MINISTRY OF HEALTH OF UKRAINE
Zaporozhye State Medical University

Pathophysiology Department

GENERAL PRINCIPLES OF INFECTIOUS PROCESS

Module № 1 General Pathophysiology
Submodule 1 General nosology

Manual for independent work for the students of the 3rd course of international faculty speciality "General medicine" English medium of instruction

Zaporozhye 2017

УДК
ББК

Затверджено на засіданні Центральної методичної Ради ЗДМУ (протокол № від 20 р.) та рекомендовано для використання в навчальному процесі.

Затверджено на методичній нараді кафедри патофізіології « » 2017 р.

Authors:

O.V. Melnikova, associate professor, Ph.D.

T.A. Grekova, senior lecturer, Ph.D.

T.V. Ivanenko, senior lecturer, Ph.D.

Y.V. Kadzharyan, senior lecturer, Ph.D.

General principles of infectious process. Module № 1 General Pathophysiology. Submodule 1 General nosology: Manual for independent work for the students of the 3rd course of international faculty speciality “General medicine” English medium of instruction / O.V. Melnikova [et al.]; – Zaporozhye, 2017. – 74 p.

УДК 616-056.7(075.8)
ББК 54.1я73

CONTENT

INTRODUCTION

Infectious diseases are scary - in part because most of us don’t know anything bout them. They are also scary because they can be lethal. Unless we happen to be healthcare professionals, or our loved ones have been person ally affected by such diseases, we only think about them when they threaten our families, our communities or ourselves. This manual practice helps advance our understanding of infectious diseases and provides perspective on the role they play in our lives.

Although many complex factors surround the definition of infectious disease, some generalizations can be made. An infection can be defined as a state in which microorganisms, bacteria, viruses, fungi and parasites survive and reproduce in the host's tissues. In many instances no noticeable changes (or symptoms) are apparent. When the organism produces sufficient tissue damage through many different mechanisms, the definition of infectious disease then applies. As in hepatitis, when liver cells are invaded and damaged by the virus. Symptoms then result and can be determined through clinical examination and laboratory tests.

If we could see millennia into the past, before people started forming societies, we would probably see them living isolated from one another - nomadic in nature. This lifestyle was a natural barrier to the spread of infectious disease. But, when they started clustering together, planting crops and staying in one place, infectiousdiseases surfaced and became lethal foes of humanity. Cities grew, people started traveling for business, soldiers traveled for war, and they were all prime candidates to be carriers of disease.

Historic Perspective Of Infectious Diseases

430 BC, the plague of Athens resulted from 200,000 inhabitants and villagers fleeing into Athens when threatened by the Spartans. An unidentified infectious agent, from Ethiopia via Egypt, killed one-third of this population and ended the Golden Age of Athens.

166 AD, the Antonine plague was brought to Rome from Syria by returning Roman troops. The plague had been introduced to Syria from India by the marauding Huns. The plague (probably smallpox, bubonic plague, and measles) devastated the Roman Empire, killing 4 - 7 million people throughout Europe. The resulting social and political upheaval led to the collapse of the Roman Empire.

Circa 160 AD, bubonic plague (‘Barbarian boils’) carried by invaders from the north, led to the collapse of the Han Empire in China.

1346 to 1350, the bubonic plague pandemic started in China and moved along the trade routes through South Russia to the Crimea, which was besieged at the time. This bubonic plague killed more than one-third of the population of Europe.

1492, influenza, smallpox, tuberculosis and gonorrhea began when Columbus went to the Caribbean. The local inhabitants did not have immunity to these endemic European infections, and as a consequence, the 8 million people on the island of Hispaniola (where Columbus first set foot in the New World) died. Replacement of the population by African slaves introduced African infectious diseases such as malaria and yellow fever into the Caribbean and Americas, which, in turn, killed many European settlers.

1542, bubonic plague started in Egypt, killed 40 percent of the population of Constantinople, and spread all over Europe.

Early trading period, blackwater fever (malaria), yellow fever, bloody flux (dysentery), and worm infestations made trading with the continent of Africa difficult. The impact on travelers and soldiers was so severe that Africa was called ‘the white man’s grave.’

16th century, similarly devastating epidemics with European and then African infections – introduced by the Spanish into Central and South America. After the Spanish invasion, the population of Mexico decreased by 33 percent in 10 years and by 95 percent in 75 years.

As trade journeys lengthened, chronic infections such as tuberculosis and venereal diseases were introduced by European sailors to the Pacific islands, which lost 95 percent of their population as a result.

Present time, even during the past few decades, there has been a resurgence of epidemics such as Lyme disease and Rocky Mountain spotted fever in the United States and AIDS, genital herpes, and chlamydia worldwide.

Because bacteria and viruses are too small to be seen with the naked eye, until 350 years ago, humans weren't sure what caused infectious diseases. Then, sometime in the mid-to late-1600s, a Dutchman named Antonie van Leeuwenhoek discovered microorganisms while looking through a microscope he had designed that could magnify over 200 times.

The microscope wasn't capable of allowing van Leeuwenhoek to identify viruses, which are much smaller than bacteria. They were discovered in the late 1800s by Dmitri Iwanowski and Martinus Beijerinck, two scientists working separately who, through a process of filtering that captured anything the size of bacteria but allowed an as yet unknown substance to filter through and cause infection, discovered what we now call viruses. Beijerinck called this substance a "soluble living germ."

It wasn't until 1940, with the use of electron microscopy, that viruses were actually seen. Although it has been presumed that viruses are smaller than bacteria, an August 2002 issue of the journal Nature presented a finding by scientists stating they have found a bacterium they call SAR11 that is smaller than some viruses. This bacterium may be the smallest living thing on Earth. It is only half a micron across, or 1/50,000th of an inch.

The Dutchman van Leeuwenhoek discovered a world of tiny organisms, but it wasn't until the work of Louis Pasteur and Robert Koch in the 1860s and '70s that the germ theory of disease was developed and proved. This theory states "a specific disease is caused by a specific type of microorganism."

Around the same time, Joseph Lister, an English surgeon, demonstrated with carbolic acid that keeping open wounds, operating tables, surgical instruments, operating rooms and surgeons clean significantly reduced death by infection.

Between 1882 and 1886 Koch and a few other scientists discovered that various species of bacteria caused such diseases as tuberculosis, cholera, diphtheria, typhoid fever, gonorrhea and pneumonia.

Scientists identified a few toxins (the poison from bacteria that does cell damage) and developed some antitoxins (antibodies that can neutralize toxins). They proved how some diseases, like yellow fever, are transmitted (by mosquitoes). It was a boom time for microbiologists that brought our understanding of infectious diseases a long way in a very short time.

Before these theories were established, people thought diseases were caused by such things as bad or foul smelling air, earthquakes or sin. Treatment frequently came from nature - almost any plant one could think of was boiled, brewed, smoked or eaten. Urine and animal waste were used in poultices and cuts were made in the skin to drain blood or leeches were placed on the skin to suck blood from the body. Hot baths and enemas were also favorite methods of ridding the body of disease. A patient was as likely to die from the “cure” as the disease.

Humans did reach the point where they understood that germs brought disease and that cleanliness, or asepsis, helped prevent infection from spreading. From that point, they had to find a way to “kill the germs without killing the patient.”

Unfortunately, the First World War interrupted the lives of many people around the world, including microbiologists, and temporarily derailed the Golden Age of Microbiology.

Infectious diseases remain extremely important today. Despite the improvement of living conditions in developed countries, widespread vaccination and the availability of effective antibiotics, infectious diseases occupy a significant place in the structure of human morbidity and mortality, giving the first place to only cardiovascular pathology and malignant diseases. In countries with hot

climate, poor living conditions and malnutrition infectious diseases kill more than 10 million people each year. The majority of deaths among patients with infection - a contagious disease of the respiratory and intestinal tract caused by viruses and bacteria.

Value of infectious diseases in human life is extremely high. The total number of infectious diseases with scientific evidence is more than 1000, but in general, more than 1,500 infections are known. Their distribution depends on the social conditions (economic level of society, living conditions, diet, level of sanitary culture and so on).

In recent decades previously unknown infection diseases have spread - Legionnaires disease, Lassa fever, Marburg, Ebola, HIV, Lyme disease, campylobacteriosis, SARS and others. It is registered the increase in incidence of viral hepatitis, acute intestinal infectious diseases, tuberculosis among the population of all countries.

Clinical manifestations of infectious diseases can be varied; sometime atypical that patient can be hospitalized to medical department of any type. The ability to recognize the infectious diseases, prescribe appropriate treatment and to ensure the necessary preventive measures is necessary for doctor of any specialty.

THE AIM AND LEARNING OBECTIVES OF PRACTICAL CLASS

1. **General aim:** to study the pathogenic mechanisms of biological factors action on human health:
    1) to review the causes and mechanisms of infection diseases;
    2) to analyze the clinical picture of the main forms of infection diseases.

2. **Learning objectives** (basic educational and training issues for extracurricular self-study):
    1) Students must know:
        a) the features of infectious diseases, infectious and epidemiological process regularities of various infectious diseases;

b) the principles of diagnosis, treatment and prevention of infectious diseases;
c) the principles of nosocomial infection and contamination of medical personnel prevention;
d) factors affecting the course of infection process;
e) the role of immunity in infectious diseases;
f) the principles of infectious diseases classification;
g) general description of the different groups of infectious diseases (intestinal, respiratory, blood, wound infections, infectious diseases with multiple mechanisms of transmission);

2) Students must be able to:

a) justify general data of patients' clinical examination with acute and chronic infectious diseases;

b) give an estimation of diagnostic and prognostic value of infectious diseases detected symptoms;

c) differentiate general and specific symptoms of infectious diseases different forms;

d) demonstrate the moral and ethical principles of medical worker with patients with infectious diseases;

3) To be aware of:

a) the capabilities of computer technology in the diagnosis of infectious diseases;
b) the most common forms of infectious diseases according to statistical researches;
c) the frequency of infectious diseases in different periods of ontogenesis and ratio of infectious pathology in the structure of morbidity and mortality.

QUESTIONS TO STUDY:

1) Classification of infectious agents, their types and properties
2) Barrier mechanisms against infections (specific and nonspecific)
3) Conditions of infection process development. Distribution and dissemination of infectious agents in the human body
4) Peculiarities of immune response in infections
5) General pathogenesis of infectious process
6) Sepsis: etiology, pathogenesis, clinical manifestations, prevention
7) Tuberculosis: etiology, pathogenesis, clinical manifestations, prevention

THEORETICAL MATERIAL

I. CLASSIFICATION OF INFECTIOUS AGENTS, THEIR TYPES AND PROPERTIES

The penetration of microorganisms into the internal environment of the human body leads to disruption of homeostasis that is manifested as a complex of physiological (adaptative) and pathological reactions which are known to be an infectious process, or infection.

Infectious process - is a complex of adaptive reactions in response to pathogenic microorganism penetration and reproduction in macroorganism aimed homeostasis and biological balance restoration with the environment. Thus, the participants of infectious process are causative microorganism of the disease, the body of the host (human) and some definite conditions including social and environmental.

The main and specific properties of microorganisms:

1. Pathogenicity - the ability of the pathogen to enter the body, to live and breed in it, cause morphological and functional disorders in organs and tissues of

the microorganism, which manifests as an infectious disease. The presence or absence of the pathogenicity allows to divide all microorganisms into pathogenic, opportunistic pathogens and non-pathogenic (saprophytic). Pathogenicity defines a number of microorganisms various properties, including toxigenicity, adhesiveness and invasiveness, presence or absence of the capsule, the capacity for intracellular parasitism, antigenic mimicry and others.

2. Toxigenicity - the ability of pathogen to synthesize and secrete exo- and endotoxins. Exotoxins are the proteins released by microorganisms in the process of vital activity. They show a specific effect, which results in selective pathological and pathophysiological abnormalities in organs and tissues (germs of diphtheria, tetanus, botulism, cholera and others).

Endotoxins get out after the death and destruction of microbial cells. Bacterial endotoxins are the structural components of almost gram-negative microorganisms' outer membrane and their biochemical structure is the lipopolysaccharide (LPS) complex.

3. Virulence - a quality display of pathogenicity. This sign is not stable and it can be changed in one microbial strain in the course of infection, including influence of antibacterial treatment. In some conditions of the microorganism (immunodeficiency states, violation of protective barrier mechanisms) and environmental conditions, the causes of infectious disease can be opportunistic pathogens and even saprophytes.

4. Adhesiveness and invasiveness of microorganisms - the ability to be fixed on the cell membrane and penetrate into cells and tissues. Ligand-receptor structures and capsules promote this process s which prevents absorption of phagocytes as flagella and enzymes that damage cell membranes.

5. Ability to intracellular parasitism - a property of many pathogens, implemented by lytic enzymes inhibition and cell reproduction in it. In these cases the pathogens escape the action of antibodies and nonspecific protective factors (complement, lysozyme, etc.), which significantly influence on the form, severity, duration and completion of an infectious disease.

6. Ability to antigenic mimicry - a property of some microorganisms, which provides by structural similarity of microbial antigens with various tissue antigens of the human body. Microorganism masks in the body with the help of this similarity, contributing to longer parasitism. Immune response development is directed not only against microbial antigens, but also against tissue antigens of own organism. As a result autoimmune processes are developed that complicates the course of infection disease.

7. Microbial persistence - one of the most important mechanisms for the preservation of the pathogen in the host, which is based on the atypical microorganism formation without cell wall - L-forms or filterable forms. Thus there is alteration of microbal metabolism, which is manifested by slowing or complete loss of enzymatic functions, the ability to grow up on the elective mediums, loss of sensitivity to antibiotics.

Classification of infectious agents

Infectious agents can be classified based on the complexity of their structure: Prions, Viruses, Rickettsia, Chlamydia, Mycoplasma, Bacteria, Fungi, Protozoa, and Helminthes.

Prions are the living protein molecules that penetrate cells of organism and can reproduce the similar ones.

Viruses are divided into DNA and RNA viruses, which are tiny, much smaller than bacteria and rickettsia. Viruses are intracellular and the most common forms of life without cellular structure. The body of the virus consists of nucleic acid and protein membrane. A virus exempts from the membrane after penetration into the cell and replicates using cellular substances as building material and inhibits its typical metabolism. The viral diseases are influenza, measles, smallpox, encephalitis, AIDS and others.

Bacteria are divided by some features:

based on their shapes - cocci, bacillus (bacilli), spirochetes and vibrios;

based on gram stains - gram-positive and gram-negative;

based on oxygen demand for living - aerobic and anaerobic.

Rickettsia and Chlamydia - are small bacteria that are obligate intracellular parasites. They are intermediate between bacteria and viruses by size

Fungi - multicellular organisms plant nature. Most of them are saprophytes and smaller part - are parasites. They are more resistant in the environment than bacteria, and are well tolerated drying and sunlight.

