**Lecture 1.**

**Medical microbiology and immunology, its goals and objectives, stages of development. Systematics and classification of microorganisms. Classification of bacteria.**

 **The purpose of the lecture:**to inform students about the subject of microbiology and immunology, sections, goals and objectives, its place in medical education, its importance for medical practice, to acquaint them with the history and stages of development of microbiology, to explain microorganisms, their main groups, systematics and classification principles. To inform students about the classification of bacteria.

 **Lecture plan:**

1. Introduction to microbiology and immunology, its place in medical education, its importance for medical practice

2. Sections, goals and objectives of the subject

3. Stages and history of development

- The first ideas about microorganisms (period of hypotheses)

- Preliminary evidence of the presence of microorganisms (morphological period)

- Study of the life activity of microorganisms, works of L.Pasteur and R.Koch (physiological period)

- Detection of protective factors of the organism, works of I.I.Mechnikov and P.Erlich (immunological period)

- Modern stage of development of microbiology (molecular-genetic period)

- Development of microbiology in Azerbaijan

4. Modern principles of classification of microorganisms. The main groups of microorganisms. Prokaryotes (bacteria, spirochetes, actinomycetes, rickettsiae, chlamydia, mycoplasmas), eukaryotes (protozoa, fungi) and viruses.

5.Taxonomy and taxonomic categories: kingdom-phylum-class-order-family-genus-species-subspecies. As a species-major taxonomic category. The concept of the categories of subspecies: biovar, serovar, fagovar. Concepts of culture, strain, clone. Nomenclature of microorganisms.

6. Bergey`s Manual of prokaryotes

 It is important to realize that our knowledge of the microbial world is evolving continually. Just as the early microbiologists built their discoveries on the foundations established by their predecessors, present and future generations will continue to discover new microbes, new diseases, and new therapies. The following chapters are intended as a foundation of knowledge that can be used to build your understanding of microbes and their diseases.

 Imagine the excitement felt by the Dutch biologist Anton van Leeuwenhoek in 1674 as he peered through his carefully ground microscopic lenses at a drop of water and discovered a world of millions of tiny "animalcules." Almost 100 years later, the Danish biologist Otto Muller extended van Leeuwenhoek's studies and organized bacteria into genera and species according to the classification methods of Carolus Linnaeus. This was the beginning of the taxonomic classification of microbes. In 1840, the German pathologist Friedrich

Henle proposed criteria for proving that microorganisms were responsible for causing human disease (the "germ theory" of disease). Robert Koch and Louis Pasteur confirmed this theory in the 18 70s and 18 80s with a series of elegant experiments proving that microorganisms were responsible for causing anthrax, rabies, plague, cholera, and tuberculosis.

 Other brilliant scientists went on to prove that a diverse collection of microbes was responsible for causing human disease. The era of chemotherapy began in 1910, when the German chemist Paul Ehrlich discovered the first antibacterial

agent, which was a compound effective against the spirochete that causes syphilis. This was followed by Alexander Fleming's discovery of penicillin in 19 2 8, Gerhard Domagk' s discovery of sulfanilamide in 1935, and Selman Waksman's discovery of streptomycin in 1943. In 1946, the American microbiologist John Enders was the first to cultivate-:viruses in cell cultures, leading the way to the large-seale production of virus cultures for vaccine development. ThQusands of scientists have followed these pioneers, each building on the foundation established by his or her predesessors, and each adding an observation that expanded our understanding of microbes and their role in disease.

 Our knowledge and practice of microbiology is undergoing a remarkable transformation founcled in the rapid technologic advances in genome analysis. Molecular diagnostic tests have been simplified and are sufficiently inexpensive to allow rapid detection and identification of organisms. Previously unappreciated insights about pathogenic properties of organisms, taxonomic relationships, and functional attributes of the endogenous flora are being revealed. The complexity of the medical microbiology we know today rivals the limits of the imagination. We now know that there are thousands of different types of microbes that live in, on, and around us, hundreds of which cause serious human diseases.

