side effects.

6.2.1. Standard Immunoglobulin: It is prepared by separating the immunoglobulin from the plasma mixture of one thousand or more donors. Here, various antibodies belonging to the donor are found together and densely. Standard Ig products are given for immunity disorders, disease protection or contact with various infectious diseases.

6.2.2. Specific Immunoglobulin: They are obtained from the plasma of people who have an infection or from volunteers who have received active immunization through vaccination. These contain intense antibodies to the agent or product of that infection. They are applied when the specific antibody they contain is required. The antibody content of specific Igs is 15-30 times higher than that of animal immune sera.

6.2.3. Different Homologous and Heterologous Serum Samples: Serum is used to create passive immunity. Since they contain readily synthesized antibodies, they show their effects when administered. However, the immunity they create is short-term, lasting approximately 3-4 weeks. In the absence of time for active immunization, they quickly establish protective and therapeutic resistance. They are named according to the type of antibody they contain.

For example

■ **Antitoxic Serums:** Gas gangrene, diphtheria, tetanus and botulismus.

■ **Antibacterial Serum:** N. Meningitidis, anthrax and whooping cough.

■ **Antiviral Serum:** Mumps, hepatitis-B and rabies**.**

■ **Antivenom Serum:** Spider, scorpion and snake**.**

Hospital Infection: Infections that develop in the hospital or are transmitted in the hospital and occur after discharge. These are observed as isolated cases or epidemics, depending on the effectiveness of the measures to be taken for this purpose in the hospital, the qualities of the services, the condition of the patient, and the virulence and characteristics of the environmental microbes. It also causes significant financial losses as it prolongs hospital stay. It has been observed that 10% of hospitalized people develop infection.

7. OCCURRENCE OF HOSPITAL INFECTIONS

7.1. Host: Characteristics of the patient in the development of infection; Age (infancy and old age), reason for hospitalization, immunity status, trauma, nutritional status, medications taken, burns and whether the natural resistance functions properly are important.

7.2. Biological Environment: It refers to the pathogens that will cause hospital infection. These factors may be of exogenous or endogenous origin. When the person's normal flora decreases the person's resistance, it creates infections and it becomes difficult to prevent them.

External source: The healthcare worker's hands, dirty medical equipment and the hospital environment. These are called "hospital flora".

Characteristics of a flora: The types of medical treatment and antibiotics administered to patients in that hospital vary depending on geographical location and time (Aktas et al., 2019).

The factors that affect the patient's flora from hospital pathogens are; the person's flora is disrupted, the length of stay in the hospital, whether or not they use antibiotics, and the use of invasive medical equipment.

The factors that cause hospital infections are opportunistic pathogens that are resistant to antimicrobial drugs. For this reason, they are stubborn and cause infections that do not respond to treatment. These bacteria are intestinal bacteria, primarily Staphylococcus aureus and E. coli. In addition, various bacteria, parasites, viruses and fungi have been shown to be the cause of hospital infections.

7.3. Physical Environment

7.3.1. Medical Equipment: Endoscopy instruments, syringes, catheters and probes used on patients increase the risk. Instrumental interventions disrupt the integrity of the host's natural resistance barriers, the mucosa and skin, making it easier for microbes to enter. For this reason, great care should be taken in sterilization in such applications. In addition, the quality of the instrument used, the duration of application and the care of the instrument used for the procedure, and

the experience and skill of the person performing the procedure are important in disease risk.

7.3.2. Hand Washing and Cleaning: All kinds of microbes can settle and spread on hands and are easily transferred between patients and healthcare personnel. For this reason, a hand washing brochure has been prepared for patients, healthcare personnel and doctors. Hands are cleaned of microbes by rubbing and washing hands with soap and water for 10 seconds or more. If hand washing is not possible, the number **of** pathogens can be reduced with various antiseptics (chlorhexidine and alcohol). Antimicrobial soap can be used in special cases such as surgery**.**

Glove Use: Healthcare workers should wear sterile gloves in areas where the patient's mucosal skin integrity is disrupted (burns, cuts, wounds and scratches), in moist wet body areas and when using any type of instrument.

Hand Washing Guide in Healthcare Institutions

■ When entering and leaving the hospital

■ Before and after intensive contact with the patient.

■ Before instrumental application to the patient.

■ Before and after touching the patient's wound

■ Before patient care (immunocompromised and newborn babies)

■ After touching contaminated materials (stool, urine containers and catheters)

■ After touching body excretions (sputum, blood, urine, stool and after toilet)

7.3.3. Objects around the patient: Includes food, drink, air and microbes. Patients are in constant contact with this environment. The most important of these are air and water.