Protozoa – are unicellular animal organisms (amoebas, Trichomonas, plasmodium malaria, etc.).

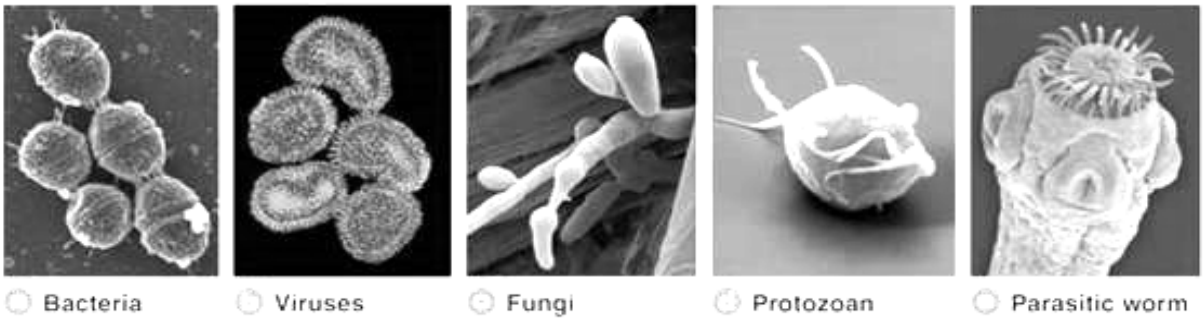

Figure 1. Major types of pathogens

Infectious diseases can be acute or chronic.

If the acute form of the disease pathogen is in the body a short period of time. Thus immunity and resistance to reinfection by the same microorganism are formed.

If pathogen presents in the body for a long time a chronic form of infectious disease is developed. In this case disease is characterized by remissions, relapses, exacerbations of pathological process. Typically, prognosis is favorable if treatment is timely, the disease is terminated in recovery.

A peculiar form of microorganisms and microorganism relationships are slow infections, which have three main features:

1) a very long incubation period - from several months to several years;

2) the course of disease is prolonged, acyclic, progressive after the first clinical symptoms and ends in extremely serious disorders and even death;

3) abnormalities are localized mainly in one body organ or one system of organs.

These infections include AIDS, subacute sclerosing panentsefalitis, kuru, scrapie, congenital rubella, rabies, Lassa fever, multiple sclerosis, amyotrophic lateral sclerosis and others.

Repeated contagion is possible due to the repeated infection by the same agent. Reinfection occurs immediately after past infectious disease. Superinfection is developed before the end of the primary infectious disease.

By the degree of pathogenicity microorganisms are divided into:

1) with high pathogenicity;

2) with low pathogenicity.

Microorganisms with high pathogenicity cause disease in normal human organism, microorganisms with low pathogenicity cause disease only if human organism is immunosupressed or immunodeficient.

Reaction of human organism to pathogen depends on its place of breeding. There are obligate and facultative, intracellular and extracellular mbacteria microorganisms by localization. Obligate intracellular bacteria can grow only in the cells of the human body using cell's metabolic apparatus for growth.

Facultative intracellular bacteria can grow both inside and outside human body cells. Intracellular breeding usually occurs in macrophages. Extracellular bacteria, based on the name, are developed within cells.

Distinctive features of infectious diseases:

- the presence of a specific pathogen;
- contagious when infected human organism becomes a source of infection;
- immune processes in consequence of which the body becomes immune to reinfection;
- process cyclicity with definite periods.

Links of infection chain.

Reservoir

The reservoir of an infectious agent is the habitat in which the agent normally lives, grows, and multiplies. Reservoirs include humans, animals, and the environment. The reservoir may or may not be the source from which an agent is transferred to a host. For example, the reservoir of Clostridium botulinum is soil, but the source of most botulism infections is improperly canned food containing C. botulinum spores.

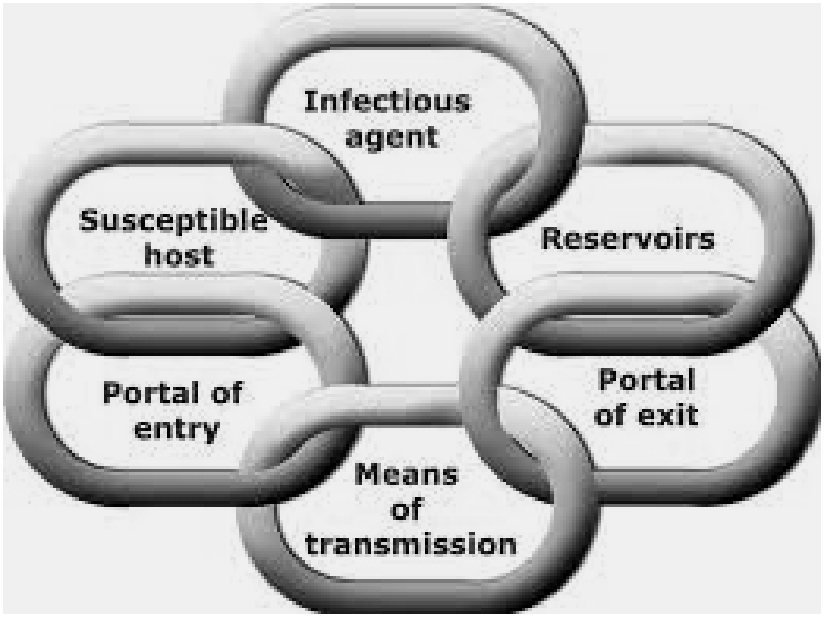

Figure 2. Links of infection chain

Human reservoirs. Many common infectious diseases have human reservoirs. Diseases that are transmitted from person to person without intermediaries include the sexually transmitted diseases, measles, mumps, streptococcal infection, and many respiratory pathogens. The are known as **antroponoses**. Because humans were the only reservoir for the smallpox virus, naturally occurring smallpox was eradicated after the last human case was identified and isolated.

Human reservoirs may or may not show the effects of illness. **A carrier** is a person with inapparent infection who is capable of transmitting the pathogen to others. Asymptomatic or passive or **healthy carriers** are those who never experience symptoms despite being infected. **Incubatory carriers** are those who can transmit the agent during the incubation period before clinical illness begins. **Convalescent carriers** are those who have recovered from their illness but remain capable of transmitting to others. **Chronic carriers** are those who continue to harbor a pathogen such as hepatitis B virus or Salmonella Typhi, the causative agent of typhoid fever, for months or even years after their initial infection. Carriers commonly transmit disease because they do not realize they are infected, and consequently take no special precautions to prevent transmission. Symptomatic persons who are aware of their illness, on the other hand, may be less likely to transmit infection because they are either too sick to be out and about, take precautions to reduce transmission, or receive treatment that limits the disease.

Animal reservoirs. Humans are also subject to diseases that have animal reservoirs. Many of these diseases are transmitted from animal to animal, with humans as incidental hosts. The term **zoonosis** refers to an infectious disease that is transmissible under natural conditions from vertebrate animals to humans. Long recognized zoonotic diseases include brucellosis (cows and pigs), anthrax (sheep), plague (rodents), trichinellosis/trichinosis (swine), tularemia (rabbits), and rabies (bats, raccoons, dogs, and other mammals). Zoonoses newly emergent in North America include West Nile encephalitis (birds), and monkeypox (prairie dogs). Many newly recognized infectious diseases in humans, including HIV/AIDS, Ebola infection and SARS, are thought to have emerged from animal hosts, although those hosts have not yet been identified.

Environmental reservoirs. Plants, soil, and water in the environment are also reservoirs for some infectious agents. Many fungal agents, such as those that cause histoplasmosis, live and multiply in the soil. Outbreaks of Legionnaires disease are often traced to water supplies in cooling towers and evaporative condensers, reservoirs for the causative organism Legionella pneumophila.

Portal of exit

Portal of exit is the path by which a pathogen leaves its host. The portal of exit usually corresponds to the site where the pathogen is localized. For example, influenza viruses and Mycobacterium tuberculosis exit the respiratory tract, schistosomes through urine, cholera vibrios in feces, Sarcoptes scabiei in scabies skin lesions, and enterovirus 70, a cause of hemorrhagic conjunctivitis, in conjunctival secretions. Some bloodborne agents can exit by crossing the placenta from mother to fetus (rubella, syphilis, toxoplasmosis), while others exit through cuts or needles in the skin (hepatitis B) or blood-sucking arthropods (malaria).

Means of transmission

An infectious agent may be transmitted from its natural reservoir to a susceptible host in different ways.

In **direct transmission**, an infectious agent is transferred from a reservoir to a susceptible host by direct contact or droplet spread.

Direct contact occurs through skin-to-skin contact, kissing, and sexual intercourse. Direct contact also refers to contact with soil or vegetation harboring infectious organisms. Thus, infectious mononucleosis ("kissing disease") and gonorrhea are spread from person to person by direct contact. Hookworm is spread by direct contact with contaminated soil.

Droplet spread refers to spray with relatively large, short-range aerosols produced by sneezing, coughing, or even talking. Droplet spread is classified as direct because transmission is by direct spray over a few feet, before the droplets fall to the ground. Pertussis and meningococcal infection are examples of diseases transmitted from an infectious patient to a susceptible host by droplet spread.

Indirect transmission refers to the transfer of an infectious agent from a reservoir to a host by suspended air particles, inanimate objects (vehicles), or animate intermediaries (vectors).

Airborne transmission occurs when infectious agents are carried by dust or droplet nuclei suspended in air. Airborne dust includes material that

has settled on surfaces and become resuspended by air currents as well as infectious particles blown from the soil by the wind. Droplet nuclei are dried residue of less than 5 microns in size. In contrast to droplets that fall to the ground within a few feet, droplet nuclei may remain suspended in the air for long periods of time and may be blown over great distances. Measles, for example, has occurred in children who came into a physician's office after a child with measles had left, because the measles virus remained suspended in the air.

Vehicles that may indirectly transmit an infectious agent include food, water, biologic products (blood), and fomites (inanimate objects such as handkerchiefs, bedding, or surgical scalpels). A vehicle may passively carry a pathogen — as food or water may carry hepatitis A virus. Alternatively, the vehicle may provide an environment in which the agent grows, multiplies, or produces toxin — as improperly canned foods provide an environment that supports production of botulinum toxin by Clostridium botulinum.

Vectors such as mosquitoes, fleas, and ticks may carry an infectious agent through purely mechanical means or may support growth or changes in the agent. Examples of mechanical transmission are flies carrying Shigella on their appendages and fleas carrying Yersinia pestis, the causative agent of plague, in their gut. In contrast, in biologic transmission, the causative agent of malaria or guinea worm disease undergoes maturation in an intermediate host before it can be transmitted to humans.

Portal of entry

The portal of entry refers to the manner in which a pathogen enters a susceptible host. The portal of entry must provide access to tissues in which the pathogen can multiply or a toxin can act. Often, infectious agents use the same portal to enter a new host that they used to exit the source host. For example, influenza virus exits the respiratory tract of the source host and enters the respiratory tract of the new host. In contrast, many pathogens that cause

gastroenteritis follow a so-called “fecal-oral” route because they exit the source host in feces, are carried on inadequately washed hands to a vehicle such as food, water, or utensil, and enter a new host through the mouth. Other portals of entry include the skin (hookworm), mucous membranes (syphilis), and blood (hepatitis B, human immunodeficiency virus).

Host

The final link in the chain of infection is a susceptible host. Susceptibility of a host depends on genetic or constitutional factors, specific immunity, and nonspecific factors that affect an individual's ability to resist infection or to limit pathogenicity. An individual's genetic makeup may either increase or decrease susceptibility. For example, persons with sickle cell trait seem to be at least partially protected from a particular type of malaria. Specific immunity refers to protective antibodies that are directed against a specific agent. Such antibodies may develop in response to infection, vaccine, or toxoid (toxin that has been deactivated but retains its capacity to stimulate production of toxin antibodies) or may be acquired by transplacental transfer from mother to fetus or by injection of antitoxin or immune globulin. Nonspecific factors that defend against infection include the skin, mucous membranes, gastric acidity, cilia in the respiratory tract, the cough reflex, and nonspecific immune response. Factors that may increase susceptibility to infection by disrupting host defenses include malnutrition, alcoholism, and disease or therapy that impairs the nonspecific immune response.

There are 3 types of microorganisms and host organism relationship:

- symbiosis - the existence of microorganisms and microorganism for relative profit (Escherichia coli in the intestine);
- commensalism - (from French. Commensal - commensal) when the microorganism and microorganism exist without relative interaction;
- parasitism – existence of microorganisms using the host organism that causes the disease.

Relationship between micro - and macroorganism can be affected in favor of microorganisms by various exogenous and endogenous factors influence, and

microorganism becomes pathogenic. In this case indifferent commensal or harmless symbiote becomes a parasite causing the disease. Such situations are possible after different types of treatment, especially antibiotic treatment, which violate the balance of microbial flora. Infectious disease can be the result of immune system and phagocytic reactions reduced activity, such as after treatment of immunosuppressant drugs and cytotoxic agents. Bacteriophages and plasmodium are active carriers of genetic elements that encode bacterial virulence factors (e.g., adhesion proteins, toxins or enzymes that are resistant to antibiotics). They are able to infect bacteria and involve themselves in their genome, thus turning previously non-pathogenic bacteria into virulent and antibiotic-sensitive microorganism - into resistant to it.

Resident flora

Many areas of the body, such as the skin, nasal cavity, and mouth, have a resident population of mixed mixroorganisms, primarily bacteria. Fifferent sites host different species. For example, streptococci, haemofilus and staphylococci are a few of the microbes found in the upper respiratory tract: staphylococcus and candida among them, occur on the skin. Some areas of the body such as the lungs, bladder and kidneys lack resident flora or are sterile under normal conditions, and properly obtained specimen from these areas should not contain microorganisms.

Table 1 presents the location of resident flora in human organism.

Table. 1

Location of resident flora

Resident flora present	Sterile area
Skin	Blood, cerebrospinal fluid
Nose, pharynx	Lungs
Mouth, colon, rectum	
Vagina	Uterus, fallopian tubes, ovary
Distal urethra and perineum	Bladder, kidney

Certain microbes in the gastro-intestinal tract are of great benefit to the host in the synthesis of vitamin K and in some digestive processes. These microbes are not pathogenic under normal circumstances but may cause disease if they are transferred to another location in the body, or if the balance among the species is not maintained (e.g., one variety becomes dominant) or if the body's defenses are impaired (in immunodeficiency state). Such infections are named opportunistic.

Resident flora are usually helpful in preventing other organisms from establishing a colony. For example, some antibacterial drugs intended to treat infection elsewhere in the body, will destroy part of the normal flora in the intestine, thus allowing for an imbalance in growth there or invasion by other microbes, causing opportunistic infection and diarrhea.