 To understand this information and organize it in a useful manner, it is important to understand some of the basic aspects of medical microbiology. To start, microbes can be subdivided into the following five general groups: viruses, bacteria, archaebacteria, fungi, and parasites, with each having its own level of complexity. Archaebacteria do not seem to cause disease but arthropods may have a disease-causing relationship with man, and they are discussed in this book.

 **Fungi**

 In contrast to bacteria, the cellular structure of fungi is more complex. These are **eukaryotic** organisms that contain a well-defined nucleus, mitochondria, Golgi bodies, and endoplasmic reticulum. Fungi can exist either in a unicellular form **(yeast),** which can replicate asexually, or in a filamentous form **(mold),** which can replicate asexually and sexually. Some fungi have a mold form in the environment and a spherical form in the body at 37° C. These are known as **dimorphic** fungi and include such organisms as *Histoplasma, Blastomyces,* and *Coccidiodes.* Fungal infections range from benign skin infections to life-threatening pneumonias, sepsis, and disfiguring diseases. Most fungi are effectively controlled by host immunity and can reside within an individual for a lifetime, but these same fungi can cause serious disease in the immunocompromised host. Antimicrobial therapy addresses unique metabolic pathways and structures of the fungi but may be toxic and requires lengthy treatments. As with bacteria, extensive use of antifungal agents in the hospital setting has resulted in the emergence of yeasts and molds that express

intrinsic and acquired resistance to several different classes

of antifungal agents.

 **Bacteria**

 Bacteria are deceptively simple in structure. They are prokaryotic organisms, which are simple unicellular organisms with no nuclear membrane, mitochondria, Golgi bodies, or endoplasmic reticulum, that reproduce by asexual division. Most bacteria have either a gram-positive cell wall with a thick peptidoglycan layer, or a gram-negative cell wall with a thin peptidoglycan layer and an overlying outer membrane. Bacteria, such as *Mycobacterium tuberculosis* have more complex cell walls and others lack this cell wall structure and compensate by surviving only inside host cells or in a hypertonic environment. The size (1 to 20 μm or larger), shape (spheres, rods, and spirals), and spatial arrangement (single cells, chains, and clusters) of the cells are used for the preliminary classification of bacteria, and the phenotypic and genotypic properties of the bacteria form the basis for the definitive classification.

 We live in a microbial world with microbes in the air we breathe, the water we drink, and the food we eat, many of which are relatively avirulent but some of which are capable of producing life-threatening disease. The human body is inhabited by thousands of different bacterial species, with some living transiently and others living in a permanent parasitic relationship. This population of microbes residing in our intestines and on our skin and other mucoepithelial surfaces (called the “human microbiome”) act almost as an organ of the body. Each of us harbor a unique microbiome, which, similar to a fingerprint, has similarities but individual differences. Although influenced by our genetics and policed by our immune system, the microbiome is sensitive to the environment, our diet, and the antibiotics and other drugs we take. As genetic analysis methods become faster and cheaper, the influences of specific types of microbes within the microbiome on our immune system, metabolism, drug metabolism, behavior, and general health are uncovered. The near future will see increased use of therapeutic manipulation of the intestinal microbiome with fecal transplants beyond the current treatment of recurrent *Clostridium difficile* colitis to correct inflammatory bowel disease, type 2 diabetes associated metabolic syndrome, and other diseases.

 Bacterial disease can result from the toxic effects of bacterial products (e.g., toxins) or when bacteria invade normally sterile body tissues and fluids. Some bacteria are always pathogenic, expressing virulence factors that cause tissue damage, here as others cause disease by stimulating inflammation, and many do both. Proper identification of the infecting bacteria allows for prediction of the disease course and appropriate antimicrobial therapy. Unfortunately, inappropriate use of antimicrobials and other factors have led to the selection of multiply antimicrobial-resistant bacteria that cannot be treated.

 **Biologic Relationships of Pathogenic Microorganisms**



• The agents of human infectious diseases are **bacteria, fungi (yeasts and molds), protozoa, helminths (worms),** and **viruses.**

• Bacterial cells have a **prokaryotic** nucleus, whereas human, fungal, protozoan, and helminth cells have a **eukaryotic** nucleus. Viruses are not cells and do not have a nucleus.