■ Devices such as steam machines, air conditioners, dialysis fluids and physical therapy tanks should be checked frequently.

■ Air is important in transmitting fungus, tuberculosis and chickenpox.

Visitors of patients do not follow the rules, carry microbes and are not aware that they are infecting the patient. Healthcare workers should also take precautions to reduce the risk of infection, adopt aseptic techniques and acquire the habit of hand washing.

7.4**. Social Environment:** Many people do not wash their hands even if they are extremely dirty and have a significant risk of disease. The lack of money to be allocated for disease control due to economic conditions also plays an important role.

8. INFECTIONS COMMONLY OBSERVED IN HOSPITALS

■ Urinary tract infection ■ Infection of surgical wounds

■ Pneumonia ■ Bacteremia

These constitute 80% of infections.

8.1. Urinary Tract Infection: Catheters are used in 10% of hospitalized patients. Therefore, it is the most common hospital disease

(E. coli) and constitutes 40%. The type of catheter and catheter, the way it is placed, the time it is used and its maintenance are effective in the development of the disease. Especially the length of time it is used creates a high risk of infection. In order to reduce infection, care should be taken to ensure sterility of the device and to use aseptic technique in its application. The device should be well maintained and its usage period should be minimized**.**

8.2. Surgical Wound Infections: It is seen in the second most common hospital infections (Gram (-) intestinal bacteria and Staphylococcus aureus) (22%). It is important in terms of aggravating the person's condition. In preventing surgical wounds; packaging, sterilization, special dressing, storage, ventilation and years of continuing education are important. In the wound; clean, clean-dish, dishwashing and dirty-infected are important data in the development of infection. In addition, those related to the development of surgical wound infection are; the person's hospitalization period before the operation and bath, shaving and cleaning of the operation area, application of antiseptic by brushing the surgeon's hand, the environment in the operating room, the duration of the operation, technique and closure of the wound**.**

8.3. Pneumonia: Its incidence (15%) is low. 80% of this table is gram (-) bacteria; Klebsiella, Pseudomonas and E.coli. S. aureus is the most common gram (+) agent.

Risk factors of nosocomial pneumonia are; old age, chronic lung disease, intubation-tracheostomy-mechanical ventilation, thoracic surgery, long-term hospitalization, intensive care, confusion, broad-

spectrum antibiotic administration and immunosuppression. In prevention, sterile breathing, equipment, solutions, attention to hand hygiene, use of gloves in approaching the patient and cleanliness of the inhaled air are important**.**

8.4. Bacteremia: Bacteria entering the blood and spreading. IV application is frequently done to patients. This is bypassing the skin resistance and entering the blood. In this process, pathogens enter the blood and facilitate the disease. The risk of bacteremia increases when any type of device in the vein remains in place. Protection; the devices applied should be sterile and with aseptic technique. There should be a suitable device and place selection. Its use should not exceed 48-78 hours.

8.5. Other Hospital Infections: Contagious infections may occur in the hospital and small or large epidemics may develop. Bacteria, viruses, parasites and fungi may be the causative agents. Soft tissue, diarrhea, skin and upper respiratory tract infections are considered among these.

9. CONTROL OF HOSPITAL INFECTION

The infection prevention committee should include an infectious disease specialist, microbiologist, surgeon, public health specialist, hospital administrator, pharmacist, nurse and staff representative and they should work in coordination. This committee should carry out activities such as patient isolation procedures, hospital order, appropriate and necessary material supply and personnel training.

What to Do to Prevent Hospital Infection

■ The patient should be monitored for hospital infection.

■ Disinfection and sterilization should be done according to the rules.

■ Waste material should be sterilized and eliminated.

■ Precautions should be taken for conscious antibiotic use.

■ Patients who can transmit the disease should be taken to a separate room and their care should be done by permanent healthcare personnel**.**

■ Patients with low immunity and serious conditions should be isolated, and special care should be applied in single rooms.

■ All kinds of instrumental applications to be performed on the patient (lancets, syringes, catheters, surgical instruments, probes and endoscopes) should be performed under sterile conditions, complying with antisepsis. The instruments applied should be single-use. In addition, instrumental interventions should not be performed unless necessary. The period of use should be short. The maintenance of the instruments used should be well. These applications should be done by experienced personnel.

