ISSN 2079-0864, Biology Bulletin Reviews, 2020, Vol. 10, No. 2, pp. 140–149. © Pleiades Publishing, Ltd., 2020.
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Principles of Interpretation of Laboratory Diagnosis and Infection Treatment at the Present Stage

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Received March 27, 2019; revised April 1, 2019; accepted April 1, 2019

Abstract—Due to the variability in the etiology and clinical manifestation of infectious diseases, immunological analysis techniques play an increasingly important role in their diagnosis. These can be subdivided into nonspecific techniques, which reveal general changes indirectly associated with the pathology, and specific techniques, which reveal the precise immune mechanism of the pathology. Some modern principles of disease treatment are discussed as well.

Keywords: antibody analysis techniques, antigen analysis techniques, infection treatment, immunomodulation

DOI: 10.1134/S2079086420020097

INTRODUCTION

Modern clinical microbiology and immunology have encountered several important problems that have been partly revised based on recently accumulated data.

These problems are related to the approaches used to detect antigens and antibodies against various pathogens, tissue components, viruses, allergens, and sensitized cells, which directly influence the precision of diagnosis and subsequent, adequate treatment of the disease.

An important role is also played by the unbiased, modern interpretation of results, as well as by complementary methods that enhance treatment efficiency, such different immunomodulation techniques, nondrug immune therapy, auto-microflora correction, and the use of antioxidants.

PRINCIPLES OF INTERPRETATION OF THE LABORATORY DIAGNOSIS OF INFECTIONS

Immunological nonspecific techniques involve the assessment of T, B, and nonspecific immunities, which is divided into quantitative and functional assessment. Quantitative assessment is based on the identification of differentiation markers of lymphocyte populations and subpopulations via enzymatic immune and radiation immune assays, direct and indirect immunofluorescence, flow cytofluorimetry, etc.; functional assessment is carried out on the basis of skin tests for antigens (Ags), the blast transformation response of lymphocytes to T- and B-cell mitogens, or the detection of normal antibodies (Abs), major classes of immunoglobulins, etc. in blood serum. The characteristics of nonspecific immunity includes neutrophil chemiluminescence, their phagocytic potency and metabolic capacity, motility, the cytolytic activity of K and NK cells, and the levels of complement, lysozyme, cytokines, etc. (Kalinina et al., 2008; *Entsiklopediya*..., 2013; Zemskov et al., 2015).

Variations in the immune indices are characterized via calculation of the degree of variation according to the formula

$$\left(\frac{\text{index value in patient index}}{\text{value in healthy individual}} - 1\right) \times 100\%.$$

When the change in the index values do not exceed 33%, they are considered insignificant (degree I). Changes between 34 and 66% are classified as degree II, and changes exceeding 66% are degree III. With the diagnostic value coefficient (*Kj*), which is calculated according to the formula

$$Kj = \frac{2\left(\delta_1^2 + \delta_2^2\right)}{\left(M_2 - M_1\right)^2},$$

where δ_1 and δ_2 are the mean square deviations and M_1 and M_2 are the mean index values, signal tests are identified and are interpreted according to the following criterion: the lower the absolute *Kj* value is, the greater is the difference. The first three indices are used to construct the immune system disorder formula (ISDF), which contains three key indices with the

Table 1. ISDF signal tests in patients with PID of different origin

Disease	ISDF
Deep pyoderma (DP)	$CIC_3^+cNK_3^+IL6_3^+$
Chronic pyelonephritis (CP)	$B_3^+MWM_3^+NBTp_2^-$
Chronic adnexitis (CA)	$T_3^-IgM_2^+IL6_2^+$
Chronic suppurative otitis media (CSOM)	$CIC_3^+IgG_2^+NK_3^+$
Purulent meningitis (PM)	$B_2^-Tc_3^+T_2^-$
Purulent chronic cholecystitis (PCC)	$PF_2^+PN_2^+B_2^+$

direction of change (+ or –) and degree of variation (1, 2, 3) in each case.

The obtained laboratory examination data for patients at the acute stage of pyoinflammatory diseases (PID) of different origin were used to construct the typical ISDFs (Table 1).