II. MECHANISM OF DEFENSE AGAINST INFECTION

The range of infectious disease manifestations can vary widely. For example, during one case of infectious disease it can be observed:

- development of bacteria carrying;
- typical or atypical clinical picture of the disease;
- development of complications;
- the death of some patients.

Such a wide range of clinical manifestations of the disease is largely due, on the one hand, to the varying protective degree of the host organism, and from the other hand – the pathogenicity of the microorganism.

The development of an infectious disease is usually accompanied by activation of organism defense reactions aimed to detect, destroy or remove the pathogen, but also to restore the structural and functional abnormalities that hasdeveloped during infectious disease.

Mechanisms and factors of the human organism that prevent penetration and vital activity of infectious pathogen in (and as a result prevent onsent and development of infectious process) can be divided into two groups:

nonspecific (play a role in contact with all or many pathoagents);

specific (directed against a particular microorganism).

A kind of synergy is present between different adaptive mechanisms that enhances the effectiveness of protection (Fig. 3).

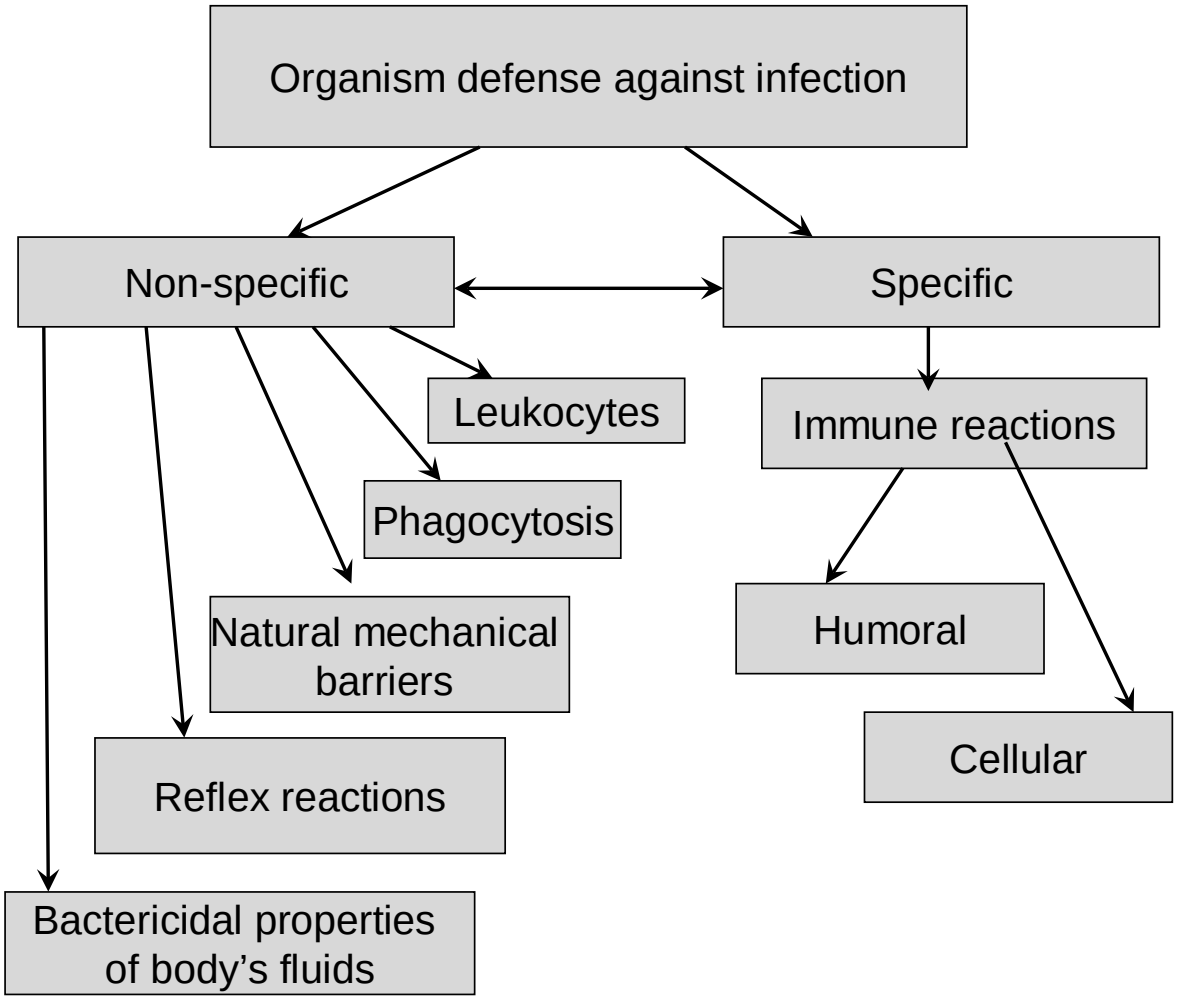

Fig. 3. Basic mechanisms of organism defense against microorganisms

Non-specific forms of defense

Nonspecific defense of the human organism against pathogens acts as the first barrier to the penetration of pathogens. The most important forms of nonspecific host defense are: barrier function and bactericidal factors of the skin, mucous membranes and other structures, leukocytes, phagocytosis of microorganisms, humoral bactericidal and bacteriostatic mechanisms protective reflex reaction.

Barrier function and bactericidal factors of the skin, mucous membranes and other structures are a first line of nonspecific defense system.

Much of pathogens (e.g. contact infections) enters the body through the ***skin*** and mucous membranes only if there are damaged. The skin has a protective stratum corneum, with desquamation epithelium which is removed with a significant amount of bacteria. Exceptions include the following:

- Human papillomavirus, which can invade normal skin, causing warts
- Some parasites (eg, Schistosoma mansoni, Strongyloides stercoralis)

Many ***mucous membranes*** are bathed in secretions that have antimicrobial properties (e.g., cervical mucus, prostatic fluid, and tears containing lysozyme, which splits the muramic acid linkage in bacterial cell walls, especially in gram-positive organisms). Local secretions also contain immunoglobulins, principally IgG and secretory IgA, which prevent microorganisms from attaching to host cells.

The ***respiratory tract*** has upper airway filters. If invading organisms reach the tracheobronchial tree, the mucociliary epithelium transports them away from the lung. Coughing also helps remove organisms. If the organisms reach the alveoli, alveolar macrophages and tissue histiocytes engulf them. However, these defenses can be overcome by large numbers of organisms or by compromised effectiveness resulting from air pollutants (eg, cigarette smoke) or interference with protective mechanisms (eg, endotracheal intubation, tracheostomy).

Gastrointestinal tract barriers include the acid pH of the stomach and the antibacterial activity of pancreatic enzymes, bile, and intestinal secretions. Peristalsis and the normal loss of epithelial cells remove microorganisms. If peristalsis is slowed (eg, because of drugs such as belladonna or opium alkaloids), this removal is delayed and prolongs some infections, such as symptomatic shigellosis. Compromised gastrointestinal defense mechanisms may predispose patients to particular infections (eg, achlorhydria predisposes to salmonellosis).

Normal bowel flora can inhibit pathogens; alteration of this flora with antibiotics can allow overgrowth of inherently pathogenic microorganisms (e.g.,

Salmonella Typhimurium) or superinfection with ordinarily commensal organisms (e.g., Candida albicans).

Genital-urinary tract barriers include the length of the urethra (20 cm) in men, the acid pH of the vagina in women, and the hypertonic state of the kidney medulla. The kidneys also produce and excrete large amounts of Tamm-Horsfall mucoprotein, which binds certain bacteria, facilitating their harmless removal.

The normal amount of self microflora of the skin and mucous membranes also plays the protective function against infectious invaders. Oppositely, dysbacteriosis promotes penetration into the body of microbes and parasites and facilitates the development of infection.

The bactericidal properties of the skin and mucous membranes are realized due to the presence on their surface of secrets containing lysozyme, secretory IgA, and IgM, glycoproteins. The most important among them is IgA. It blocks the binding site on the surface of bacteria and thus creates an obstacle to the attachment of bacteria to specific receptors on the surface of epithelial cells.

The presence of fatty acids on the skin surface creates a low pH which is not suitable for bacteria. In addition, the sweat glands produce lactic acid, which blocks the vital activity of many microorganisms.

White blood cells or leukocytes are vital cells of the immune system protecting the human body against infections, bacteria, microbes, viruses and pathogens. These cells are produced in the stem of the bone marrow and are composed of granulocytes (neutrophils, eosin ophils, and basophils) and non-granulocytes (lymphocytes and monocytes). Leukocytes which are constantly circulating through the blood stream and present in all tissues of human body provide an effective non-specific bactericidial action on many of the microorganisms.

Phagocytosis

When invading an pathogen penetrates the tissues, the inflammatory response is immediately started. Part of this response leads to the recruitment of phagocytes at the site of inflammation. Phagocytes are a class of cells which are

capable of ingestion (engulfment) and destruction of microorganisms and viruses. First to accumulate around the invaders and initiate the process of phagocytosis are neutrophils. Later, local and blood-derived macrophages also migrate to the tissue site and initiate phagocytosis. Neutrophils and macrophages are sometimes referred to as professional phagocytes for their roles in this process. Tissue derived macrophages are present almost in all body tissues (in liver – Kupffer cells, in skin – Langerhans cells, in bone – osteoclasts, in nervous tissue – microglia, in lung – alveolar and bronchial machrophages, etc.).

Phagocytes can kill bacteria with two types of mechanisms: oxygen-dependent and not depending on the oxygen (fig.4).

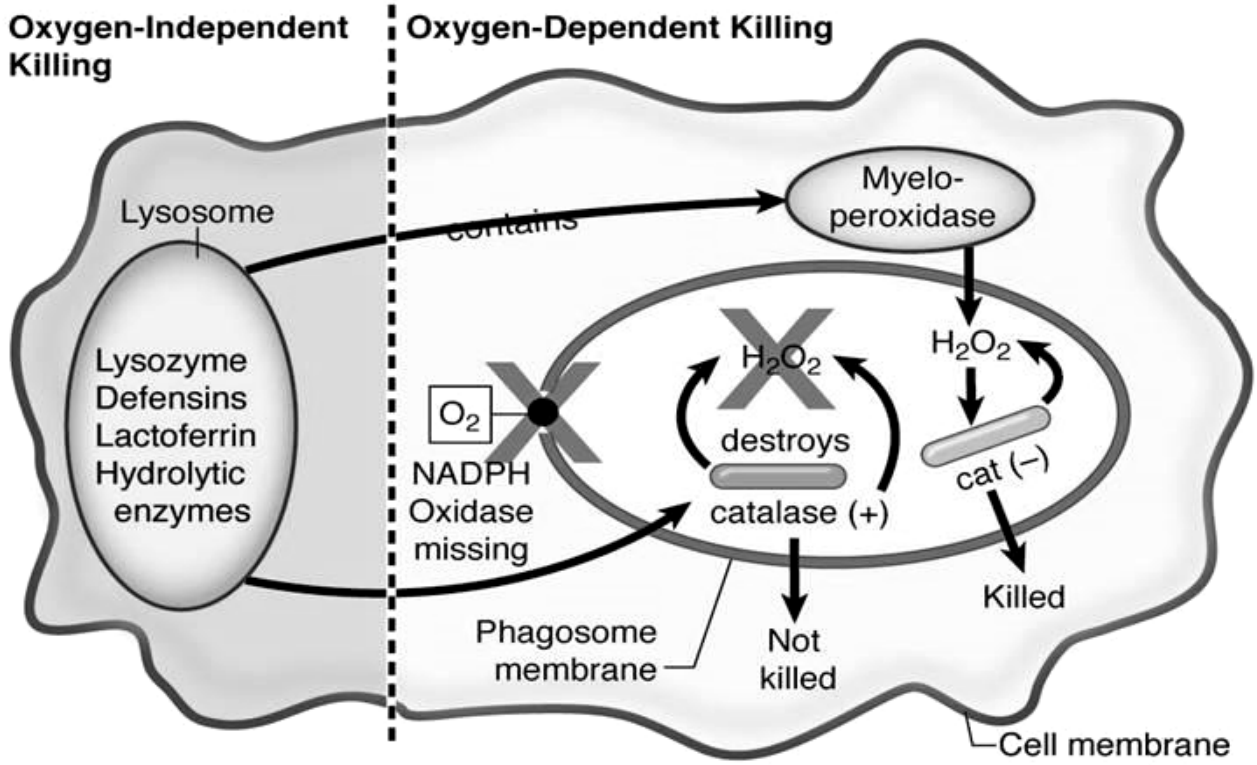

Figure 4. Mechanisms of bacterial killing by phagocytes

Oxygen-dependent killing - respiratory burst.

During phagocytosis the phagocytic cell undergoes an increase in glucose and oxygen consumption termed the respiratory burst. The respiratory burst generates several oxygen-containing compounds that kill the bacteria undergoing phagocytosis – oxygen-dependent intracellular killing.

1. Oxygen-dependent myeloperoxidase-independent intracellular killing.

During phagocytosis, glucose is metabolized via the pentose monophosphate shunt, with formation of NADPH. Cytochrome B from the granulocyte-specific granule combines with and activates plasma membrane NADPH oxidase. The activated NADPH oxidase then employs oxygen to oxidize the formed NADPH with resultant production of superoxide anion. A portion of the superoxide anion is converted to H_2O_2 plus singlet oxygen by superoxide dismutase. Additionally, superoxide anion can react with H_2O_2, resulting in the formation of hydroxyl radical plus more singlet oxygen. Together these reactions produce the toxic oxygen compounds superoxide anion (O_2^-), H_2O_2, singlet oxygen ($^1O_2$) and hydroxyl radical (OH•).

2. Oxygen-dependent myeloperoxidase-dependent intracellular killing

Fusion of azurophilic granules with the phagosome causes release of myeloperoxidase into the phagolysosome. Myeloperoxidase utilizes H_2O_2 and halide ions (usually Cl-) to produce highly toxic hypochlorite. Some hypochlorite spontaneously breaks down to yield singlet oxygen. Together these reactions produce toxic hypochlorite (OCl-) and singlet oxygen ($^1O_2$).

3. Detoxification reactions

Neutrophils and macrophages are able to protect themselves by detoxifying the toxic oxygen intermediates that they generate. Granulocyte self-protection is achieved in reactions employing the dismutation of superoxide anion to hydrogen peroxide by superoxide dismutase and the conversion of hydrogen peroxide to water by catalase.

