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Immunology of Infections at the Present Stage: Immunology of Nosocomial Infections

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Abstract

Analysis of etiology, pathogenesis, evolutionary specifics of causative pathogens of nosocomial infections, infection mechanisms, diagnosis principles, prevention, treatment, immunotherapy specifics of individual disease forms.

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Introduction

Nosocomial Infections (NCIs) are any clinically identifiable or asymptomatic microbial or viral disease that affects a patient as a result of admission to a health care facility or after receiving medical care. This category also includes medical staff, who carries out official duties in Health Care Institutions (HCI) [1].

The NCIs include: infectious diseases, which occurred in a hospital; infections acquired outside the hospital, but manifested in it (drifts); infections acquired in a hospital or other health care facilities, but manifested outside the hospital. The totality of nosocomial infections is divided into several groups: purulent-septic infections leading cause of morbidity; airborne infections; acute intestinal infections; viral hepatitis [2].

NCIs constitute 2-30% of all infection types, with a lethality of 3.5 to 60%. In case of generalized forms, mortality can reach 100%. At autopsy, infections are registered in 50% of cases; in about half of patients they are the cause of death. Nosocomial infections are found in any given medical clinic. Every 7 days of hospitalization, the number of infected people increases by 10%. In surgical clinics, the frequency of infection is 46.7 cases per 1000, in therapeutic hospitals - 36.6, in gynaecological - 28.1, in maternity wards - 15.3, in pediatric - 13.9 per 1000 [3].

Etiology and Pathogenesis of NCIs

Simultaneous circulation of pathogens such as anthroponoses, zoonoses, sapronoses is possible at a health facility. Most frequent are mixed infections caused by several pathogens, mostly of exogenous nature. A combination of bacteria with viruses, protozoa, fungi is possible. As a rule, infections occur simultaneously, but can also be successive.

Pathognomonic pathogens include more than 200 species of pathogenic and opportunistic microorganisms belonging to non-

fermenting Gram-negative aerobic bacteria- a heterogeneous group of non-spore sticks or coccobacilli from several families. They constitute a part of the resident microflora of the mucous membranes and human skin.

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Gram-negative bacteria - non-fermenting sticks (*Pseudomonas*, *Acinetobacter*), *Escherichia coli*, *Klebsiella*, *Proteus*, *Enterobacter*, *Alcaligenes*- constitute 49% of the healthcare-associated infections, mainly affecting the genitourinary tract. Gram-positive pathogens - *Staphylococci*, *Streptococci*, *Enterococci* - cause 45% of hospital infections, especially in surgical, obstetrical, pediatric and oncological facilities, as well as carried by 15-72% of medical staff; *Legionella* multiply in water conditioners and cause outbreaks of pneumonia in closed facilities.

The taxonomic list of microorganisms participating in the epidemic process of NCIs is unlimited and includes all major groups of known microorganisms, such as representatives of normal human microflora (viruses, bacteria, fungi, protozoa). The etiological agents of NCIs are pathogenic, opportunistic and free-living microorganisms. The causative agents involved in the epidemic process differ significantly in the main ecological reservoir. Infectious process can be caused by both obligate and facultative parasites, as well as by saprophytes in the parasitic phase of existence.

Pathogenesis of NCIs

The patterns of biochemical and energy processes in microorganisms in a hospital can significantly differ from those in a natural environment. Additionally, for intra-hospital infection-following invasive interventions - to occur, a high virulence of the pathogen is not required, the dose of the causative agent is far more important. While adapting to the aggressive effects of unfavourable factors of the hospital environment, the survival time of bacteria on objects can be quite long. It has been established that, as a rule, epidemic spread of the hospital strain of the causative agent of anthroponous infection is not found in washings from environmental objects. Under unfavorable conditions, bacteria become uncultivated, form dormant forms with reduced metabolism, do not multiply, but remain quite viable, retaining virulence. When these conditions change, these resting forms are reversed into vegetative forms, again registered with the bacteriological method. Microorganisms exist in 2 types - in mobile form and in fixed biofilm [4].

The following features of circulating NCI pathogens were revealed: 1 - aerotolerance, ratio to the concentration of oxygen ions, hydrogen (anaerobes, aerobes). 2-abiotic factors affecting the state of the population of microorganisms - intensive exposure to ultraviolet radiation, X-rays, a variety of drugs, antiseptic and disinfectants. 3-biotic factors - micro- and mesofauna, unicellular algae.