■ The fluid, medicine, blood and blood products to be given to the patient should be sterile. In particular, blood and blood products should be checked for contagiousness (Hepatitis-B and C, Syphilis and AIDS tests). ■ External pathogens should be recorded and the hospital's visit times should be organized in a certain order. Following visits, the hospital should be disinfected with antiseptics**.**

CHAPTER 6

MICROBIOLOGICAL DIAGNOSIS METHODS

Introduction

The diagnosis of the disease is examined in two ways, clinical and laboratory. In microbial diseases, clinical examination and definitive diagnosis are made with laboratory tests. In infectious diseases, rapid and accurate diagnosis is important. When the diagnosis of the disease is delayed, treatment is also delayed. Therefore, there will be more contact and it will spread to people around and pose a danger.

Laboratory examinations are grouped under two headings.

Clinical Laboratory Test

Hematological Test: Peripheral blood smear, leukocyte count, hemoglobin amount, erythrocyte count and erythrocyte sedimentation rate.

Biochemical test: Microscopic and chemical examination of urine, C-Reactive protein and liver function test are considered. In addition, examination of the person's tissue piece in the pathology laboratory is also important in diagnosis. These tests do not show the microbial agent.

1. MICROBIOLOGICAL LABORATORY TESTS

Definitive diagnosis in infections is based on the agent. They are in two groups.

1.1. Direct Microbiological Diagnosis: It is performed to determine the microorganism that is the cause of the infection in the sample, to grow it and to prove that it is the agent that causes the disease. When a positive result is obtained, it has definitive diagnostic value**.**

1.2. Indirect Microbiological Diagnosis: It is performed to determine the specific immune response that develops in the living being against the antigen of the causative pathogen during the course of the infection. These are serological tests that determine the specific antibodies formed in the humoral immune response and skin tests that show the formation of a cellular immune response.

2. DIRECT MICROBIOLOGY DIAGNOSIS

A definitive diagnosis is possible by revealing the microorganism that is the causative agent of the disease. A sample must be taken from the infected person and sent to the laboratory, and this sample must be made by the officer under the supervision of the responsible physician. The samples to be taken from the infected person (such as sputum, urine, blood and stool) have their own method of collection. The samples taken for this purpose are presented here as a list.

Microbiological examination material

■ Eye sample ■ Nasal secretion ■ Sinus sample ■ Nasopharynx swab ■ Throat swab ■ Mouth rinse ■ Ear samples ■ Lower respiratory tract and sputum sample ■ Fasting gastric juice, which is the contents of the stomach ■ Duodenal and bile fluid ■ Feces ■ Urine ■Genital samples ■ Wound samples ■ Blood ■ CSF ■ Hair, skin scrapings and nails ■

Puncture samples; pleura, pericardium, peritoneum, joint fluid and aspiration fluid

3. EXAMINING PATIENT SAMPLES IN MICROBIOLOGICAL DIAGNOSIS

3.1. EXAMINATION OF SAMPLES IN MICROBIOLOGICAL DIAGNOSIS

3.2. Macroscopic Examination: Visual examination of samples is useful first. In diagnosing infection; turbidity of CSF in meningitis suspect and spider web formation at the bottom when left to stand; blue-green color of pus; bloody-mucous stool in diarrhea provide clues.

3.3. Microscopic Examination: It is done in two ways

3.3.1. Direct, Unstained, Fresh Examination: A small amount of the patient's sample is taken and placed on a slide and examined under a microscope without staining, fresh. Watery samples such as CSF and urine are first centrifuged and a fresh preparation is prepared from the sample taken from the sediment and examined. Here; the appearance of bacteria and leukocytes suggests the disease. In stool, when the direct sample is examined under the microscope, the appearance of parasites, erythrocytes and leukocytes is helpful in diagnosis. In sputum, pus and genital samples; examination is done fresh, without centrifuging**.**

3.3.2. Stained Microscopic Examination: A small amount of the patient's samples or the agent produced as a pure culture is taken and spread thinly on a slide to be detected. Then, it is stained with

appropriate staining methods and examined under a microscope. Gram staining method is mostly used in microbiology. In this staining, the presence of bacteria in the preparation, Gram (-) or (+), arrangement and shape can be observed.

Other Staining Purposes and Methods

■ **Ziehl-Neelsen (ARB:** Acid-Resistant Staining): It is applied in the staining of Mycobacterium tuberculosis, which is resistant to acid.

■ **Fungal Examination:** Samples are examined by treating them with a dye called cotton blue or with a 10% KOH solution.

■ **Silvering Method:** It is applied directly in the microscopic examination of bacteria (syphilis), which are spiral-shaped and do not take simple dyes.