Table 1 shows that the accumulation of third-degree, aggressive, circulating immune complexes (CICs), cytotoxic natural killers, and proinflammatory interleukin 6 were key in the case of DP. In the case of CP, the accumulation of B lymphocytes and medium-weight molecules (MWMs), toxemia markers, and a moderate decrease in neutrophil metabolism (NBT) were among the important parameters. For CA, the decrease in the number of T cells and the accumulation of second-degree IgM and IL6 were predominant. In the case of PM, a decrease in the B- and T-cell contents and an increase in the cytotoxic T-lymphocyte content was registered. For PCC, the induction of the phagocytic function (PF) of phagocytes and increases in the second-degree B-lymphocyte numbers and the phagocyte number (PN) were observed in two tests. The provided data specify the pattern of immune disorders in six different PIDs (Zemskov et al., 2007).

Specific immune techniques are based on the different means of interaction between microorganisms and the human immune system with subdivision by the individual forms of interaction: antibody production, immune phagocytosis, cell-mediated killing, hypersensitivity responses, and the formation of immune memory or immune tolerance (Kishkun, 2009).

All methods based on the use of immunoreactions are subdivided into in vitro laboratory techniques (actual immune techniques) and methods applied to the patient in vivo (allergy tests). Bacteriological analysis (pathogen culturing on nutritive media), microscopy, immunofluorescence, and various DNA-diagnostics techniques may be included within the direct diagnostics methods, while histology and instrumental and serological analyses are considered to be indirect methods.

Due to their high specificity and sensitivity, immunoreactions are used not only to detect Ag and Ab but also to measure their quantity (and to determine the viral load with DNA techniques), which is required to determine the indications for the initiation and cessation of treatment, to assess treatment effectiveness, to control for possible disease recurrence after treatment cessation, etc. The immunological diagnosis of infections is based on highly specific immunoresponses executed by sensitized lymphocytes or Abs that are able to specifically recognize foreign Ags. It is currently believed that information on the interaction between the macroorganism and the infectious agent can be obtained in the four following ways: the detection of (1) immunocompetent cells or (2) humoral Abs provide reliable evidence only for pathogen occurrence in the organism; the detection of (3) free Abs or (4) circulating immune complexes (Ag–Ab) demonstrates the presence of the pathogen in the macroorganism at the time of the test but provides no evidence on the patient's immunoresponse.

Therefore, better reliability may be achieved with a combination of diagnostic approaches (Khaitov et al., 2009).

Specific diagnosis implements a variety of techniques:

—The use of sera, including agglutinating, hemolytic, luminescent, and antiglobulin sera;

—The use of cellular diagnostic arrays (killed microorganisms, molecular Ags, or erythrocytes with conjugated active structures), which are sensitized with the use of such compounds as tuberculin, brucellin, tularin, anthraxin, etc., while subcutaneous administration of low toxin doses is used in the case of toxemia (Schick test, Dick test, etc.).

—The use of molecular biology and molecular genetics techniques, which are subdivided into six categories: (1) fractionation (electrophoresis and flow microcytofluorimetry); (2) visualization of the Ag–Ab interaction and the Ab particulate (agglutination, haemagglutination, latex agglutination, and nephelometry); (3) visualization via hemolysis (complement fixation test and Jerne test); (4) immunohistochemis-

try (immunofluorescent microscopy and tissue and cell microscopy with fixed fluorescently labeled antibodies); (5) immunological assays (radio and enzymatic immunologic assays), and (6) molecular-biology techniques, including polymerase chain reaction (PCR), immunoblotting, etc. (*Meditsinskaya...*, 2008).

Laboratory Panel

Serological reactions are used in two ways: to detect Abs in the patient's blood serum for diagnostic purposes and microorganism identification by genus, species, and type or to detect Ags by their reaction with known immunosera.

In the direct agglutination test (DAT), Abs (agglutinins) directly agglutinate corpuscular Ags (agglutinogens) or microorganisms, e.g., as in the Wright test for brucellosis. Rough (laminary) DAT is performed on slides, and complete DAT is performed in tubes or plates.

The direct cell agglutination test (leukocytes, platelets, and other cells) is used to detect autoantibodies or Ags (receptors) on these cells, to determine the blood group, etc. The test is performed on slides and in tubes (plates).