In the opinion of several authors, one of the regularities in the etiology of NCIs is the high rate of pathogen evolution: 1- an increase in the composition of pathogen species, primarily represented by opportunistic and saprophytic bacteria and fungi. 2- an increase in the number of infections of enterobacteria, non-fermenting gram-negative bacteria (*Pseudomonas*, *Acinetobacter*, *Alcaligenes*, etc.) in the etiology of coagulase-negative staphylococci, nonclostridial anaerobes. 3- increase in the resistance of NCI pathogens to antibiotics, antiseptics and disinfectants and, as a result, a change in the etiological role

of different bacterial groups in the development of NCIs. 4- the development of new biotopes by pathogens in the human body, the growing adaptation of bacteria to the biotope conditions, which leads to an increase in recurrent and chronic forms of the disease, the formation of stable bacterial and bacterial-fungal associations in various hospitals. 5- the dependence of the evolution of NCI pathogens on the types of hospitals, nosological forms of diseases, the nature of surgical interventions, the methods of diagnosis and treatment, the nature of antimicrobial activities, the extent and types of using antimicrobial agents - antibiotics, antiseptics, disinfectants. 6- dependence of the frequency of stabilization and the rate of its formation on the microbe type, the type of preparation, the scale and validity of its use, the degree of heterogeneity of hospital bacteria ecowars in resisting antimicrobial agents. For example, *Salm typhimurium* forms hospital strains in 1 day, *Pseudomonas aeruginosa* in 27 days, with multi resistance to almost all antibiotics, and ability to overproduce and transmit its own beta-lactamase to enterobacteria, widespread in health facilities, and resistant strains spread all over the world [5].

Mechanisms of transmission of nosocomial infections

In medical-prophylactic institutions, both natural (airborne, food, aspirating, fecal-oral, contact, vertical, transmissible) and artificial (artificial manipulation- associated with invasive diagnostic procedures, therapeutic invasive and noninvasive procedures) mechanisms can be realized.

Pathogens are found in: urinary catheters, artificial respiration apparatus, other respiratory equipment, hemodialysis machines, distillers, antiseptic solutions, blood pressure gauges, blood for transfusion, medicaments, sticks, staff hands, hospital linen, food, water, etc. NCI pathogens can happen to be the freely living species on food products, in water, drugs. Human parasites constitute the largest portion - though a permanent inhabitant of many biotopes of the human body and symbiotic with it - under certain conditions they can turn competitive and cause illness.

Pathogenicity

Pathogenicity of germs is low, variable, determined by a set of aggressive factors at high concentrations of pathogens, and marked by intra and inter population variability. These microorganisms have a pronounced resistance to antibiotics, sulfonamides, other antibacterial drugs, to antiseptic drugs-chlorhexidine, hexachlorogen, etc. One pathogen can be resistant to 4-5 antibacterial drugs.

Susceptibility and contingents of increased risk of nosocomial infections

A feature of NCIs is that they affect only certain contingents of patients. The probability of the development of an infectious disease in patients under MPI conditions depends on many factors: the pathogen properties ("hospital strain"), the magnitude of the infecting dose, and the state of general and local immunity, i.e. susceptibility [6,7].

Factors influencing the susceptibility of the organism to infections are: 1- age (newborns, children, elderly). 2- malnutrition, alimentary dystrophy. 3- concomitant chronic somatic diseases. 4- changes in normal microflora; - impaired immune status. 5- disruption of skin integrity (extensive burns, wounds). 6- invasive treatment and diagnostic procedures. 7- unfavourable environment (ionizing and non-ionizing radiation, and other abiotic factors).

Features of nosocomial infections

1- pathogens do not have a pronounced organ tropism. 2- the same species can cause various diseases (organ damage). 3- polyethiologic, i.e. the same nosological form of the disease can be caused by any potentially pathogenic microorganisms. 4- the clinical nature of the infections depends more on the affected organ than on the type of pathogen. 5- infections often occur as mixed micro-infections, more often with open, less often with closed processes, more frequent with chronic flow than with acute. 6- infection is characterized by a chronic course that can either slowly progress or transition from the initial pathological acute process to prolonged chronic. 7- infections have a pronounced tendency to generalization and complications. 8- reduction of the localizing abilities of the body (inferior inflammation). 9- infections are characterized by slow development and low intensity of acquired immunity, which causes refractoriness to the therapy. 10- pathogens possess a wide polyresistance to antibacterial drugs, high heterogeneity and variability, signs of connection with auto-infectious agents, with multiple sources of infection [7].