■ **Fluorescent Staining:** Many pathogens can be observed directly in patient sample preparations with the fluorescent antibody (FAT) method.

■ **Parasite Stain:** Parasites are examined in tissue and stool with Eosin, Giemsa and Lugol**.**

4. CULTURE METHODS

The aim of diagnosing microbial diseases is to produce pure and identify the causative microorganism in samples taken from the person. For this purpose, the samples are planted in appropriate media as soon as they arrive at the microbiology laboratory. When the examination, for example, medium, growth temperature and duration, and oxygen

concentration of the investigated disease are kept under optimal conditions, causative pathogens are produced and identified. Microbes produced in patient samples (blood, urine and CSF) that are devoid of normal flora and must be sterile are largely disease agents. Infectious pathogens reproduce together with normal flora in samples such as sputum, stool and throat swab. The infectious agent produced as a pure culture is then subjected to an identification process to try to identify the microbe. The agent of the microbial disease is isolated and for effective treatment in diagnosis; an antibiotic sensitivity test is performed to determine the effective antibiotic..

5. WORKING PRINCIPLES FOR MICROBIOLOGY LABORATORY

In working with disease agents; examination sample, preparation created from these samples, cultivation, culture produced, table, floor, air and equipment are the source of the disease. Laboratory workers are primarily responsible for protecting themselves, their families and those around them. In addition, pure culture and medium should not be contaminated for the quality of the experiment.

Working Principles in Microbiology Laboratory

■ While working in the laboratory, a white and clean apron with long sleeves and length should be worn and the front should be buttoned. When working with an extremely infected sample, an operating room style apron tied at the back should be worn in addition. Mask, gloves and headgear should also be worn when necessary. When leaving, the

clothes worn should be removed and placed there.■ Do not move around the laboratory too much, do not create loud noise, do not sit on the tables, and external entrances by the employee should be prevented. ■ Smoking, eating and drinking are dangerous in the microbiology laboratory. ■ When working with infectious materials; the employee should not contaminate himself, the people around him and his environment. ■ Hands, fingers, pens, paper and other objects should not be touched to the face and mouth. Labels and envelopes should not be applied to the tongue and wetted. ■ Hands should be washed frequently with soap, rubbed and washed. Then they should be disinfected with antiseptic solution. ■ Long beards, hair, moustaches and nails facilitate contamination. ■ Disruption of skin integrity such as cuts, wounds, burns and eczema increases the risk of infection. ■ The tools used should be well-maintained and clean. Water, gas, vacuum taps and electricity should be checked when the work is finished or when leaving the laboratory. ■ Used and contaminated tubes, coverslips, slides, pipettes, tubes and other equipment should be placed in designated disinfectant containers. Loops should be burned before and after the procedure and should not be left lying around. Tubes or petri dishes contaminated with microbes should not be placed openly on the table. Cultured material should not be left in the pocket of a shirt. ■ Hazardous materials and cultures should not be taken outside the laboratory.■ Equipment whose sterility is questionable should not be used. ■ Laboratory accidents should be reported to the relevant parties. When contaminated material is spilled on the floor or table, it should be covered with a disinfectant cloth and plenty of disinfectant should be

added. It should be left for a few hours and then cleaned. If clothes are contaminated, they should be washed by autoclaving. ■ There should be no insects and flies, and they should be combated. ■ Regular disinfection and cleaning should be done in the microbiology laboratory. ■ Records of the studies should be made accurately, completely and on time.

6. INDIRECT MICROBIOLOGICAL DIAGNOSIS METHODS

It is difficult and not always possible to show, produce and reveal the agent in diagnosing the infection. In these cases, revealing the specific immune response that develops in the living being for the agent during the illness is useful for diagnosis.

7. THE PLACE OF SEROLOGICAL TESTS IN MICROBIOLOGICAL DIAGNOSIS

Since the discovery of the immune response, serological tests that reveal the specific antibody developed for the agent in infectious diseases have been used in diagnosis. It is used to search for microbe antigens, not only specific antibodies. In addition, these tests are applied not only in serum but also in other body fluids or secretions when necessary. The Test Based on Combination of Antigen and Antibody is Used for Two Purposes in Microbiology. ■ It is the search for specific antibodies in the patient's CSF, serum and other body fluids using the known antigen of the disease agent.■ These are tests performed to search for and identify antigens using known antibodies (Antigen search). In infection, antibodies begin to develop at the end of