Oxygen-independent killing

Bacteria can also be killed by pre-formed substances released from granules or lysosomes upon bacterial fusion with the phagosome – oxygen-independent intracellular killing. Such substances include:

- cationic proteins (cathepsin) released into the phagolysosome can damage bacterial membranes mostly of Gram-positive microorganisms;

- lysozyme breaks down bacterial cell walls together with the lysosomal hydrolase. Most sensitive to lysozyme are Gram-positive bacteria: staphylococcus, streptococcus. Gram-negative microorganisms are less exposed to this influence;

- lactoferrin chelates iron, which deprives bacteria of this required nutrient and causes bactertiostatic action;

- hydrolytic enzymes break down bacterial proteins.

Thus, even patients who have defects in the oxygen-dependent killing pathways are able to kill bacteria. However, since the oxygen-dependent mechanisms are much more efficient in killing, patients with defects in these pathways are more susceptible and get more serious infections.

Nitric oxide dependent killing

Binding of bacteria to macrophages, results in the production of tumor-necrosis factor-alpha, which acts in an autocrine manner to induce the expression of the inducible nitric oxide synthase gene resulting in the production of nitric oxide. Nitric oxide released by the cell is toxic and can kill microorganism close to macrophage.

Acidosis

The range of pH between 4,0 and 6,5 can cause bactericidal and bacteriostatic influence.

Low level of pH 4,0-4,5 inhibits the formation of surface charge of bacteria. This is accompanied by inhibition of membrane processes, which leads to death of bacteria.

Accumulation of H^+ ions is also accompanied by formation of bactericidal factors in phagocytes: nitrites, aldehydes, singlet oxygen and others.

In acidic conditions the permeabiltity of lysosomal membranes and their hydrolytic activity too.

Bactericidal and bacteriostatic humoral mechanisms

Humoral bactericidal and bacteriostatic mechanisms of the human organism include: lysozyme, lactoferryn, beta-lysine, transferrin, factors of the complement system and others.

Lysozyme (muramidase) effectively destroys muramic acid of peptidoglycan in the outer cellular wall of gram-positive bacteria. This leads to osmotic lysis of the latter.

Lactoferrin and transferrin - alter the metabolism of iron in bacteria. It breaks the cycle of their life and causes death.

Beta-lysine is bactericidal for most Gram-positive bacteria.

Factors of complement system provide opsonization of the most of microorganisms and facilitate phagocytosis of them.

Reflex protective reaction

With protective reflex reactions like coughing and vomiting from the respiratory tract and stomach many infectious agents are removed.

Specific defense mechanisms

The most effective defense mechanism of the body in the infectious process is the activation of immune response. Microorganisms have a variety of different antigen determinants. The role of immune system is to recognizes them as foreign, non-self cells, and perform humoral and cellular immune response mechanisms.

The way of entrance and features of the pathogen in many ways determine which form of immune response will more likely develop cellular or humoral.

The contamination of microorganisms that usually multiply extracellularly is predominantly accompanied by a humoral immune response.

The invasion of microbes that can multiply intracellularly, is more frequently accompanied by activation of cellular immune response.

Exotoxins that are critical in the pathogenesis of a number of infections (tetanus, diphtheria, gas gangrene), are usually neutralized by humoral antitoxins. If toxin is present in blood, the specific antibodies (antitoxins) neutralize it, preventing the pathogenic action. Nevertheless, antitoxin formation during primary infection usually develops slowly, and they can not effectively protect the body of the sick person.

Viruses that spread by the hematogenous routs (such as of poliomyelitis, measles, epidemic parotitis), are neutralized mainly with of factors humoral immunity.

Viruses that multiply in the site of entrance (e.g. influenza) in primary infection switch on first of all the mechanisms of local immunity (IgA). When viral replication occurs intracellularly cellular immunity plays the important role in antiviral defense.

In fungal diseases mainly cellular immunity is activated.

Agents of protozoal infections are characterized with wide antigenic diversity. Worm infestation is usually accompanied by stimulation of the IgE synthesis. In the place of parasite entrance infiltrate consisting of phagocytes, lymphocytes, eosinophils, basophils, tissue basophils is often found.

Long-living lymphocyte clones (immune memory cells) are responsible for formation and maintaining of long-term immunity which occurs after an exposure of pathogen antigens to immune system. In some cases this process develops lifelong immunity, while in others - for the short term immunity. The reasons of such differences are still not clear. Possibly the continuance of immune response may depend on the following factors:

- low immunogenicity of the pathogen (intestinal infection);
- intracellular parasitism of the pathogen;
- alterations in the structure of a virus (e.g. influenza, gripp virus);
- disturbances of immune response development under the influence of immunosuppressive factors;
- lifelong immunity in several viral infections, determined by persistence of the pathogen in the organism (this phenomenon is named as a non-sterile immunity).

III. CONDITIONS OF INFECTIOUS PROCESS DEVELOPMENT.

Conditions of infectious process development are determined by routs of microorganism entrance, ways of their distribution in the organism, mechanisms of anti-infectious resistance

Place of infection entrance it is the site where the microorganisms penetrates the human organism. Different ways of penetration are possible for different microorganisms. Here are the examples of places of infection entrance:

- skin (e.g., malaria, typhus, leishmaniasis of the skin);

- mucous membranes of the respiratory tract (for agents of influenza, measles, scarlet fever, etc.)

- mucous membranes of the gastrointestinal tract (e.g., agents of dysentery, typhoid);

- urinary tract mucosa (for agents of gonorrhea, syphilis and others.)

- walls of blood vessels or lymphatic vesssels through which the agent enters the bloodstream or lymph (eg, bites of arthropods, animals, injections and surgery).

The entrance place can define nosological form of the disease. So, getting of Streptococcus in tonsils causes tonsillitis, through the skin - erysipelas or pyoderma, in the uterus - the inflammation of endometrium.

Dissemination of microorganisms within the body

Some microorganisms proliferate locally (e.g. papilloma visuses, dermatophytes proliferate exclusively in epithelial cells), at the site of initial infection, whereas others penetrate the epithelial barrier and spread to the distant body sites by different ways:

- some extracellular bacteria, fungi and helminthes secrete lytic enzymes which destroy tissue and allow direct invasion. For instance, staphylococcus aureus secretes hialuronidase, which degrades the extracellular matrix between the host cells. Invasive microbes initially follow tissue planes of least resistance and drain to regional lymphatic nodes. S.aureus may travel from a localized abscess to the draining lymphatic nodes that can sometimes cause bacteremia and spread to deep organs (heart, bones);

- microorganisms may be disseminated by the blood or lymph either free in extracellular fluid or within host cells. Some viruses (e.g. poliovirus, hepatitits B virus), most bacteria and fungi, some protozoa and all helminths are transported in blood, free in plasma. Leukocytes can carry herpesviruses, human immunodeficiency virus, mycobacteria, leishmania and toxoplasma. Such parasite as Plasmodium is carried within red blood cells;

- most viruses spread locally from cell to cell by replication and release of infectious virions, but others may propagate from cell to cell by causing fusion of host cells, or by transport within nerves (rabies virus, varicella-zoster-virus

Most of pathogens have the tropism for specific tissues of host organism. This is determined by the presence of microbial adhesion molecules and specific receptors in human organism cells, leading to the accession of bacteria to cell receptor targets.

Mechanisms of antiinfectious resistance

There are effective safety systems that prevent the penetration of pathogens in the body, their reproduction and realization of their pathogenic effects. A wide list of the factors that impede penetration of pathogenic or opportunistic bacteria exist. As an example, Table 2 presents the main protective factors of the gastrorointestinal tract.

Table 2

Main protective factors of the gastrorointestinal tract

Part of GIT	Protective factor
Mouth and pharynx	Lysozyme, proteolytic enzymes in saliva, secretory Ig, endogenous microflora
Stomach	The acidic environment, proteolytic enzymes, peristalsis
Small intestine	Bile acids, proteolytic enzymes, secretory Ig,

	intestinal microflora, mucin, epithelial desquamation, lymphoid structures, peristalsis
Colon	Intestinal microflora, secretory Ig, mucin, epithelial desquamation, peristalsis

Taking into account the presence of protective factors in the human organism, the penetration in it of the infectious agent does not necessarily mean, the development of infectious disease. Depending on the conditions and the state of anti-infection protection systems, infectious process may not develop or run in the form of bacteria carrying. In the latter case, any systemic response of the body (including the immune) will not be detected.

IV. PECULIARITIES OF IMMUNE RESPONSE IN INFECTIONS

In response to different mechanisms of immune defense microorganisms have developed many means to resist and evade the immune system. These mechanisms which are important determinants of microbial virulence and pathogenicity include antigenic variation, resistance to innate immune response, impairment of effective T cell antimicrobial responses by specific or non-specific immunosuppression.

Some microbes can evade immune response by varying the antigen which they express on the surface of the cell with the help of reassortment of viral genome. For instance Trypanosoma species have many genes encoding their major surface antigen and can vary the expression of surface protein. At least 80 different serotypes of S.pneumoniae , each with a different capsular polysaccharide have been recognized.

Certain microorganisms have developed methods to resist immune defense:

- Cationic antimicrobial peptides provide important defnde against invading microbes. These peptides bind to the bacterial membrane and form pores killing the bacteria by hypoonkotic lysis. Some bacteria (Sigella spp., S. aureus) effectively avoid such killing by making surface molecules that resist binding of

antimicrobial peptides, or inactivate antimicrobial peptides by different mechanisms.

- To escape phagocytosis many bacteria that cause pneumonia or meningitis (S, pneumoniae, H.influenzae) produce carbohydrate capsule on their surface. That makes them more virulent and prevent phagocytosis. S.aureus and S. pyogenes epress on their surface specific proteins that inhibit phagocytosis. Many bacteria produce proteins that kill phagocytes, inhibit their migration, or decrease the intensity of oxidative burst.

- Viruses have developed a large number of methods to fight against interpherons, which are the mediators of innate immunity. One of them is the production of soluble homologues of interpheron receptors that bind and inhibit them. Viruses may even block the process of apoptosis in the host cell, which may give the viruses time to replicate, persist or transform host cell.

- Some microbes produce factors that decrease recognition of the infected cells by T-helpers and T-killer cells. For example, several DNA viruses (e.g. herpes virus, cytomegalovirus, Epstein-Barr virus) can bind or alter localization of major histocompatibility complex class I protein, impairing peptide presentation to T-killer cells. Herpesviruses can target major histocompatibility proteins class II molecules for degradation , impairing antigen presentation to T-helper cells. Viruses also can affect leukocytes directly to compromise their function (e.g. Human immunodeficiency virus infects T-helper cells, macrophages and dendritic cells).

Other mechanisms of microorganisms evade host organism defense are given in the table 3.

Table 3

Mechanisms of microorganisms evade human organism defense systems

Defense factors of human organism	**Mechanisms of microorganisms**	**Example**
Chemotaxis	Release of substances that inhibit hemotaxis	Migrastatin (Streptomyces), metalloproteinase Legionella
Phagocytosis	Inhibition of phagolysosome formation	Ammonium compounds Mycobacterium, Leishmania
	Release of substances toxic to phagocytes	Leukocidins Staphylococcus, Clostridia
	Inhibition of proton pump in lysosomes, lysosomal acidification disturbance	Inhibitors of H + -ATPase Yersinia, Mycobacterium
	Inactivation of hydrogen peroxide release in oxidative burst	Catalase Staphylococcus, Enterococcus and other microrganisms
Antigen presentation	Disturbance of antigen presentation by infected cell	Toxins of Mycobacterium, Escherichia coli
	Splitting of transcription factor required for MHC expression	Protease Chlamydia
Immunoglobulins	Antigenic variability	Campylobacter, Gonococcus, Mycoplasma

		and most of microorganisms
Complement	Sialisation of cell surface prevents the activation of complement components (C3b)	Sialic acids кислот of Meningococcus and other microorganisms
	Adsorption of C3b ihibitors on the surface	Elastase Pseudomonas aeruginosa
	Expression of membranes associated enzymes that hydrolyse components of the complement	Protease Borrelia, Yersinia, Pseudom
	Inactivation of chemotactic properties of complement components (C3, C5)	Gelatinase E Enterococcus faecalis
Cytokines	Block of macrophages activity	Lipoarabinomannan Mycobacterium
	Induction of interleukins 10 and 12 synthesis which inhibit apoptosis of monocytes	Chlamydia

Deviations from the classic version of the immune response in infectious process

In some cases the features of pathogens and their antigenic substances cause disruption of normal flow of the immune process that leads to long-term persistence of the pathogen or the chronic infectious process.

The consequence of resistance of mycobacteria to immune reactions is granulomas formation in tuberculosis and leprosy. Granuloma – is an accumulation

of activated macrophages containing non-destroyed mycobacteria inside them that can multiply. This cluster is surrounded by activated T cells. In the central zone much of macrophage dies; in addition, some cells fuse to form symplast also declining soon. Such symplast is formed also in viral infections: viruses and some other infectious agents have property to damage host cellular membranes followed by their "wrong" reparation, resulting in merge cells. Under unfavorable course of the process at the center of the granuloma disintegration of cells is increasing, and are festering masses (cheesy decay, forming cavities in tuberculosis). The development of granulomas as a rule is thought to be a sign of an inefficiency of the immune defense system.

Virus transition to latent form can also cause the alteration of adequate immune response which usually results in elimination of the pathogen. This is manifested in stopping of viral replication and formation of new viral particles. Viral antigen stops its expression on the cell surface and pathogen becomes reachless to the immune factors. The immune process fades until the next phase of the virus activation will begin. The most known examples of this kind are infections caused by the herpes virus, cytomegalovirus and others.

Persistence of the pathogen is also possible in the case of viral antigen variability, which manifests itself in the specific diseases, such as sleeping sickness (trypanosomiasis).

An extreme manifestation of pathogens adaptation to immune response is the infectious processes in which the proliferation of activated lymphocytes is necessary for virus replication. For example, lymphocytic choriomeningitis virus in the case of neonatal infection (immunological tolerance is formed toward viral antigens) while maintaining thymus-dependent factors of the immune system, the virus replicates in proliferating T cells.

Another variant of pathogens damaging effect, which is realized by the immune system of the human body is associated with antigen cross-reactivity of micro- and macro-organisms. A widely known example of this situation is the development of an autoimmune process (rheumatic autoimmune process induced

by streptococcal infection). Antibodies are synthesized against epitope which is common to streptococcus type A and human cells. Antibodies react with a number of human tissues which express cross-reactive polysaccharide: heart muscle, heart valves, synovial membrane of joints, and at the same time, epithelial cells, including those with localized in the thymus. The latter is explained by the following fact: antibodies are also directed to specific components of the cytoskeleton - keratin epithelial cells.

Interaction between microorganisms and phagocytes

Interaction of pathogens and phagocytes plays a key role in the mechanism of infectious process development. The result of this interaction determines the peculiarities of infection. In the classic variant phagocytes play the protective role which results in engulfment and destruction of microorganisms. However, some pathogens of infectious diseases are resistant to effector mechanisms of phagocytes and even are to live and multiply inside them (such as herpesvirus, poxvirus, rikketsiyi Provatseka, Mycobacterium tuberculosis, Mycobacterium leprae, Brucella, Legionella, simple - Trypanosoma, Toxoplasma.