The state of the immune system

One of the causes of nosocomial infections is damage to skin, mucous membranes and formation of immunodeficient conditions. Such patients show an imbalance in immunity T-link indicators, as well as an excessive activation of humoral protective reactions, especially IgM, a phagocytosis insolvency - a disproportion between the absorbing and oxygen-producing capacities of corresponding cells, type changes in the cytokine status.

Diagnosis and Treatment of NCI miRNAs as Diagnostic Markers of Prostate Laboratory diagnostics of infections

1- bacteriological diagnosis (pathogens slowly grow on nutrient media, sometimes only at room temperature, identification of microorganisms is difficult due to low enzyme activity, there is no single classification of pathogens). 2- polymerase chain reaction. 3- immunological diagnostics (use of counter immune electrophoresis, accuracy of diagnosis - 68-100%, reaction of conglutination (CON) - 46, 5-78, 6%, enzyme immunoassay - 93, 3-100%, latex agglutination - 90-90, 6%, radioimmunoassay) [8].

Principles of treatment and prevention of infections

1- sanitation - specific and nonspecific - of pregnant women, surgical patients in the preoperative period, before organ transplantation, etc. 2- use of antibacterial reserved drugs and their combinations. In reality, this leads to the replenishment of the hospital resource of antibiotic-resistant bacteria. 3- use of antimicrobial sanitation drugs - hexachlorophene, chlorhexidine. They are dangerous in terms of induction in patients with malignant tumours, liver damage, pancreas, etc. 4- administration of bacteriophages to patients, especially locally as an ointment. 5- correction of dysbiosis. 6- effective airborne disinfection. 7- antimicrobial underwear with antibacterial impregnation. There is a real risk of getting toxic drugs through wound pathways into the body of patients, through the breast milk to children. 8- active and passive immunotherapy. 9- inoculation of the contingent threatened for IHI (interhospital infections) with low immunogenic vaccines (Bronchomunal, Paspat, IRS-19, etc.). 10- differentiated immunotherapy.

In general terms, the general principles of immunotropic treatment of purulent-inflammatory diseases imply the use of intravenous immunoglobulins (Pentaglobulin etc.), lycopide, myelopid, imunofan, polyoxidonium, diuzyphon, betaleukin, roncoleukin, kipferon, tactivin, thymogen, leacadin, leukinferon, plasmapheresis, hemosorption and other methods of detoxification therapy, hyperbaric oxygenation, etc.

Ideologically, the modular immune prophylaxis and immunotherapy of nosocomial infections have been developed - the administration to patients the medicinal modules - sets of immunoactive drugs [9,10].

Prophylactic module

This is a method of protection against NCIs by creating or enhancing specific artificial immunity. Types: 1- specific active - introduction of vaccines / toxoids; 2- specific passive - introduction of serum preparations/Ig-globulins; 3- phage-vaccine - a combination of bacteriophages and antigenic drugs; 4- active-passive - combination of vaccines and specific serum drugs; 5- nonspecific active for antigenically non-specific infections - introduction of normal donor Ig-globulins, modulators of general action.

Monovalent therapeutic module

This therapeutic module signifies the use of pharmacological or non-drug mono immunotherapy to prevent or correct changes in the function of the immune system. Types: 1- specific active stimulating (therapeutic vaccines). 2- specific adaptive (transfer factor). 3- specific passive, substitutive (antibodies). 4- nonspecific active stimulating (adjuvants, modulators). 5- nonspecific adaptive stimulating (thymo/myelo-peptides). 6- non-specific passive substitute (antibodies, immunocompetent cells). 7- systemic - effect on the main links of the immune system (T-, B-, phagocytic). 8- local - activation of local resistance in organs

communicating with the external environment. 9- metabolic, auxiliary (metabolites, vitamins, membrane-protectors, energy, adaptogens). 10- non-pharmacological (ozone solutions, sorption methods, plasmapheresis, physiotherapy methods - laser, ultrasound, ultraviolet and magnetic-infrared-laser exposure), etc.

Polyvalent therapeutic module

This is the simultaneous or sequential administration of several actions to a patient with different mechanisms of action to eliminate immunological disorders and improve the effectiveness of traditional treatment of diseases. Types: 1- immuno-metabolic (combination of modulators with metabolites/antioxidants). 2- pharmaco-non-pharmacological (sequential or simultaneous appointment of pharmacological and non-drug correctors to patients). 3- regional-systemic (combination of modulators of regional and systemic immunity). 4- combined (two pharmacological corrector or - non-drug factors with different mechanism of action). 5- adjuvant active (vaccine + adjuvant/modulator). 6- adjuvant passive (serum+adjuvant/modulator). 7- alternative (simultaneous or sequential use of stimulants and depressors of protective reactions). 8- complex (combination of more than two immunotropic effects). 9- complex sequential- (using 2-3 correctors of different mechanisms of action against the background of metabolic cocktails with an interval of 2-3 weeks).