incubation, increase in disease, and remain high for a while after recovery. Afterwards, the antibody level decreases. However, in some diseases, it can be observed throughout life. There is IgM in the acute phase of the disease and IgG antibody afterwards. For this reason, with a sensitive serological test; it shows the infection that has been passed in the determination of specific IgM. In serological tests where the immunoglobulin class is not determined; antibodies should be searched in two serum samples, one at the beginning of the disease and the other in the recovery period (2-3 weeks apart). An increase in antibody in the test in two sera is in favor of the diagnosis of the disease. When the test is performed on a single serum sample, a very high antibody makes the diagnosis. Determining the antibody level is also important in serological tests. For this reason, in most infections, the serum is diluted to determine the antibody titer. For example; first, the serum is halved (1/2), then the titration is made by diluting (physiological serum) and titrating to 1/2, 1/4, 1/8, 1/16, 1/32, etc. If no reaction occurs in the dilution as a result of the test, the test is considered (-) negative and it means that the antibody sought is not present. If there is a reaction in the serological test tube, there is an antibody. The dilution of the last tube in which the reaction is observed is the antibody titer of that serum (such as 1/80).

7.1. Agglutination Test: When erythrocytes and bacteria-like cells encounter antibodies against Ag on their surface, they cluster. In addition, the desired Ag is glued to bentonite, latex-like synthetic particles. When these structures encounter their specific antibodies, they form visible clusters. This is called latex agglutination. If the cell

that clusters in the agglutination test is an erythrocyte, this test is called hemagglutination. Agglutination tests are performed by adding a drop of patient serum and a drop of Ag solution to the slide and mixing, and this is called slide agglutination. For example; RF, CRP and latex slide agglutination. These tests give results in 1-2 minutes. Tube agglutination test is more sensitive. Serum is diluted in a serological test tube. Ag is added and incubated for a while. The results in the tube where agglutination is observed are expressed as titers. For example; Such as Wright agglutination in Brucellosis and Gruber-Widal agglutination in Salmonellosis. Examples of hemagglutination tests are; determination of blood group and cold agglutination in atypical pneumonia. In addition, there is an agglutination test named after him in many infectious diseases, such as the Listeria agglutination test**.**

7.2. Precipitation Test: When water-soluble, particle-shaped Ag combines with antibodies, turbidity and then sedimentation are the main principles. This test is performed in a tube with dilution. However, the most commonly applied one is precipitation performed in an agar or gel. Specially prepared agar or gelatin is poured onto a slide or petri dish and frozen. Small holes are opened in the agar. Antibody (patient serum) is placed in one of the holes and Ag in the other. Both diffuse in the agar. A white, turbid precipitation band develops in the area where they meet. In the precipitation test performed in agar, when low voltage electric current is applied, the diffusion of antibody and Ag accelerates, thus shortening the test duration. This is called electroimmunodiffusion.

7.3. Complement Combination Test: It is applied in determining the antibody (IgM and IgG) that binds the complement. For example; Weinberg, which is applied in the diagnosis of hydatid cysts, and Kolmer in syphilis. 7.4. Labeled Antibody Test: It is aimed at searching and detecting the other by using one of the known antibodies and antigens with specific binding. With labeled antibody tests, the presence of antigen or antibody, even if small, is shown, measured and which antibody is sought (IgG, M and A) is determined. In this case, it creates reliable information about the acuteness or chronicity of the disease. Here; FAT, radioimmunoassay (IUD) and enzyme-immunoassay (EIA) techniques are used. Its basic principle is; the known antigen (FAT on a slide, on the inner surface of microplate wells or polystyrene tubes in IUD and EIA) is detected on a fixed surface beforehand. The patient serum for which the antibody is sought is placed in the medium. In the presence of the antibody sought in the serum, it can combine with the detected, bound antigen. In the antibody-antigen combination, the second antibody with a label is added to the medium and its binding to the immune structure is ensured. Then, the binding of the antibody with the label (the antibody is easy to measure since it is labeled) is measured and the experiment is evaluated. If there is no antibody sought in the serum, the immune complex will not form and it will not bind with the labeled antibody added later. When those that cannot be bound by washing are removed from the environment in the experiment, the labeled antibody cannot be determined during the measurement. The absence of the labeled antibody indicates that the specific antibody sought is not present, that is, the experiment is

negative. The labeled antibody applied in this experiment is called a conjugate. Radioactive substance, enzyme and fluorescent dye are used to label the antibody. The experiment names are also given according to the marker (FAT, EIA and RIA).Enzim İmmün Assay. To reveal the combination of the sought antibody with the antigen, an enzyme-labeled secondary antibody is used. This secondary antibody in the structure of the enzyme-labeled anti-immunoglobulin is attached to the immune complex. When the substrate on which the enzyme acts is added to the medium, the color development is measured and evaluated by special EIA readers, which are basically spectrophotometers. EIA is used to diagnose many microbial diseases. It has brought innovation and convenience to the microbiology laboratory in the search for specific antibodies and the detection of microbe antigen, especially in fungal, bacterial, parasitic and viral infections that are difficult to show with culture and microscopy methods. In addition, EIA is an immunological test used in the determination of drug levels, hormones and tumor markers.