V.GENERAL PATHOGENESIS OF INFECTIOUS PROCESS

Classification of infection:

- *Primary infection:* Initial infection with organism in host.
- *Reinfection:* Subsequent infection by same organism in a host (after recovery).
- *Superinfection:* Infection by same organism in a host before recovery.
- *Secondary infection:* When in a host whose resistance is lowered by preexisting infectious disease, a new organism may set up in infection.
- *Focal infection:* It is a condition where due to infection at localized sites like appendix and tonsil, general effects are produced.
- *Cross infection:* When a patient suffering from a disease and new infection it set up from another host or external source.
- *Nosocomial infection*: Cross infection occurring in hospital.

- *Subclinical infection:* It is one where clinical affects are not apparent.

Types of infectious diseases

- *Septicemia* is the condition where bacteria circulate and multiply in the blood, form toxic products and cause swinging type of fever.
- *Pyemia* is a condition where pyogenic bacteria produce septicemia with multiple abscesses in the internal organs such as the spleen, liver and kidney.

Depending on the spread of infectious disease in the community they may be classified into different types.

- *Endemic* diseases are ones that are constantly present in a particular area. Typhoid fever is endemic in most parts of India.
- An *epidemic* disease is one that spreads rapidly, involving many persons in an area at the same time. Influenza causes annual winter epidemics in the cold countries.
- A *pandemic* is an epidemic that spreads through many areas of the world involving very large numbers of persons within a short period (Influenza, cholera, plaque).

Links of pathogenesis

Infectious process is typical pathological process; its major links of pathogenesis are: fever, inflammation, hypoxia, metabolic disorders and dysfunction of organs, tissues and their systems.

Fever

Fever is the most common component of infectious diseases. Pathogens with the help of primary pyrogens stimulate the synthesis and release of leukocytes secondary pyrogens - leukocyte cytokines. This starts the development of the fever.

Inflammation

Inflammation occurs in response to a penetration of infectious agent to the human body or activation of the pathogens persisting in it. The development of inflammation has two meanings - both protective and pathogenic one. The protective role is to limit the dissemination of the pathogen and its toxins and pathogenic role - the release of mediators of inflammation and tissue damage in the

site of inflammation. This may worsen the metabolic function of many organs, hemodynamic, trophic and so on.

Hypoxia

Violation of biological oxidation is an important component of infection. The type of hypoxia that develops in infectious process largely depends on the characteristics of infectious disease. Thus, respiratory hypoxia can occur as a result of toxins depressing action on the respiratory center; circulatory - due to violations of microcirculation. Hemic type of hypoxia can develop due to decreased number of red blood cells (e.g., malaria). Tissue hypoxia develops as a result of dissociation of oxidation and phosphorylation under endotoxin influence (e.g., Salmonella, Shigella).

Metabolism disturbances

In the initial stages of infection catabolic processes dominate including: proteolysis, lipolysis, the collapse of glycogen (and as a result - hyperglycaemia). At the stage of recovery anabolic processes are activated.

Violation of certain types of metabolism that will predominate is dependent on the ethiology of infectious process. Thus, in the course of intestinal infections disorders of fluid and electrolyte and acid-base balance mainly occur, hepatitis causes protein metabolism disturbances, sepsis disturbs all types of metabolism at different degrees.

All above mentioned links of pathogenesis as a rule lead to disturbances of function of tissue, organs and organ systems.

Functional disorders

If protective mechanisms are not sufficient to localize the infection, it is generalized and general reactions of various systems of the patient manifest.

Nervous system

Microbial invasion especially with high amount of microorganisms is a reason of non-specific responses:

• stress reaction development;

• activation of resistance mechanisms.

When intoxication is significant activation of the central nervous system changes to its depression.

In some infections (e.g., botulism) trophic function of the nervous system is also disturbed.

Changes in the functional state of the central nervous system lead to the restructuring of the organs and systems functions that is aimed to localization and destruction of pathogen infection and later to normalization of vital activity of the organism. These changes can result both in activation and in suppression of an organ or physiological system function.

In the course of infection development infection-specific structural and functional changes in the nervous system also occur, which reflect the features of the pathogen and state of human organism reactivity.

Immune system

Activation of immune system is primarily directed to anti-infectious immunity development. Besides that pathological immune reactions may develop in the course of infectious process: allergy, autoreactivity, and immunodeficiency.

Alergic reactions

Type III hypersensitivity reactions – immune complex (by Gell and Coombs) are observed most commonly. Immune complex hypersensitivity reactions occur in the case of massive release of antigens resulting from the death of microorganisms in the previously sensitized patient's organism. Thus, glomerulonephritis caused by immune complexes often develops as a complication of streptococcal infection. Immunocomplex reactions often develop in chronic infectious diseases of bacterial, viral and fungal etiology, and in the parasitic infestation.

Autoreactivity

Autoreactive processes often accompany infectious diseases. The reason omay be the following:

- modification of own antigens under the influence of microorganism;

- similarity of patient’s antigens with antigens of microorganism;

- integration of viral DNA with the patient's genome.

Immunodeficiency

Immunodeficiency is transient in infectious process, as usual. The exception may be a disease in which virus selectively affects immune cells (e.g., AIDS), blocking the formation of the immune response. Chronic infections may reduce the effectiveness of local immunity mechanisms (e.g., intestinal infections) or immune system in general (e.g., malaria).

Cardiovascular system

Arrhythmias, coronary insufficiency, cardiac failure, redistribution of blood flow, microcirculation disturbances may develop in the course of infectious process. The main causes of these disorders are microbial toxins, imbalances in water-electrolyte exchange, alterations of the physical and chemical state of the blood.

Respiratory system

The possible increase of respiratory system activation in infectious process may be changed to its depression by the following reasons:

- depression of respiratory center neurons activity by the toxins of microbial origin and those which are formed in the body as a result of infectious process;

- affection of the organs of respiratory system by the infectious pathogens (e.g. pneumococci).

Infectious process development may also alter the function of other organs and systems: liver, kidneys, gastro-intestinal tract etc. As a rule these alterations are determined by the nature of infectious agent; they are discussed in the course of infectious diseases.

Stages of infectious process development

Stages of infectious process development are one of their most pathognomonic features. Four stages of infectious disease development are distinguished: incubation stage, prodromal stage, stage of clinical manifestation and outcome of the disease.

Incubation stage

The incubation stage is the time from infection penetration into the human body till the first clinical signs of the disease appear. It is characterized by:

• reproduction and selective accumulation of microorganisms in certain organs and tissues, which will be predominantly damaged in the course of an infectious disease;

• mobilization of defense mechanisms of the body.

The duration of the incubation stage lasts from a few hours (acute intestinal infections) to several years (in AIDS, wound infections) and is mainly determined by the properties of biological agents. The duration of incubation stage is a characteristic feature of certain species of microorganisms.

Prodromal stage

Prodromal period is the stage of infection from the onset of nonspecific clinical manifestations of the disease to the complete development of its symptoms. Such clinical manifestations may be observed in this stage:

• decrease of the host organism defense reactions effectiveness;

• increase the microorganism degree of pathogenicity (multiplication, production and release of endo- and exotoxins);

• clinical manifestations at this stage of infection are not specific to the infection. It includes general malaise, weakness, discomfort, headache, fever, muscle and joint pain, nausea etc.

Prodromal period is seen not at all infectious diseases and usually lasts from several hours to several days.

Stage of clinical manifestation

The stage of disease clinical manifestation is characterized by the development of specific signs of the disease. They depend on:

• specific pathogenic properties of the infectious agent;

• the nature of the relevant organism reactions, which are formed on the basis of adaptive mechanism failure.

The duration of this period depends on nosology and varies widely. Many infectious diseases (measles, scarlet fever, typhoid) is characterized by relatively constant duration of that period.

Subclinical forms

Subclinical forms of infectious diseases are possible along with typical forms of infectious diseases. Clinical manifestations of the infection is not registered in the patients after microorganisms invasion. However, the study of immune status and a number of indices of organism vital activity are specific for this infection changes.

Disease outcome

The stage of disease outcome has several variants: recovery, death of the patient, complications development and bacteria carrying

Recovery

Recovery occurs at the favorable outcome of disease. There is a gradual reduction in the severity and consequent disappearance of the main clinical signs of infection. Recovery can be complete and incomplete.

Complete recovery of the patient is most often the result of acute infectious process and usually ends with removal of the pathogen from the body (sanitation). Infectious disease duration is characterized by the fact that clinical recovery occurs much earlier than structural and functional impairments which result from an infectious process are restored. Thus, duration of the complete recovery of the liver functions after viral hepatitis lasts from 6 months to one year, while the disease clinical manifestation lasts 1-1.5 months.

Infectious disease typically ends with the formation of immunity that provides insusceptibility to the body of the certain type of infection and its re-infection.

The effectiveness and duration of acquired immunity differs in various infectious diseases from a pronounced and sustained that virtually eliminates the possibility of re-disease throughout life (such as smallpox, measles), to the weak

and short forms, allowing the secondary occurence of the disease in a short time (e.g., dysentery).

Incomplete is recovery characterized by the persistence of residual effects of the disease.

Complication

Specific and nonspecific complications can develop in any period of infectious disease.

Specific complications are those whose development is directly linked with the basic pathogenesis of infection (e.g., perforation of the intestinal wall and intestinal bleeding in typhoid fever, hypovolemic shock in cholera, etc.).

Non-specific complications include conditions that are caused, for example, by activation of secondary infection or superinfection.

VI.Sepsis: etiology, pathogenesis, clinical manifestations, prevention

Sepsis is the medical and general biological problem now as pathogenetic mechanisms of its development, approaches to treatment and prevention are important for general mechanisms of homeostasis and inflammation understanding.

Purulent and septic diseases issues in people of different age groups is defined by tendency to increase, the severity of course, high mortality, difficulties therapy that is not always effective because of the many reasons. According to WHO statistics about 14 patients die from sepsis every minute in the world.

Sepsis is defined as a generalized form of pyoinflammatory infection caused by opportunistic bacterial flora, pathogenesis of which is the rapid development of systemic (generalized) inflammatory reaction in response to primary septic site.

Systemic Inflammatory Response Syndrome (SIRS) – is the general biological nonspecific immunocytological reaction of the human organism in response to endogenous or exogenous damaging factors. Systemic inflammatory response caused by proved infection is defined as a sepsis. Sepsis and its complications are the consecutive clinical and pathophysiological phases with increasing of their severity: sepsis, severe sepsis, septic shock (hypotension and hypoperfusion of

tissues which are refractory to appropriate workload and required inotropic myocardium support), multiple organ failure syndrome.

SIRS is characterized by systemic inflammation manifestations: fever or hypothermia, leukocytosis or leukopenia, tachycardia, tachypnea, increased minute volume ventilation. Inflammatory cascade in sepsis can be done not only live bacteria, but its fragments (bacterial exotoxins and endotoxins, modulins). Thus sepsis is fundamentally different from other infections that its development involves opportunistic pathogen, and therefore convalescence is possible without their complete elimination from the body.

Massiveness of bacterial infection is of great importance to the sepsis development due to influence on phagocytes of human organism. In this regard sepsis can be defined as a generalized inflammation that develops in response to excessive amount of microorganisms or their fragments.

However, for the sepsis development is important not direct influence of microbes on the human's body, but substantial violations in the immune system state from over-activation (phase of hyperinflammation) to the immune deficient syndrome development (phase of immune paralysis).

The concentration of bacteria or their fragments in the blood may be inadequate for the immune system, and also can be excessive, leading to its collapse. Excessive microbial load leads to functional failure of protective factors (phagocytosis, complement system). The last one causes cellular and humoral immunity dysfunction and decrease in resistance to infection.

Anti-infectious barriers

Excessive concentration of microbial agents suppresses immune system of the body, which combines three levels.

The first level – is the competitive interaction with bacteria of human organism normal microflora. Irrational antibacterial therapy, intestinal passage disturbances contributes to the destruction of this barrier.

The second level - are barriers to infection penetration: skin, mucous membranes and secrets with bacteriostatic and bactericidal properties, which

promote mechanical removal of microorganisms and inhibition of their reproduction.

The third level - phagocytic system of the organism, represented by circulating monocytes and neutrophils, macrophages and cells of lymphocytic system, and the antibodies mediated immune response. The weakening of protective barriers promotes microorganisms' penetration into tissues and activation of phagocytosis. Thus there is lysis of bacteria and presentation of antigens for further immune responses. Therefore the starting mechanism of sepsis development is the bacterial membrane lipopolysaccharide (endotoxin).

Sepsis etiology

Sepsis is a generalized infection of bacterial origin, caused exclusively conditionally pathogenic flora. In some cases, such as AIDS, sepsis can be part of a generalized infection - bacterial, viral and fungal. Over time, total evolution of etiological structure of disease take place, associated with changes in the volume and nature of medical activity, premorbid state of the patient (increase in the number of premature newborns, increasing the number of patients with immunodeficiency, etc.). Over the past 10 years the role of gram-positive and gram-negative opportunistic microorganisms in the etiology of sepsis was almost equivalent due to growing of streptococci, staphylococci, enterococci role last time.

Etiological importance have the microorganisms isolated from sterile normal biological environments and tissues (cerebrospinal fluid, blood, exudates, biopsies) or from inflammatory sites. Potential pathogenic are microorganisms that colonize the mouth, mucosa of intestine, upper respiratory tract.

Among the pathogens of purulent infection gram-negative bacteria of the family Enterobacteriaceae draw attention last tame, which are the part of normal intestinal flora, but more often there are cases of their elimination under the influence of antibiotic therapy.

R. aeruginosa, Acinetobacter (gram-negative bacteria) are the most serious problem of nosocomial infection due to their high multidrug resistance to

antibiotics. There is appearance of bacteria with particularly high resistance in response to implementation of new groups of antimicrobial medications - P. Maltophilia, P. Cepacia, Flavobacterium meningosepticum.

The role of anaerobes has taken on increased significance in the most difficult inflammatory diseases, and their number being up to 155 strains in recent years. The places for Bacteroides and Clostridium penetration into human organism are gastrointestinal tract and genital tract, for anaerobic cocci – respiratory tract. B. fragilis is often sown in anaerobic septicemia. Clinical features of this infection are jaundice, septic thrombophlebitis and metastatic abscesses. Lung infections are often caused by anaerobic Fusobacteria, Peptostreptococci and Bacteroides, most of them produce β-lactamase. B. fragilis are characterized by ability to cause pathological process independently (to form abscess) while other require synergy between bacteria - mixed infection.