Epidemiology of NCIs

Nosocomial infections develop in conditions of artificially created specific ecological system of health facilities. The biotic and abiotic factors operating in this ecosystem are unique, and the ongoing inter-population processes differ significantly from those in nature.

The epidemic process manifests as sporadic as well as epidemic morbidity. The manifestations of the epidemic process in different hospitals depend on the leading etiological agents, the profile of the hospital, the volume of the medical and diagnostic procedures performed. A distinctive feature of the epidemic process of NCI is its autonomous development with the formation of persistent (long-term) nosocomial outbreaks (for example, salmonellosis). According to statistics, in Russia the number of outbreaks and the number of people affected by NCIs persist at a high level, which is associated, as a rule, with a violation of the sanitary and anti-epidemic regime in a health facility.

Epidemiological surveillance of NCI includes: 1- registration. 2- deciphering of the etiological structure of the disease. 3- sanitary-bacteriological examination of objects. 4- characteristics of the isolated strains. 5- control of staff health. 6- epidemiological analysis of all the data obtained.

Clinical forms of NCIs

The spectrum of lesions in the NCIs is extremely wide: meningitis,

encephalitis, mastitis, pneumonia, septic endocarditis, lesions of the urogenital organs of the urological sphere, purulent infections of the soft tissues, infection of the perianal zone, wounds, including postoperative, burns, deep pyoderma, diarrhea, sepsis, septicopyemia, etc. [7].

Bacteraemia

A phase of some common and systemic infectious disease pathogenesis. At a certain stage, the pathogen from the primary focus enters the bloodstream and circulates in it. As a result, a significant portion of the microorganisms dies and causes intoxication. Reproduction of pathogens in the blood does not occur. This phase is regular in diseases transmitted by bloodsucking insects (recurrent typhus, malaria) and also with typhoid fever, leptospirosis, brucellosis, listeriosis. Short-term (transient) bacteraemia is possible with starvation, over-fatigue, overheating, hypothermia, trauma, surgical interventions, etc.

Sepsis

A severe generalized acute or chronic infectious disease of the blood on the background of deep immunodeficiency or allergy. The main habitat for microbes is blood. In case of *septicaemia* (primary sepsis) the agent immediately penetrates into the blood from the entrance gate and multiplies in it. There is no primary local inflammation focus; secondary metastases develop. Secondary metastatic sepsis (*septicopyjemia*) occurs as a result of the generalization of the local infectious process. It can be wound, postnatal, umbilical, urogenital, genital, etc. Sepsis refers to polyethiologic diseases (*pyogenous staphylococcus*, *Escherichia coli*, *Proteus*, *Klebsiella*). The etiological structure of *septicopyjemia* reflects the type of disease. For example, wound sepsis is more often caused by *staphylococci*, urogenital - by gram-negative bacteria, dental - by asporogenous anaerobes, burned - by *Pseudomonas aeruginosa*. The leading factor in the development of sepsis is deep immunological failure, an inferior inflammatory reaction. The clinical situation of sepsis caused by various microorganisms is near.

Treatment of generalized infections

The intravenous immunoglobulins (pentaglobin enriched with IgM), the methods of detoxification therapy (plasmapheresis, hemo-immunosorption), the monoclonal antibodies blocking pro-inflammatory cytokines. Several auxiliary agents are used - lycopide, myelopid, imunophan, polyoxidonium, betaleukin, leukiniferon and others.

Purulent infection of wounds

Wounds are mechanical damage to tissues disrupting their integrity. Wounds can be operational, domestic, production, combat. Infection of wounds is carried out by pyogenic, *Staph. aureus*, *Proteus*; bacteroides, enterobacteria, *Pseudomonas aeruginosa* (wounds of the perineum, pelvis, abdominal cavity). The necessary requirement for the development of wound infection is suppressed local and systemic immunity in patients. Burn wounds get infected immediately after the burn with microorganisms from intact skin, air, clothes; usually it is a little-

virulent flora, poly-antibiotic-resistant epidermal *staphylococcus*, *Pseudomonas aeruginosa*, *E. coli*. With deep burns, there are anaerobes, as well as *Staphylococcus aureus*, *pseudomonas*. Immune status is characterized by the activation of all links. The main method of activation of anti-infective resistance (treatment) is the use of large doses of immunoglobulins; stimulation of other types of protective reactions is ineffective. The immunotherapy should include - thymus derivatives, imunofan, myelopid, gepon, lycopide, polyoxidonium, diucifon, preparations of immunoglobulins, metabolites, antioxidants, non-drug correction means - ozonized sodium chloride solution, low-intensity laser radiation, etc.