Radio Immun Assay (RIA): In this experiment, an antibody labeled with a radioactive substance is added to the experiment to detect antibody-antigen combination. The result of the experiment is evaluated sensitively in a device called Gamma Coonter, which measures radioactive substances. The places where it is used are the same as EIA.

Fluorescent Antibody Test: Antibody labeled with fluorescent dye is used. The result of the experiment is evaluated under a fluorescent microscope. The area used is the same as RIA and EIA.

8. SKIN TEST: It is the investigation of the existence of a previous immune response in the organism for this Ag by applying liquid Ag into the skin and performing an allergy test. Positivity in this test indicates that the person has previously encountered the Ag tested for. However, skin tests do not report the time of exposure to Ag or microbe (skin test is positive (+) throughout life in many microbial diseases). For this reason, the result of the skin test should be evaluated in addition to laboratory and clinical findings.

Skin test is done for two purposes

■ First: Detection of anaphylactic type hypersensitivity reactions. It results in 5 - 30 minutes and is used to detect the allergen.

■ Second: Cellular type shows hypersensitivity and results in the most urgent 24 hours. It is used to diagnose the infection. These are; Casoni skin test in hydatid cyst and PPD in tuberculosis.

CHAPTER 7

IMMUNOTHERAPY DRUGS

INTRODUCTION

1. IMMUNE SYSTEM SUPPRESSIVES APPLIED IN ORGAN TRANSPLANTATION

"Tissue rejection" in organ transplantation is a response of the body's protective system for foreign material. Antigen, antibody and T lymphocyte are responsible for the protective reaction shown for the transplanted tissue. This situation, which is beneficial for the recovery of the patient in infections, poses a danger to life in tissue transplantation. For this reason, drugs that prevent the immunological response that causes rejection in organ transplantation should be used.

Treatment with **Immunosuppressants**: Weakens the immune defense of the living being,

■ Significantly increases the formation of superinfection in the patient. During treatment; blood analysis, pulse, blood pressure and fever should be checked and signs of viral, bacterial and mycotic superinfection should be investigated. A hygienic environment should be created for the patient. In this case, cancer formation, autoimmune disorders and drug metabolism disorders increase (Aktas et al., 2025).

1.1. Cyclosporine: It acts by inhibiting the activity of the T-cell. It is applied in combination with corticosteroids and other drugs. It inhibits the production of some cytokines, including IL-2 production from the

T lymphocyte. It enters the cytoplasm of the T lymphocyte. Here, it attaches to an immunophilin called cyclophilin, which is an enzyme. In addition to IL-2 production, it also destroys cytokines involved in tissue rejection, such as IL-3 and IL-4, GM-CSF and TNF.

Application

■ Organ transplantation; liver, heart, kidney and KI transplants. It is used together with prednisolone to prevent tissue rejection. ■ Nephrology, to treat the second stage of nephrotic syndrome with glomerular lesions,

■ Dermatology, to treat widespread and severe psoriasis resistant to other treatments, ■ Rheumatology, to treat very active and severe forms of rheumatoid arthritis,

Effect: Arterial hypertension and renal failure (Anonymous, 2020d Yan).

1.2. Tacrolimus: Its mechanism of action is the same as cyclosporine. It inhibits T-cell function and prevents liver damage. But instead of cyclophilin, it attaches to a protein called FK binding protein (FKBP). Tacrolimus-FKBP complex prevents the formation of Nuclear factor of activated T cell (NF-AT). It inhibits early calcium-dependent T cell activation and cytokine production after T lymphocyte stimulation. While it inhibits T cell proliferation, IL-2, IL-3, IL-4, IFN-γ, TNF and GM-CSF production, it does not disrupt the T cell's response to this cytokine.