• Ali cells contain both DNA and RNA, whereas viruses contain either DNA or RNA, but not both.

• Bacterial and fungal cells are surrounded by a rigid cell wall, whereas human, protozoan, and helminth cells have a flexible cell membrane.

• Most bacteria have cell walls that contain **peptidoglycan,** whereas the fungal cell wall contains chitin.

** Comparison of Medically Important Organisms**

 **Characteristics of Prokaryotic and Eukaryotic Cells**

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 **Viruses**

Viruses are the smallest infectious particles, ranging in diameter from 18 to 600 nm (most viruses are <200 nm and cannot be seen with a light microscope). The genome of human viruses consists of either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA). The viral nucleic acids required for replication are enclosed in a protein shell with or without a lipid membrane envelope. Viruses are true parasites, requiring host cells for replication. The cells they infect and the host response to the infection dictate the nature of the clinical manifestation. More than 2000 species of viruses have been described, with approximately 650 infecting humans and animals. Infection can lead either to rapid replication and destruction of the cell or to a long term chronic relationship with possible integration of the viral genetic information into the host genome. The factors that determine which of these takes place are only partially understood.

Viral disease can range from the benign common cold to life-threatening Ebola, with acute, chronic, and even cancer-pro JTioting presentations. The immune response provides both protection and pathology and may be the primally cause of illness. Often initiated with nonspecific flulike symptoms caused by host responses to the virus in the blood, viral disease is characterized by the target tissue(s) infected by the virus. Classic symptomatology guides diagnosis with confirmation by isolation in cell culture, detection of viral components, or antiviral immune responses with a prominent role for genetic detection and sequencing. Treatment has advanced so that there is now a tolerable cure for hepatitis C virus and lifelong maintenance of human immunodeficiency virus (HIV) infections. New vaccines have reduced the risk for several viruses, and vaccines for human papillomavirus and hepatitis B virus are also preventing cancers.

 **Parasites**

 Parasites are the most complex microbes. Although all parasites are classified as eukaryotic, some are unicellular and others are multicellular. They range in size from tiny protozoa as small as 4 to 5 μm in diameter (the size of some bacteria) to tapeworms that can measure up to 10 m in length and arthropods (bugs). Indeed, considering the size of some of these parasites, it is hard to imagine how these organisms came to be classified as microbes. Their life cycles are equally complex, with some parasites establishing a permanent relationship with humans and others going through a series of developmental stages in a progression of animal hosts. Parasitic disease is diagnosed by symptoms, a good patient history, and detection of the microbe. Helpful hints are obtained from the travel and dietary history of the patient, because many parasites are unique to different global regions. Therapies exist for some but not all parasites, and the development of resistance to antiparasitic agents complicates the prevention and treatment of many infections involving parasites.

 **Immunology**

 It is difficult to discuss human microbiology without also discussing the innate and immune responses to the microbes. Our innate and immune responses evolved to maintain our normal flora microbiome and protect us from infection by pathogens. Physical barriers prevent invasion by the microbe; innate responses recognize molecular patterns on the microbial components and activate local defenses; and specific adapted immune responses target invading microbes for elimination and block their toxins. Unfortunately, the immune response is often too late or too slow to prevent or limit the spread of the infection. The ensuing war between the host protections and microbial invaders escalates and, even when successful, the inflammatory response that results often contributes to or may be the cause of the symptoms of the disease. To improve the human body’s ability to prevent infection, the immune system can be augmented either through the passive transfer of antibodies present in immunoglobulin preparations or through active immunization with components of the microbes (vaccines). Ultimately, the innate and immune responses are the best prevention and cure for microbial disease.

 **Diagnostic Microbiology**

 The clinical microbiology laboratory plays an important role in the diagnosis and control of infectious diseases. Newer molecular, proteomic, and immunologic technologies are being used to enhance the information that the laboratory can provide.