For sepsis development not only bacteria play an important role, but lipopolysaccharides, in particular lipopolysaccharides of Gram-negative bacteria. Sepsis often appears as a reaction to the excessive microbial load in blood circulation caused by living microbes and the formation of metabolites of microbial origin. First of all it comes down to interstitial edema, as well as with progression - to cellular energy deficit. Lack of energy determines the increased protein breakdown, abuse electrolyte transport through the cell membrane. The cell loses potassium and retains sodium and water. As a result, intracellular edema develops with the injury of lysosomes and increase in proteases (pathological “protease explosion”). Metabolic disorders (primarily lactic acidosis), products of fibrin breakdown which were formed during intravascular coagulation, bioactive amines and proteases further block lymphocyte-macrophage system. This makes it difficult to clean the body from toxins, sensitizes it to the following toxic effects. The intoxication becomes cascade generalized process.

Pathogenesis of sepsis

In the pathogenesis of sepsis and its complications the leading role is assigned to: endogenous mediators, violation of peripheral microcirculation, myocardial

suppression, reduction of oxygen transport and its utilization by tissues. It has been proved that the body itself produces substances that can cause SIRS, septic shock and multiple organ failure. Massive tissue damage, especially in combination with Gram-negative infection, is accompanied by widespread and uncontrolled activity of mononuclear phagocytes.

"Cytokine storm". Neutrophils and monocytes produce prostaglandins, leukotrienes, nitric oxide, free oxygen radicals, pro- and anti-inflammatory cytokines during the immune response in adequate initial microbial load. This process is accompanied by the release of a large number of inflammatory mediators (cytokines) from majority of the human body cells, including immunocompetent cells, which enter into the systemic blood flow and cause a systemic response. Among them tumor necrosis factor (TNF), interleukins (IL) are essential which are formed in response to microbial toxins influence and promote leukocytes adhesion to endothelial cells, release of proteases, arachidonic metabolites, activation of blood coagulation.

IL-1 and IL-8 play a particularly important role in the maintenance of tissue inflammation. IL-6 and IL-10 intensify the effect of acute-phase reagents and antibodies, suppress the function of T-lymphocytes and macrophages. Metabolites of arachidonic acid (thromboxane A2, prostaglandin E) take part in the pathogenesis of fever, tachycardia, tachypnea, ventilation-perfusion disorders lactic acidosis development. Leukotrienes (LTB-4, LTC-4, LTE-4, GM-CSF, IFN-f, lipid-associated protein (LAP)) play an important role in the inflammatory process through the promotion of prostaglandins, free radicals, nitric oxide production, and each of them is a strong impact factor on the cellular level. This orientation of mediators' response to the stimulus is interpreted as SIRS with predominantly anti-inflammatory direction.

It has been established that excessive inflammatory response with hyperproduction of TNF, IL, prostaglandins is replaced by phase of immune paralysis, which is characterized by decreased activity of monocytes and increased formation of anti-inflammatory cytokine IL-10. Reducing of the inflammatory

reaction is due to a compensatory release of anti-inflammatory mediators (IL-10, histamine, transforming growth factor, serotonin, Hageman's factor, platelet activating factor, endorphins). IL-10 starts the compensatory anti-inflammatory response. All the above processes characterize SIRS with predominantly anti-inflammatory direction.

One of the most difficult and least controlled situations is mixed antagonistic response - SIRS dysregulation, "mediator chaos," "cytokine storm."

IL-6 regulates antibody production, stimulation and release in the systemic circulation of acute phase proteins (CRP, α2-macroglobulin, fibrinogen) with subsequent activation of complement by the classical pathway.

Depression of specific antibodies production develops in sepsis system response to an infectious inflammation. Excess of anti-inflammatory cytokines (IL-10, TGF-β1) reduces antibodies production by plasma cells and violates the start of the complement system classical pathway from antigen-antibody complex. Meanwhile in the pre-septic period it is observed an increase in Ig content and decrease in IgA, IgM, IgG on the background of a sharp increase in the IgE content. The last one is directly related to the development of allergic reactions in sepsis. Increased IgE plasma level in sepsis has transient nature.

Excessive stimulation of inflammatory cytokines and T-lymphocytes may lead to their apoptosis - programmed cell death, and necrosis, which defines the damaging effect of SIRS on the human organism.

Lipopolysaccharides (LPS) of gram-negative bacteria can cause apoptosis of alveolar macrophages, which clinically manifested by destructive processes in the lung tissue. LPS-induced apoptosis significantly increases due to action of leukotriene-IFN and decreases under the influence of anti-inflammatory cytokines. Syndrome SIRS as a nonspecific general biological reaction of the human organism is the basis of all serious both infectious and noninfectious diseases (trauma, ischemia, autoimmune process).

Nitric oxide (NO). Increased synthesis of endogenous NO is associated with the immune system stimulation. There is a correlation between the production and

balance of pro- and anti-inflammatory mediators. The increase in inflammatory cytokines level induces the synthesis of nitric oxide by the endothelium, hepatocytes and phagocytes. Rising concentration of anti-inflammatory cytokines inhibits its production. Production of nitric oxide in sepsis is increased by intestinal mucosa, leading to its damage, increased permeability and promotes translocation of bacteria.

The main clinical effect of nitric oxide is hemodynamic instability that develops due to relaxation of vessels smooth muscles and leads to hypotension, which becomes to be uncurable even with the help of cardiotonic support.

In the mediator cascade course definite phases should be distinguished: the phase of endotoxin exposure, the phase of activation, mediator phase, immunological paralysis and final phase. It has been established that excessive inflammatory response with hyperproduction of TNF, IL, prostaglandins was changed to phase of immune paralysis, which is characterized by decreased activity of monocytes with increased formation of anti-inflammatory cytokines (IL-10, TGF-β, IL-1RA).

Reducing of the inflammatory reaction is explained by a compensatory release of inflammatory mediators (IL-10, histamine, transforming growth factor (TGF-β, serotonin, bradykinin, Hageman's factor, platelet activating factor, endorphins). The start of compensatory anti-inflammatory response provides IL-10.

The clinical picture is characterized by multisystem lesions. The main changes in the organs and systems that occur in sepsis are given in the Table 4.

Table 4

The main changes in the organs and systems that occur in sepsis

Organs and system of organs	Disturbances
Respiratory System	Respiratory alkalosis; hyperventilation; weakening of the respiratory muscles work; dyspnea, cyanosis, adult type of respiratory distress syndrome; diffuse infiltrates in the lungs; the need for respiratory support.

Cardiovascular System	Increase in cardiac output in the beginning of disease with a consequent decrease one; reduction of peripheral vascular resistance, vasodilation; endothelial cells damage, decrease in vascular tone and blood pressure (early shock); tachycardia, bradycardia; myocardial depression, hypoperfusion of organs; refractory hypotension (late shock), the need for hemodynamic support.
Mental Status	Hypoperfusion of the brain, increased production of endorphins; disorientation; drowsiness; agitation or retardation; stupor, coma; increase in protein level in cerebrospinal fluid with normal cytosis.
Urinary System	Hypoperfusion of the kidneys, renal tubular injury (azotemia and oliguria); edematous syndrome.
Liver	Enlargement of the liver, jaundice; moderate dysfunction as early symptoms; hypoproteinemia, increase in bilirubin and enzymes (AST, ALT, LDH) as unfavorable prognostic sign.
Hematological Parameters	Neutrophilic leukocytosis in the initial stage (not always); vacuolation and toxic granularity of neutrophils (always); thrombocytopenia, DIC-syndrom; eosinopenia; decrease in serum iron (the phenomenon of redistribution and binding with protein) as a constant symptom; hemorrhages; necrosis.
Endocrine System	The adrenal insufficiency (decrease in cortisol, thyroid hypofunction (reduced T3 and T4 with normal TSH).

Respiratory disorders in the early stages of sepsis are manifested by hyperventilation (tachypnea), which leads to the development of respiratory alkalosis and respiratory muscles fatigue, progressive respiratory failure. The last

one can be eliminated with the help of timely intubation and artificial lung ventilation. Increase of hypoxemia and interstitial pulmonary edema shows the development of respiratory distress syndrome (RDS), which is the main cause of death in septic patients.

Cardiovascular response also is the result of subcellular dysfunction and metabolic disorders due to the cytokines complex influence. Typical cardiovascular disorders in sepsis are tachycardia, hypotension, increased cardiac index, reduction of left ventricular stroke volume and decrease in myocardial contractive function. Renal failure with azotemia and oliguria associates in the later stages of sepsis, as well as liver dysfunction with hyperbilirubinemia, violation of aminotransferase activity. Thrombocytopenia and disseminated intravascular coagulation syndrome develop. CNS dysfunction is possible with violation of consciousness (disorientation, agitation, psychosis).

The phenomenon of bacterial translocation with subsequent penetration to the portal system and then into systemic blood flow as a result of increased intestinal permeability is also important in the pathogenesis of multiple organ failure.

Terminal part of ileum and cecum are the natural reservoir of gram-negative bacteria. In certain pathological conditions or diseases (ischemia, intestinal wall injury, hemorrhagic shock, ileus) bacteria can pass through the intestinal wall, reach the mesenteric lymph nodes, portal circulation, intra- and extraperitoneal organs. If the liver can not cope with the barrier function, microbial toxins fall into the blood circulation.

Furthermore, translocation of bacteria and toxins causes local activation of immune cells, production of cytokines and other mediators. These processes further break the barrier function of the intestine and as the result the "vicious circle" is formed. It is necessary to take into account the fact that the intestine and its associated lymphoid tissue are the largest organs of the immune system in human organism.

The following factors contribute to increasing intestinal barrier permeability:

1) damage of the intestinal barrier (epithelium);

2) hemodynamic violations with regional hypotension development;
3) stresses;
4) immune insufficiency;
5) dysbiosis: violation of the normal intestinal flora ecological balance and excessive growth of pathogenic bacterial flora;
6) increase in toxins and other biologically active substances concentration in the small intestine opening;
7) disturbances of intestinal mucosa epithelial cells renewal.

Thus, the presence of microbial markers in the blood indicates the microbial composition of the patient, regardless of the bacteria or local inflammation presence. Markers of prevailing in the healthy human intestine bacteroides, eubacteria and bifidobacteria are either absent or found in small quantities in the blood. This is an indirect proof of the current hypotheses concerning immunological tolerance to anaerobic symbionts and therefore low probability of these bacteria phagocytosis. That is why markers of bacteria, which are identified in blood, are not necessarily present in the form of bacteremia. Small molecules can penetrate into blood circulation system from the natural breeding places (from biocenosis) and / or from other local inflammatory lesions.

Risk factors for sepsis development:

- Age (neonates, infants, elderly persons);
- Prematurity (reduction of gestation period increases the risk of infectious complications);
- Burns, traumas;
- Prolonged use of invasive methods of diagnosis and treatment;
- Chemotherapy, the use of immunosuppressive drugs;
- inadequate nutrition (malnutrition);
- Genetic predisposition (inadequate immune response, reduced immunological reactivity, tendency to thrombi formation, the lack of the complement system, etc.).

Septic shock – is an extremely severe clinical syndrome which manifests in the violation of human organism to support the hemodynamics and homeostasis as a

result of inadequate tissues oxygenation and circulatory disorders that occur with systemic inflammatory response to infection. Resistant hypotension and perfusion violations are uncorrectable by adequate infusion, inotropic and pressor therapy.

Reduced systemic vascular resistance and hypotension with increased cardiac output are typical for septic shock. One of the remarkable sign of septic shock is the inhibition of myocardial contractive capacity as a result of lactic acidosis and proteolysis increasing.

In the development of septic shock two stages are distinguished:

1. Hyperdynamic - reducing peripheral vascular resistance and reflexively increased heart work (increased cardiac output).

2. Hypodynamic – secondary violation of perfusion and oxygenation in relation to regional vasoconstriction and myocardial dysfunction.

Objective criteria for septic shock are:

- Blood pressure is lower by more than 1/3 of the age norm;

- Arterial hypotension persists after infusion therapy using crystalloid or colloids, need for inotropic or pressor support;

- A combination of hypotension with one of the criteria for severe sepsis (impaired consciousness, lactate-acidosis or oliguria).

Adequate breathing in patients with septic shock usually remains saved to the terminal stage, however artificial ventilator requires most of them (~ 80%). The disturbances of cardiovascular system are manifested with the prevalence of heart or vascular failure and their combination. In some cases, even with vasoactive support perfusion and blood pressure can not be restored, there is a risk of adrenal insufficiency. Mortality in septic shock is very high (> 80%).

Multiple organ failure (MOF)

MOF combines various syndromes such as respiratory distress syndrome adult type, acute adrenal insufficiency, acute liver failure, acute renal failure, DIC-syndrom, dysfunction of the central nervous system. Lung is the first organ function of which is uncompensated in MOF and is accompanied by high mortality. The high vulnerability of lung is explained by the theory of the "first

filter", according to which the activated blood cells ("neutrophil respiratory burst"), cytokines, toxins, tissue detritus entered in pulmonary capillaries fastest.