Application

■ Against organ transplant rejection. ■ In liver transplantation, together with low-dose steroids, it is effective in primary maintenance immunosuppression treatment.■ In treating psoriasis and focal glomerulosclerosis, ■Ointment, in the treatment of end-stage psoriasis and atopic dermatitis

Side Effect: Impairment of kidney function, risk of diabetes, hyperkalemia and lymphoma formation (Anonim, 2020d).

1.3. Rapamycin: It creates an effect by inhibiting some cells responsible for immunity. It is also used with tacrolimus and cyclosporine. It shows a different effect in spite of binding to the protein called FKBP 12. It cannot inhibit IL-production, but it prevents its effect from occurring.

■ It is used to prevent tissue rejection in kidney transplantation.

Side Effect: Its nephrotoxicity is lower than other immunosuppressants, but it causes significant pneumocystis, hypertriglyceridemia and carinii **(**Aktaş and Bilgic, 2025a; Anon, 2022d).

1.4. Glucocorticoids: They show this by inhibiting the expression of genes that regulate cytokine production. They also suppress the pre-inflammatory period of the immune reaction non-specifically. They prevent the secretion of cytokines by T lymphocytes and thus the initiation of cellular immunological reactions. They prevent the activation of the complement system, which contributes to the

formation of immunological inflammatory reactions. In this context; prednisolone and prednisone are applied.

■ It is also effective in the treatment of graft versus host disorder that develops in KI transplantation.

Side Effect: In long-term maximum dose application, symptoms such as Cushing's, adrenal cortex shrinkage, disease resistance and digestive tract mucosal ulcers and bleeding are observed**.**

1.5. Mizoribine: Imidazole type nucleoside antibiotic. It causes RNA and DNA inhibition in purine biosynthesis. It is effective in cellular **and** humoral immune response. Prednisolone, mizurbine and cyclosporine application are effective in immunosuppression treatment.

1.6. Deoxypergualin: It is an antitumoral antibiotic obtained from B. lateroporus. Its effects are; suppression of macrophage functions, blocking of IL-1 synthesis and prevention of free oxygen radical formation in monocytes, reduction of class II antigen expression in splenic macrophage and suppression of cytotoxic T lymphocyte proliferation.

Application: When applied together with methylprednisolone, it is 80-90% effective in kidney allograft rejections.

Side Effect: KI suppression.

1.7. Mycophenolate: Prevents cell proliferation by inhibiting the enzyme in DNA synthesis. It prevents the development of new lymphocytes in the activation of immunity. It is an antifungal drug that

prevents the de novo production of purine bases. It inhibits the inosine monophosphate dehydrogenase enzyme, which is involved in purine production in B and T lymphocytes. It suppresses the reproduction of B and T lymphocytes and reduces the production of cytotoxic T lymphocytes.

■ It is applied to people with acute rejection or those prone to rejection.

■ It is effective in cases of acute tissue rejection resistant to corticoids.

■ It is applied in liver transplantation.

Side Effect: It causes an excessive decrease in platelets and erythrocytes along with lymphocytes due to the suppression of KI.

1.8. Azathioprine: It is applied in organ transplantation and autoimmune disorders such as purpura, rheumatoid polyarthritis and lupus**.**

2. IMMUNESTIMATORS

They are substances that strengthen the defense of the living being against AIDS, KI depression, neoplasm and chronic infections that develop in the absence of immunity.

2.1. Synthesis Compound

Levamisole: Directly stimulates lymphocytes, macrophages and granulocytes. Increases their secretion, movement and reproduction. It is more effective on cellular immunity compared to humoral immunity.

In order for the immunostimulatory effectiveness to be apparent, it should be applied with an antigen-like stimulant.

Application:

■ Recurrent viral herpes, cancer and leprosy,

■ Hodgkin's disease, colorectal cancer and rheumatoid polyarthritis,

■ For colon cancer; It is applied in adjuvant treatment with fluorouracil after surgical removal of the tumor**.**

Side Effect: Immuno-allergic reaction (agranulocytosis, dermatosis and vascularitis) and renal dysfunction (nephropathy with proteinuria).

2.2. Bacille calmette guerin (BCG): Live strain of M. bovis. Stimulates cellular immunity (T cell).

Application: In the treatment of intravesical bladder cancer.

Side Effect: Shock and fever.

2.3. Immunoglobulin: Immunoglobulin (Ig) obtained from healthy human serum,

Application

■ As a protector in supporting humoral defense,

■ Hepatitis B and A, rubella (pregnant women), measles, chickenpox, mumps and polio,

■ Antibody deficiency due to immunosuppression and cytostatic treatment,

■ Protein loss due to nephrological and hematological disorders and burns,

■ Primary humoral immune deficiency is applied.