 Many of the diagnostic tests require viable samples, and the quality of the results depends on the quality of the specimen collected from the patient, the means by which it is transported from the patient to the laboratory, and the techniques used to demonstrate the microbe in the sample.

 In addition, the collected specimen must be representative of the site of infection and not contaminated during collection with other organisms that colonize skin and mucosal surfaces. Antimicrobial susceptibility determinations require viable and representative microbes purified from the clinical sample. Knowing the minimal inhibitory or biocidal concentrations for specific drugs is important for prescribing the best treatment. The procedures for genome and antigen analysis have become less expensive and available for more pathogens. These procedures may not require viable samples. These assays are very sensitive and specific and can speed up the analysis.

 **Microbiology and Immunology in the Clinic**

 Relatively few organisms are classified as always pathogenic (e.g., rabies virus, *Bacillus anthracis*, *Shigella*, *Sporothrix schenckii*), whereas some establish disease only under well-defined circumstances or under certain conditions (e.g., opportunistic infections of immunocompromised individuals). Some diseases arise when a person is exposed to organisms from external sources, which is called an **exogenous infection** (e.g., influenza virus, *C. tetani, N. gonorrhoeae, Coccidioides immitis,* and *Entamoeba histolytica),* but most human diseases are produced by organisms from the person’s own microbial flora that spread to normally sterile body sites (e.g., blood, brain, lungs, peritoneal cavity) in which disease can ensue **(endogenous infections).** Some infections cause a single well-defined disease, which is oftentimes caused by the action of a virulence factor, such as a toxin (e.g., *C. tetani* [tetanus]), whereas others can cause several manifestations of disease (e.g., *Staphylococcus aureus* causes endocarditis, pneumonia, wound infections, food poisoning). The same disease can also be caused by different microbes (e.g., meningitis can be caused by viruses, bacteria, fungi, and parasites). By understanding the characteristics of the microbe and the host’s response to infection, a Sherlock Holmes–like approach can be applied to the microbial villain to solve the clinical infectious disease case. In addition, proper precautions can be taken to protect oneself and others from infection, and a sensible approach to prescribing appropriate therapy can be designed. Although the distinction of bacterial, viral, fungal, and parasitic infections can oftentimes be made from the history and physical presentations of the patient, certain laboratory tests can help focus the diagnosis.

For example, bacterial infections are often accompanied by increases in serum levels of C-reactive protein and procalcitonin, which are components of an inflammatory response. Once a differential diagnosis (a list of most probable villains) is obtained, then confirmatory tests can identify the disease-causing microbe, introduce the different types of tests and their application to each of

the microbes to be discussed. In addition to knowing the most appropriate test for a microbe or microbial syndrome, it is also important to know the limitations, sensitivity, and specificity of the tests.

 More and more individuals are living with immunodeficiencies caused by treatments for cancer, autoimmune diseases, or infections (e.g., AIDS). These individuals become susceptible to infections caused by less virulent or nonvirulent microbes that do not affect other individuals. The importance of the deficient immune response becomes very apparent for protections against these microbes. Bacterial disease is usually determined by the microbe’s virulence factors. For some, it is a one–one correspondence, such as for toxin-producing *Corynebacterium diphtheriae, Vibrio cholera,* and *C. botulinum*. For others, the disease may result from colonization, toxic by-products, or the immune and inflammatory responses to the microbe. Immune and inflammatory responses are triggered by structures of the microbe. Repetitive microbial structures provide pathogen-associated molecular patterns that induce innate responses, whereas specific structures are recognized by the immune response. In addition, extracellular bacterial and fungal structures usually trigger the activation of a cascade of soluble proteins of the complement system, which recruits macrophages and neutrophils to the infection site, initiates inflammation, activates antibody production, and generates a molecular membrane pore in the microbe.