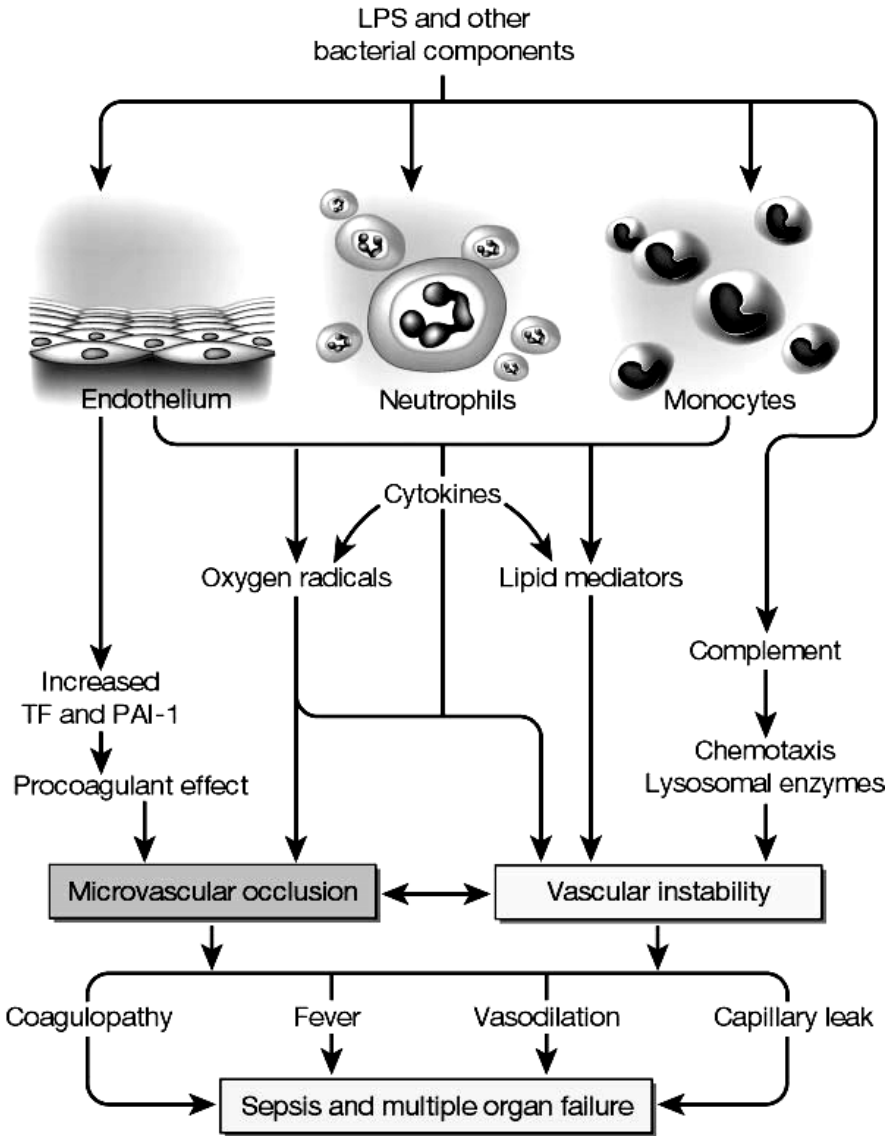

Figure 4. Scheme of multiple organ failure pathogenesis

Acute sepsis - septicemia

Septicemia – is a clinical form of sepsis, when signs of increasing bacterial toxicity are pronounced while local septic processes are absent. This superinfection is circulating in blood bypassing natural barriers, multiplies rapidly, deposits in tissues, causing formation of small abscesses in the organs and tissues. This is characterized by neutropenia, agranulocytosis. Local septic foci are appeared.

Bacteremia means isolation of microorganisms from the blood. It is a possible, but not obligatory, manifestation of sepsis. Lack of microorganisms' isolation from patient's blood should not exclude the diagnosis with presence of only above mentioned sepsis criteria. Even the most strict observance of blood sampling principles and use of modern microbiological technology in the most severe patients can reveal bacteremia no more then 45% of cases. The clinical significance of bacteremia registration is the follows:

- to confirm the diagnosis and identification of the infection process etiology;
- to proof mechanism of sepsis;
- to define the severity of pathological process (bacterial endocarditis, etc.);
- to explain the choice of antibiotic or treatment regime changes;
- to evaluate the effectiveness of therapy.

The treatment of sepsis

Complex treatment consists of conservative and operative measures. The last one is the radical elimination of inflammatory site (necrectomy).

Intensive therapy includes antibiotic, extracorporal detoxification and hemocorrection, infusion therapy, tissues and organs perfusion restoration, immunocorrection, desensitization using glucocorticoids and inhibitors of free radicals.

Complications of sepsis

The main and most dangerous complication of sepsis is septic shock. Sepsis can have other consequences in the form of various pathologies and diseases: endocarditis, thrombosis, pneumonia, bedsores, embolism, hepato-renal syndrome and bleedings.

The prognosis for sepsis depends on the timeliness and adequacy of treatment, virulence of microorganisms and resistance of human organism. Unfortunately mortality exceeds 50%.

Prevention of sepsis is subject to the following recommendations:

- to strength the patient's immune system;
- to minimize the injuries;

- to timely diagnose and treat any infectious and inflammatory diseases;

- to strictly follow the all rules of aseptic and antiseptic for various invasive manipulations, surgery, infusion therapy, and so on.

VII. TUBERCULOSIS: ETIOLOGY, PATHOGENESIS, CLINICAL MANIFESTATIONS, PREVENTION.

Tuberculosis – is an infectious disease caused by Mycobacterium tuberculosis (MBT) and characterized by the development of cellular allergy, polymorphic clinical picture and the formation of specific granulomas in various tissues and organs.

Tuberculosis refers to chronic infectious disease known since ancient times. The name of the disease comes from the Latin word tuberculum – tubercule. Today the disease is acute social and medical problem. Tuberculosis is the disease of one third of the world's population.

The rapidly increasing incidence of tuberculosis and deaths from it all age groups, but the most alarming is the fact that children also are infected.

The main causes of increased morbidity from tuberculosis:

• global drastic decline in living standards, which lead to deterioration in the quality of nutritional status;

• increased migration of persons from epidemic unfavorable areas;

• emergence of Mycobacterium tuberculosis resistant strains for specific therapy;

• declining quality and extent of tuberculosis-care;

Etiology

The causative agent of tuberculosis is Mycobacterium tuberculosis, which was discoverd in 1882 by Robert Koch (that is why another name is bacillus or Koch's bacillus). There are species of mycobacteria: human, bovine, chicken and mouse. They differ in the degree of virulence, pathogenicity, stability and influence on the disease cource. The most pathogenic for man that causes tuberculosis disease is the human type, less pathogenic - bullish. Mycobacterium persistent in the environment, in water can be stored more than 1 year, on the pages of books - 3 - 4

months, in milk - up to 10 days. Under direct sunlight die for 1 - 1.5 hours, during boiling - 5 - 10 minutes, resistant to bases, acids, alcohols. The main feature of the Mycobacterium species are pathogenic, namely the ability to live and multiply in the tissues of a living organism.

Epidemiology

The main source of infection is a sick person with tuberculosis. Sometimes the source can be sick animal (cattle).

Pathways of Mycobacterium tuberculosis in humans or animals organism are: aerogenic (aerosol-transmission and dust), nutritional, or water, contact (through damaged skin) and germinal (intrauterine).

Aerogenic way is a major (90 - 95%). During speaking and coughing the tuberculosis patient secretes drops of saliva and sputum that are spreade to 1.5 - 2 meters and can be present in the air approximately 1 - 1.5 hours, and then settle. This way of Mycobacterium infection spreading is called aerosol-transmissive. Epidemiological importance of this route of infection is a large gathering of people and the conditions of people communication in the family. Infection is possible through inhalation of dust (dust pathway) containing Mycobacterium tuberculosis (droplets of saliva and sputum dry and mixed with dust).

In the room where the tuberculosis patient presents Mycobacterium tuberculosis are found in 30% of cases, sometimes even after 1.5 months. By the certain rules of hygiene (sputum disinfection, cleaning room) air does not include Mycobacterium tuberculosis even in tuberculosis hospitals. Infection of sensitive human organism is possible through inhalation of several Mycobacteria tuberculosis that are suspended in the air. The degree of probable infection correlates with the number of microorganisms isolated from sputum and duration of contact with the patient. In breathing the most part of inhaled droplets and dust settles on the nasal mucosa, tonsils and throat. Intact mucous membrane of the trachea and bronchi is a barrier for the Mycobacterium tuberculosis penetration. First of all, it is the ciliated epithelium of bronchi, mucus produced by glandular cells, plasma surface-active substances (lysozyme, complement, properdyn, β-

lysine). Mycobacteria tuberculosis in a small amount and with normal functioning of these systems are eliminated from the respiratory tract without causing harm to the human organism. In case of the mucous membrane injury or inflammation, they can penetrate the boundaries of the trachea and bronchi. However, in most cases, the Mycobacterium tuberculosis penetration in the internal environment occurs in the alveoli in state of surfactant system violations. Then the agent enters the intrathoracic lymph vessels and lymph nodes, lymphatic thoracic duct and blood.

Alimentary way of infection penetration is observed in the case of food products consumption from animals which are infected with Mycobacteria tuberculosis and through contaminated food and dishware. People are infected with tuberculosis by alimentary route most of all through the milk consumption from cows with tuberculosis. Meat and eggs of animals with tuberculosis have less epidemiological significance because these products almost always before eating subjected to heat treatment. Thus tuberculosis pathogen enters the stomach and then in the intestine where over lymph enter into lymph nodes and blood.

Contact route of Mycobacterium tuberculosis penetration can be observed among surgeons and pathologists, butchers, laboratory, milkmaids when tuberculosis pathogen enters directly through damaged skin or mucous membranes (conjunctiva).

Cases of intrauterine infection of the fetus are described rare. Typically, even women with active tuberculosis birth full-term healthy babies. If immediately after the birth children are isolated from the mother, and then are vaccinated and with appropriate hygienic-dietary conditions for their development, children grow up healthy. Intact placenta is a barrier to the penetration of the Mycobacteria tuberculosis from maternal blood into fetal blood. Intrauterine infection is possible only in generalized form tuberculosis process or placenta damages with tubercles.

Factors that cause the disease are: decreased immunity, frequent diseases of the upper respiratory tract, poor living conditions, humid climate, cooling.

The factors influencing risk of tuberculous infection are shown at Figure 5.

Factors influencing risk of TB infection	
Exposure	The longer the exposure to infection (longer period of time breathing air shared with someone with infectious TB) the greater the risk.
Air Volume	Exposure in small shared spaces (occupying a small enclosed space with someone with infectious TB) increase the risk of infection.
Ventilation	Lack of or poor ventilation (circulation of air) in the space where exposure occurred increases risk of infection
Bacillary Load of the Infectious Patient	The following factors increase the number of mycobacteria generated by a person with TB • Disease of the lungs, upper airways or larynx, • Presence of cough or other forceful expiratory measures (sneezing, singing, etc.), in particular when the patient • fails to cover the mouth and nose when coughing or sneezing, • Presence of cavitation and extent of cavitation by chest radiograph, • Absence of or insufficient TB treatment.

Figure 5 Factors influencing risk of tuberculous infection

Pathogenesis

After pathogen penetration into blood by any of the possible routes and primary generalization in many organs arise morphological changes of the lymphoid infiltration type. The sites of tuberculosis inflammation appear in organs with dissemination into regional lymph nodes in case of tuberculosis process progression.

Unlike endotoxins, exotoxins or enzymes that are defined in the cells of many other pathogenic organisms, damaging effects of tuberculosis are largely determined by protective reactions of human organism in response to the presence of Mycobacteria tuberculosis in tissues. Mycobacteria tuberculosis should stimulate their uptake by macrophages for surviving. Mycobacteria tuberculosis begin to multiply in phagosome of alveolar macrophages, thus macrophages are completely destroyed. As a result, ATP-positive protons production and

mycobacterial sulfatides prevent fusion of phagosome with lysosome and are able to avoid destruction by macrophages. Mycobacteria tuberculosis reproduce slowly (within 15 - 18 hours). However, uncontrolled reproduction can lead to a large number of Mycobacteria tuberculosis, more than 500 million within 20 days. In cases where the process of Mycobacteria tuberculosis digestion is blocked, macrophages are destructed and Mycobacteria tuberculosis released out of the cells. Macrophages secrete in extracellular space the damaged fragments of Mycobacteria, proteolytic enzymes, neurotransmitters that activate T-cells. Thus, an immune response is formed, that plays an important role in the pathogenesis of tuberculosis.

Local changes in the place of Mycobacteria tuberculosis penetration are caused, first of all, by the reaction of polynuclear cells, which are further changed by more perfect form of protective reactions with macrophages participation. They implement phagocytosis and destroy Mycobacteria tuberculosis. The result of macrophages and Mycobacteria tuberculosis interaction is determined by the state of immunity system and other factors, including those that cause digesting ability of macrophages. Mycobacteria tuberculosis from macrophages come to the lymphatic vessels that drain the lungs, and form some foci in the lymph nodes of the root of lungs, then through the thoracic duct can extend through blood vessels in various organs. Phase of bacteremia is asymptomatic. After 3 - 6 weeks in the infected person hypersensitivity to the pathogen develops, and in the places of Mycobacteria tuberculosis localization granulomatous inflammation develops with tuberculous granulomas which has caseous necrosis in the central area, that surrounded by epithelioid and multinuclear (giant) cells Pirogov - Langhans.

As a result of the pathogen with macroorganism first meeting primary tuberculosis forms - 7 - 10% of infected persons who are not able to develop complete immune response. Others persons respond to primary tuberculosis infection without clinical manifestations and define it only by reaction to tuberculin change. The period from Mycobacteria tuberculosis penetration till

positive reaction to the tuberculin appearance is called the period of "latent microbism". It lasts an average 4 - 6 weeks.

Primary tuberculosis is characterized by lymphotropic effect, imperfect immune response, general reactions, tendency to process generalization, and then if sufficient immune response is formed recovery is possible. The consequence of primary tuberculosis is the Ghon's focus formation. It is the calcified pulmonary component of primary tuberculosis complex and calcified lymph nodes that do not have epidemiological significance.

After primary tuberculosis both lymphogenous and hematogenous dissemination is possible with productive inflammation identification in lungs.

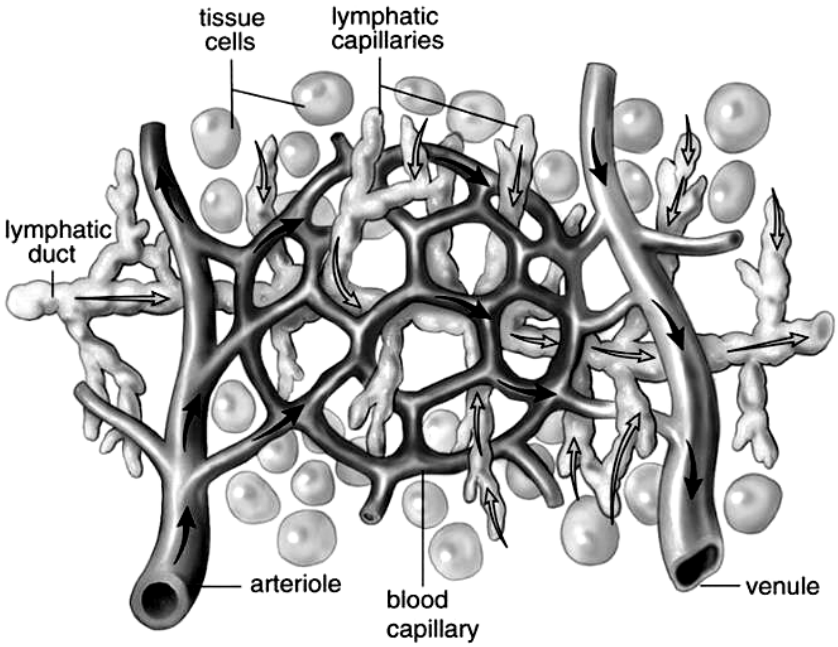

Figure 6. Scheme of Mycobacteria tuberculosis dissemination

Secondary tuberculosis is formed after repeated meeting of macroorganism with Mycobacteriua tuberculosis, and accompanied by endogenous reactivation of old focal lesions. Secondary tuberculosis is characterized by organs disorders and manifests with the formation of focus of infiltration or cavity without involvement of lymph nodes. The basis of reactivation is progressive reproduction of bacterial population and increase in the number of Mycobacteria. However, still remains unknown exactly what conditions can promote Mycobacteriua tuberculosis

reversion, which were in a state of persistence. It has been found that tuberculosis reactivation and development of its various clinical forms more often observed in patients with residual changes with the presence of factors that reduce immunity. There is another way of secondary tuberculosis development – exogenous which is associated with new infection (re-infection) with Mycobacteriua tuberculosis (superinfection). However, when exogenous pathway of secondary tuberculosis development it is not enough mycobacteria penetration in the already infected human organism, even with a massive re-infection or superinfection. Complex of conditions and risk factors that reduce immunity is necessary in this case. Secondary tuberculosis is characterized by a large variety of clinical forms. The main types of pathological changes in the lungs and other organs are characterized by:

1) the foci with predominantly productive tissue reaction, positive chronic cource and the tendency to healing;

2) infiltrative-pneumonic changes with predominantly exudative tissue reaction with a tendency to caseous necrosis development or resorption of inflammatory reaction;

3) tuberculosis cavity which is formed as a result of caseous masses rejection through drainage bronchi.