Immunoglobulin Given for Therapeutic Purposes:

■ Gammaglobulin 5%, ■ Immunoglobulin G, ■ HB's antibody,

■ Tetanus immunoglobulin, ■ Rabies immunoglobulin,

■ CMV immunoglobulin, ■ Varicella zoster immunoglobulin,

■ Anti Rho Ig

Side Effect: Anaphylaxis (Rarely).

2.4. Growth Factor: The self-renewal and transformation of blood cells is driven by the hematopoietic growth factor called colony stimulating factor (CSF). The growth factor applied in anticancer treatment is (Aktas and Yahyazadeh, 2022),

■ Granulocyte macrophage (GM)

■ CSF

Molgramostim (GM-CSF): It is a glycoprotein secreted by macrophages, T lymphocytes, endothelial cells and fibroblasts. It increases the production of macrophages, neutrophils and eosinophils.

Application:

■ It accelerates the recovery of myeloid structure after KI transplantation,

■ It is applied to treat leukopenia developed with chemotherapy.

Side Effects: Pain in the bone, splenomegaly, flu, precardiac and pleural adhesion, increased tumor growth (Yarsan and Aktas, 2012).

Filgrastim (G-CSF): Human granulocyte colony stimulating factor produced using E. coli and recombinant DNA technology. It affects CI and causes white blood cell growth and development.

Application:

■ In treating neutropenia developing after myelosuppressive chemotherapy in cancer patients, ■ Neutropenia, ■ KI transplantation, ■ Congenital agranulocytosis, ■ Leukemia, ■ AIDS, ■ Myelodysplastic syndrome. ■ In reducing the side effects of the drug on white blood cells

Side Effect: Pain in the bone, pain during urination, increase in the biological parameter dehydrogenase lactate and alkaline phosphatase activity.

2.5. Interferon: They are glycoprotein cytokines that prevent viral division. There are 3 main groups of interferons that are immune stimulatory and prevent proliferation.

■ IFN-α obtained from leukocytes, ■IFN-b obtained from fibroblasts,

■ γ-IFN obtained from sensitive lymphocytes, driven by antigen.

Interferon is broad-spectrum and antiviral. The effect starts with binding to a specific receptor on the cell and stimulates the production of the cell protein that interacts with multiplication. Interferon interacts

with the virus by decapsidation, penetration, mRNA production and methylation, viral protein translation and virus accumulation and secretion. The main effect is to prevent protein translation. This event is due to the catalyzing of the production of 2.5-oligoadenylate, which breaks down the viral mRNA and activates ribonuclease.

Interferon α 2a and IFN α 2b in Treatment:■ Hepatitis B, C and D, ■ Condyloma, ■ Papilloma, ■ Viral laryngeal juvenile papillomatosis, ■ Hairy cell leukemia, ■ Malignant melanoma, ■ AIDS ■ Kaposi's sarcoma, ■ Chronic myeloid leukemia, ■ Metastatic kidney cancer, ■ Basal cell carcinoma

Side Effect: Pseudoflupal syndrome, cardiac arrhythmia and neuropsychiatric disorder.

2.6. Interleukin 2: T cell growth factor. It is dissolved in plasma in various disorders such as tumor, immunological or bacterial, viral and parasitic. It is an IL-2 receptor. IL-2 is obtained by gene cloning and is called recombinant IL-2.

Application:

■ Treatment of metastatic kidney cancer and melanomas.

Side Effect: Side effect is dose-related. Infarction-like cardiac disorder.

2.7. Erythropoietin: Increases reticulocyte count and accelerates hemoglobin production. Effective on maturation stages of erythrocytes in KI and peripheral blood.

Application:

■ Anemia of non-renal origin, ■ Increasing the patient's blood reserve before surgery, reducing the need for blood transfusion and accelerating erythropoiesis after surgery, ■ Elimination of premature anemia, ■ Anemia observed before and after kidney transplantation, ■ Cancer, ■ Myeloma, ■ AIDS, ■ Proximal nocturnal hemoglobinuria, ■ Treatment of anemia observed in arthritis and sickle cell anemia.

Side Effect: Arterial resistance, platelets, blood viscosity, increase in erythrocyte mass, arterial hypertension, medullary fibrosis, bone pain, hyperkalemia, and thrombosis risk develop.

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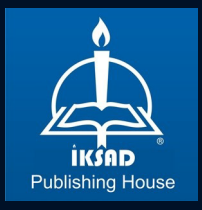

ISBN: 978-625-378-569-7