Acute otitis media

Disease complication of the upper respiratory tract, or a consequence of hematogenous drift from other purulent-inflammatory foci of *staphylococci*, *pyogenic streptococci*, *klebsiella*, *E. coli*, *anaerobic streptococci*, hemophilic stick, especially in children. Often associations of gram-negative bacteria with *Pseudomonas aeruginosa*, bacteroides, fusobacteria are formed. For the treatment of patients, additional assignment of activators of the T-link of immunity, interferons, interferonogens and local anti-infective resistance is recommended.

Acute pancreatitis

At the stage of destruction, novocaine, antimetabolite (5-fluorouracil), then endoxane, cyclophosphamide to suppress the synthesis of autoantibodies, are administered. Later, patients are prescribed leacadin, tactivin, thymalin, roncoleukin, derinat, imunophan, UVO-irradiation of blood, hyperbaric oxygenation.

Sinusitis, frontitis

Complications of rhinitis or periodontal inflammation caused by staphylococci, streptococci. Principles of immunotherapy apply, as in the previous case.

Mastitis

An inflammation of the glandular and interstitial tissue of the mammary gland in the postpartum period and breastfeeding period. Its etiology is *Staphylococcus aureus*, pyogenic *streptococcus*, gram-negative bacteria, actinomycetes, mycobacteria. A surgical manual with passive immunotherapy with immunoglobulins is recommended.

Felon

Purulent inflammation of the fingers. There exist isolate cutaneous, subcutaneous, tendon, articular, bony, subungual panaritium. They are determined by *Staphylococcus aureus* and *epidermidis*, *E. coli*, *Proteus*, *bacteriomas*. Given the high risk of osteomyelitis formation, a combination of immune correction is recommended.

Cholecystitis

An inflammation of the gallbladder with *E. coli*, *staphylococci*, *proteus*. Hematogenous and enteral invasion of microbes is possible. Among the immunotropic interventions, the use of non-drug correction (low-intensity laser irradiation, the introduction of an ozonized solution of sodium chloride) is recommended.

Purulent mediastinitis

A complication of surgical interventions on the heart and lungs. It is caused by anaerobic streptococci and hospital ecowars of *staphylococci*. Immunotherapy should be complex and continuous.

Purulent-inflammatory diseases of the skin and subcutaneous tissue

These are furuncles, carbuncles, abscesses, phlegmon, hydroadenitis, pyoderma, panaritium, erysipelas. Pathogens are recorded from the external environment through cracks, abrasions, scratches, injections, scratching, but can be of hematogenous and lymphogenic origin from infected foci in other parts of the body. Etiologically significant are *pyogenic streptococcus*, *Escherichia coli*, *Proteus*, *Pseudomonas aeruginosa*, *bacteroides*, *Mycobacteria*, *Staphylococcus aureus*. For treatment, the use of differentiated pharmacological and non-drug monoimmunocorrection is recommended.

Uroinfections

The specific ones are gonorrhea, tuberculosis, mycobacteriosis, actinomycosis, chlamydiosis, mycoplasmosis. Nonspecific ones occur due to epidermal *staphylococcus*, *fecal streptococcus*, *E. coli*, etc. Some common infections are accompanied by *bacteriuria* (brucellosis, leptospirosis, sepsis, typhoid fever). As an immunotropic support, it is recommended to use a combination of local and systemic pharmacological and non-medicated modulation, aimed at stimulating all the main links of immunity.

Purulent paraproctitis

An inflammation of the cellulose surrounding the rectum caused by the association of gram-negative and gram-positive aerobic and anaerobic bacteria. The development of this infection is a sign of reduced regional and general anti-infectious resistance, which requires the administering of complex immunotherapy to patients.

Osteomyelitis

An inflammation of bone tissue. Can be specific (tubercular, syphilitic, leprosy) and nonspecific (opportunistic). The treatment requires a combination of surgical methods, with profile antibacterial drugs and immune modulating agents chosen according to the nature of immunopathology in the patient.

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