The described above manifestations caused by pathological changes that develop as a result of an imperfect protective response. Rather than to absorb the Mycobacteriua tuberculosis, the majority of macrophages and leukocytes break down and release a large amount of proteolytic enzymes. This leads to microorganism tissue destruction and local thrombosis of blood vessels. The result of this is a "dilution", which becomes a breeding ground for progressive and resistant growth of extracellular located Mycobacteriua tuberculosis. Bacterial growth increases the inflammation until tissue destruction and process spreads into bronchial tubes. Diluted mass penetrates the airways and cavity is formed in the lung.

A variety of tuberculosis pathological manifestations makes the conditions for various tuberculosis changes, especially in chronic disease with periods of process exacerbation and chronization. Mycobacteriua tuberculosis can be distributed over the blood or lymph from the destructive zones to various undamaged tissues and organs. The outcome of the disease depends on the course - progressing or regressing, effectiveness of treatment and the possibility of pathological changes regression.

Reducing the Mycobacteriua population under the influence of specific chemotherapy does not always result in a cure. Termination of tuberculosis and the subsequent cure depend not only on reducing the Mycobacteriua tuberculosis population, but also on the ability of the human organism to provide reparative processes for tuberculosis regression and its termination.

Factors contributing to the tuberculosis process reactivation are different diseases: diabetes mellitus, Hodgkin's disease, silicosis, gastric ulcer and duodenal ulcers, post gastrectomy and duodenal rejection states, chronic inflammatory lung diseases, mental disorders with depressive syndrome, alcoholism, stresses, AIDS, prolonged use of glucocorticoids, cytotoxic drugs and immunosuppressive therapy. If protective systems are insufficient, the Mycobacteriua tuberculosis are distributed with lymph and blood flow from primary focus in various organs, including lungs, bones, skin and others.

Prevention of tuberculosis

Isolation of tuberculosis infection source is the most important epidemiological measure in the collective or family. Patients must be treated at hospital during all the time of bacteria releasing to stop contact with them.

Adults who were in contact with the patient must be examined annually by X-ray, children and adolescents - through tuberculin test. Also preventive treatment with antituberculosis chemotherapy for 3 months must be carried out. Current disinfection must be done in hospitals, apartments or resorts.

Prevention of tuberculosis consists of the following components:

1. Social - improvement of environmental conditions, improving living conditions and health, to limit alcoholism, drug addiction, smoking and others.
2. Sanitary - implementation of measures to prevent infection with Mycobacteriua tuberculosis and to make safe contact with tuberculosis patients in the active form.
3. Specific - is vaccination and revaccination with BCG vaccine. In vaccinated at birth children immunity persists for 5 - 7 years.
4. Chemoprophylaxis - is the use of antituberculosis drugs to prevent tuberculosis in people who have a great risk to be infected. Among persons after chemoprophylaxis, the number of diseases in 5 - 7 times less compared to persons who were not performed one.

EXAMPLES OF TESTS:

1. Tests to control the initial level of students' knowledge:

1) Which bacterial structure from listed below defends it from phagocytes?
   A) Cellular membrane
   B) Endospores
   C) *Capsule
   D) Fimbriae
   E) Pili
2) Quantitative manifestation of microorganism pathogenicity is:
   A) *Virulence
   B) Toxicity
   C) Invasiveness
   D) Adhesiveness
3) Which way of microorganism transmission is associated with invasive medical, diagnostical and cosmetical procedures?

A) Airborne
B) Droplet
C) Vertical
D) Vector
E) *Parenteral

4) Viral antigens and antigens of Major Histocompatibilty Complex are present on the membranes of virus-infected cells. Which cells of immune system can directly identify these antigens and cause cytotoxic influence on them?
A) Macrophages
B) Cells that produce antibodies
C) Cells that produce interferons
D) *Natural killers
E) Neutrophils

5) Tubercule bacilli can affect many tissues of the human organism. Choose the tissue which is affected less then others.
A) Skin
B) *Nervous
C) Lymphatic nodes
D) Bone
E) Serous membranes

6) Tuberculosis infection of bones and joints usually develops as a result of hematogenous transmission of the infection from the site of primary inflammation. Choose the most common place of primary infection in the described case:
A) Liver
B) Brain
C) *Lungs
D) Heart
E) Kidney

7) A positive Mantoux test indicates:
   A) The organism susceptibility to tuberculosis aggression
   B) The absence of mycobacterium tuberculosis infection in organism
   C) *Tuberculosis contamination
   D) All of the named above
   E) None of the correct answer
8) Bacterial sowing of blood in sepsis is necessary to be done:
   A) At normal body temperature of the patient
   B) *During shivering
   C) After 6 - 12 hours of antibiotics withdrawal
   D) *At the height of temperature reaction
   E) Immediately after the temperature decrease
9) The constant symptoms of sepsis are :
   A) *Chills
   B) Low body temperature
   C) Bacteremia
   D) *The presence of purulent focus
   E) Yellowness of the skin and sclera
10) Manifestations of Inflammatory Response Syndrome to inflammation are:
   A) Apathy
   B) Swelling of the legs
   C) Yellowness of the skin
   D) *Respiratory rate over 20 per minute
   E) *Leukocytosis than 12 × 109 / L
11) What are the main features of bacterial toxic shock:
   A) *Oliguria
   B) *Hypotension
   C) Hypertension

D) Bradycardia

E) Leukopenia

2. Tests to control the final level of students' knowledge:

1) Septic endocarditis was diagnosed in the patient. Body temperature for 5 days was around 39,5°C -40,2°C. On the 6-th day body temperature dropped quickly to 35,2°C. Acute vascular insufficiency – collapse – has developed. Choose the main mechanism of collapse development:

A) *Vasodilation

B) Hyperventilation

C) Increase of sweating

D) Tachycardia

E) Polyuria

2) Isoniazidum is used in clinics for treatment of tuberculosis. This medicine is known as anti-vitamine that can enter tubercule bacilli. Tuberculostatic effect is explained by the disturbance of replication and oxidation-reduction reactions due to altered co-enzyme formation. Choose this coenzyme from the given:

A) *NAD

B) FAD

C) FMN

D) TDF

E) CoQ

3) 47-year-old patient has been ill with tuberculosis for 3 years. Patient complains of breathlessness, dull pain in the right side of chest, body temperature 37,7°C. Right-sided exudative pleuritis was diagnosed. The patient was made pleural puncture. Which type of the cells will predominate in exudate?

A) *Lymphocytes

B) Neutrophils

C) Erythrocytes

D) Atopic cells

E) Eosinophils

4) Patient C., 40 years old was operated to drainage phlegmon of the lower back area. On the 3rd day after operation his body temperature has suddenly risen, symptoms of intoxication appeared, white blood cells count has significantly increased. The process of wound healing has stopped. Wound exudate became purulent. Which complication has developed in the patient?

A) *Sepsis

B) Putrefactive phlegmon

C) Erysepelas

D) Allergic reaction

E) Eryzepeloid

5) Patient has been admitted to a hospital from a local ambulance where five days later linear section of anthrax was performed. In the early postoperative period patient's condition remained difficult. Patient's examination: tachypnea, tachycardia, leukocytosis, hyperthermia. In bacteriological examination of blood hemolytic streptococcus is revealed. What is your prospective diagnosis?

A) Abscess of back development

B) *Sepsis

C) Fever resulted from toxins resorbption

D) Systemic inflammatory response

E) Septic shock

6) The patient of 20 years died with symptoms of intoxication 8 days after artificial criminal abortion on pregnancy term 14 - 15 weeks. At autopsy the dead body: sclera yellow color, purulent necrotic endometrium, multiple abscesses in the lungs, spleen hyperplasia with a large number of neutrophils in its sinuses. Which post-abortion complications developed in a patient?

A) Hemorrhagic shock

B) Hepatitis A

C) *Septicopyemia

D) Chronic sepsic

E) Septicemia

7) After two days postpartum women developed the clinics of shock with the syndrome of disseminated intravascular coagulation, that resulted in death of the patient. At autopsy it was found: endomyometritis purulent, purulent lymphangitis and regional lymphadenitis, suppurative thrombophlebitis. In parenchymal organs - degenerative changes and inflammation. What is the most likely diagnosis?

A) Cystic entry

B) Syphilis

C) Genital tuberculosis

D) Thromboembolism with amniotic fluid

E) *Sepsis

8) Child 3 weeks is hospitalized in serious condition with symptoms of purulent omphalitis and sepsis beginning. What is the way of infection entrance in this case is the atrium?

A) * Umbilical wound

B) Skin

C) Oral mucosa

D) Lungs

E) Mucosa of gastrointestinal tract

9) The child is 2 years old is diagnosed with stage septikopiyemic of the sepsis. The patient is treated with antibiotics and immune-stimulating therapy. During the last days bleeding from the injection site appeared, skin rash developed in the form of petechiae and ecchymosis, extravasation. Which complication has developed in a child?

A) Anaphylactic reaction

B) *Disseminated intravascular blood clotting

C) Hemolytic crysis

D) Drug allergy

E) Toxic shock

10) The patient was operated on acute paraproctitis. On the 5th day after operation on the background of antibiotic therapy and detoxification with the positive local dynamics of the disease chills, hyperthermia, tachycardia and euphoria were appeared. The doctor suspected sepsis development in this patient. Which additional method of patient's examination can confirm the diagnosis?

A) X-ray of the lungs

B) Ultrasound of the liver

C) *Blood cultures for the pathogen

D) Determination of microbial contamination of the wound

E) The definition of middle molecules

11) Patient L., 56 years old, is suffered from fibro-cavernous pulmonary tuberculosis. In the last 3 weeks increased cough, weakness, amount of purulent-mucous sputum with blood admixture. What is the cause of respiratory failure that is developed in this patient?

A) *Reduction the number of functioning alveoli

B) Violation of the respiratory center

C) Violation of nervous – muscular apparatus

D) Violation of the chest mobility

E) Violation of the airway

12) The drugstore of regional tuberculosis health center has got a number of therapeutic and diagnostic products, including tuberculin. What purpose will be used this drug for?

A) Serological diagnosis of tuberculosis

B) Specific prevention of tuberculosis

C) Specific therapy of tuberculosis

D) Identification of mycobacterium phagotype

E) *Allergic diagnosis of tuberculosis

13) The patient has suffered from tuberculosis for many years. On the patient's clinical examination: swelling of the neck veins, edema of the lower extremities, enlargement of the liver, ascites. At auscultation the heart sounds are muffled. On ECG – reduction of voltage; on echocardioscopy - heart chambers are not enlarged, the chest X-ray revealed calcifications. What is the mechanism of blood congestion in the big circle of circulation?

A) Lack of tricuspid valve
B) Reduction of contractility of the right ventricle
C) *Violation of right ventricular diastolic filling
D) Increased pressure in the pulmonary artery
E) Stenosis of the right atrioventricular opening

14) After BCG vaccination of newborn anti-tuberculosis immunity exists until the body has live bacteria vaccine strain. How is this kind of immunity named?

A) Humoral
B) Congenital
C) Specific
D) *Unsterile
E) Cross

15) A man, who lived in the endemic region, suffered a three-day malaria. After moving to the non endemic area in 1.5 years he got sick with malaria again. Which form of malaria is the most likely in this case?

A) *Relapse
B) Reinfection
C) Superinfection
D) Persistent infection
E) Secondary infection

16) The patient recovered from dysentery Sonne and re-infected with the same pathogen. How is this form of infection named?

A) Persistent infection
B) Relapse
C) Super infection
D) *Reinfection
E) Chronic infection

17) Patient was prescribed specific medication for improving wound healing of oral mucosa. This medication is the thermostable protein which is found in human tears, saliva, breast milk, and also can be identified in fresh chicken egg. It is know that it belongs to the human organism natural resistance factors. What is this protein named?

A) Complement
B) Interferon
C) *Lysozyme
D) Interleukin
E) Imanin

18) It is known that three links are involved in the development of infectious and epidemic process. The first link in the infectious process is a pathogen. What is the first link of epidemic process?

A) *The source of infection
B) The dose of microorganism
C) The pathway of infection penetration
D) Certain environmental conditions
E) Reactivity of human organism

19) Patient was treated for a long time in a department of pulmonology with severe pneumonia, which was cured badly with antibacterial therapy. Microscopic examination of sputum revealed bacteria - Candida albicans. Which group of infections has caused the disease of this patient?

A) *Opportunistic infections
B) Zooanthroponotic infections
C) Primary infection

D) Zoonotic infection

E) Local infection

Literature:

1. General and clinical pathophysiology: textbook for students of higher educational institutions, of IV th level of accreditation / A. V. Kubyshkin [et al.] ; ed. by.: A. V. Kubyshkin, A. I. Gozhenko . - 2nd ed. - Vinnytsya : Nova Knyha Publishers, 2016. - 656 p

2. Simeonova, N. K. Pathophysiology : textbook for students of higher medical educational institutions of the III-IV accreditation levels approved by the Ministry of Public Health and the Ministry of Science and Education of Ukraine / N. K. Simeonova ; ed. by V. A. Mikhnev. - 2nd ed. - K. : AUS Medicine Publishing, 2015. - 544 p.

3. Pathophysiology : textbook for students /P.F. Litvitsky, S.V. Pirozhkov, E.B. Tezikov).- Moscow:Geotar-Media.-2016.- 432P

4. Robbins Basic Pathology/ Kumar, V., Cotran, R. S., Robbins, S. L. .-7th ed.- Philadelphia, PA, Saunders.-2003.- - 873 p

5. Gould's Pathophysiology for the Health Professions/ Karin C. VanMeter, Robert J. Hubert.- 5th ed.- Elsevier Saunders.-2014.-694 p.