 Intracellular infections, including viruses, bacteria, fungi, and parasites, require a different immune response, and the consequences are also different. Human cells respond to an intracellular microbial infection by shutting down cellular processes and by activating cytolytic cellular responses (natural killer [NK] cell, T cell, and macrophage responses) that kill or wall off the infected cells. Antibody is generated to inactivate toxins, to prevent binding of the microbe, and to facilitate its uptake and clearance by macrophages and neutrophils. The nature of the disease and susceptibility of an individual to a pathogen is determined by how soon the protective response can act on the infection, the efficacy of the response, and the immunopathologic consequences of that response. Inflammation accompanies most immune responses and sometimes it is just as important to treat the inflammation as it is to treat the infection to reduce the severity of the disease.

 The fourth question should take considerable thought:Should the microbe be treated and, if so, what is the best treatment? Designing appropriate therapy is necessary for those infections that do not resolve on their own. Although safe, antibiotic treatment can disrupt the normal flora which may allow more pathogenic bacteria or fungi to take their place. Proper therapy requires getting enough of the right antimicrobial drug to a sensitive target within the microbe

at the site of infection in the body. The antimicrobial potency and spectrum of activity and the pharmacologic properties of the drug are determined by the structure and mode of action of the drug. Microbes may be naturally resistant,

mutate, or acquire genetic information to make them resistant and those that are resistant to antibiotics will be selected and will endure. Initial antimicrobial choices may attempt to cover all possible pathogens, but on identification of the microbe and its antimicrobial susceptibilities, antibiotics that are more specific, less expensive, easier to administer, and with fewer side effects should be prescribed. Proper **antimicrobial stewardship** will reduce cost, side effects, and potential development of resistant strains. Antimicrobial drugs are discussed.

 In addition to the four questions relating to the patient, the care provider must also know how to protect themselves and others from infection. Key questions include: Is there a vaccine? What safety precautions should be taken? How can hands, objects and contaminated surfaces be disinfected? The best means to protect an individual from infection is to prevent exposure or contact, and the second best means is to be immunized against the microbe, by prior infection, or vaccine. Proper sanitation and disinfection techniques are discussed, and vaccines are discussed. Restricting access to infected individuals or areas by **quarantine** helped prevent the spread of the smallpox virus and with an effective vaccine and worldwide vaccination program, it led to the elimination

of the virus. Knowing the epidemiologic characteristics of the microbe helps determine the potential for exposure and identify who is at risk to infection. This includes the means of spread, the vector, if utilized, geographical distribution, and seasonal presence of the microbe, as well as the influence of personal health, genetics, habits, and lifestyle, which increases risk of infection and disease. Asking a patient whether they have traveled recently has become a key question in obtaining a diagnosis and is an indication of the globalization of disease.

 DESCRIPTION OF THE MAJOR CATEGORIES AND GROUPS OF BACTERIA

 ***Bergey’s Manual of Systematic Bacteriology***

 The definitive work on the taxonomic organization of bacteria is the latest edition of *Bergey’s Manual of Systematic* *Bacteriology*. First published in 1923, this publication taxonomically classifies, in the form of a key, known bacteria that have or have not been cultured or well described. A companion volume, *Bergey’s Manual of Determinative Bacteriology*, serves as an aid in the identification of bacteria that have been described and cultured. The major bacteria that cause infectious diseases, as categorized in *Bergey’s Manual*, are listed. Because it is likely that emerging information concerning phylogenetic relationships will lead to further modifications in the organization of bacterial groups within *Bergey’s Manual*, its designations must be regarded as a work in progress. As discussed, there are two different groups of prokaryotic organisms, eubacteria and archaebacteria.

 Both are small unicellular organisms that replicate asexually. Eubacteria refer to classic bacteria as science has historically understood them. They lack a true nucleus, have characteristic lipids that make up their membranes, possess a peptidoglycan cell wall, and have a protein and nucleic acid synthesis machinery that can be selectively inhibited by antimicrobial agents. In contrast, archaebacteria do not have a classic peptidoglycan cell wall and have many characteristics (eg, protein synthesis and nucleic acid replication machinery) that are similar to those of eukaryotic cells.

**Major Categories and Groups of Bacteria That Cause Disease in Humans as Part of an Identification Scheme Described in *Bergey’s Manual of Determinative Bacteriology*, 9th Ed.**

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