The indirect (passive) hemagglutination reaction (IHA or PHA) with carriers (erythrocytes) loaded with certain Ags, or vice versa, with conjugated Abs, detects circulating Ags. It is used for the diagnosis of salmonellosis, including typhoid fever and paratyphoid fever, dysentery, yersiniosis and other enteric infections, rickettsiosis, etc.

The direct and indirect Coombs anti-immunoglobulin tests detect incomplete (nonagglutinating Abs) in the case of rhesus incompatibility, autoimmune diseases, and certain infections. In the direct test, anti-immunoglobulin serum is added to the patient's washed erythrocytes, while free antierythrocyte Abs in the patient's blood serum are used for the indirect reaction.

The hemagglutination inhibition test (HI) is used for viral identification based on the Ags.

The precipitation reaction (PR) is the formation and precipitation of Ag–Ab complexes. The reaction involves soluble Ags (precipitinogens) and Abs (precipitins). The aggregation of the former results in clouding of the transparent medium. PR is used to determine toxigenicity, to detect bacterial antigens, and to diagnose infectious diseases. PR may be carried out in liquid phase (ring precipitation) or agarose gel (simple one-dimensional diffusion) and as a two-dimensional diffusion, radial diffusion (Ouchterloni diffusion), or during electrophoresis, etc.

The complement fixation test (CFT), which involves complements in addition to Abs and Ags, is used to detect Ags via antigen diagnostic assays in the presence of the corresponding antisera or Abs and to diagnose infections.

Lysis reactions take place when specific Ab interact with the cellular (erythrocyte, bacteria, leukocyte) Ags. The test is generally used to determine the histocompatibility of Ag types, etc. (Tsarev, 2010; Pokrovskii et al., 2013).

Techniques based on the binding of labeled Ags and Abs are highly sensitive. Ags are labeled with fluorescent dyes, radioactive isotopes, enzymes, etc.

Immunofluorescence assay (IFA) is based on the binding between the microorganism Ags and specific Abs labeled with the corresponding dye (fluorescein isothiocyanate). IFA can be direct (DIFA), which is seldom used, or indirect IFA (IIFA), which is used for the early, express diagnosis of infections. The Coons direct immunofluorescence assay is a single-step procedure based on the interaction between the fluorochrome-labeled Abs and Ags located on the cell, within the cell, and in tissues and produces a green glow under UV light or an orange-red glow with the use of tetramethylrhodamine isothiocyanate.

Enzyme immunoassay (EIA) is rather simple and sensitive. The reaction is usually performed in the wells of plastic plates. Abs against the studied Ag are attached to their walls. The studied object containing the target Ag is added to the wells. The latter binds the Abs with the formation of the Ag–Ab complex. The studied substrate is then removed, and Abs labeled with a certain enzyme, e.g., horseradish peroxidase, are added to the wells. The Abs bind with the Ag–Ab complex and become fixed on the wall as a result. A substrate that yields color in the presence of horseradish peroxidase is added into the system. The results are assessed by color intensity. EIA allows IgG and IgM to be detected separately. Its specificity with the use of the best recombinant test systems approaches 100%. The Ab avidity, which considerably expands the diagnostic possibilities, is also evaluated. The use of monoclonal Abs expands the potential of the method.

Radioimmunoassay (RIA) is one of the most sensitive techniques. It is used to detect viral Ags in patients. The method involves the addition to the studied serum of a reference serum containing Abs against the analyzed pathogen, incubation for 1–2 days, and the subsequent addition of the reference antigen labeled with ^{125}I, followed by 24 h of incubation. Precipitating antibodies against the reference serum are then added to the obtained soluble Ag–Ab complex, which leads to precipitate formation. The results of the reaction are determined based on the presence and number of impulses recorded in the precipitate by the counter.

Immunological chips are used for the diagnosis of TORCH infections, complexes of tick-born infection, including anaplasmosis, ehrlichiosis, and Lime borreliosis or tick-borne encephalitis, West Nile fever, and Crimean–Congo hemorrhagic fever; a complex of parenteral infections, including hepatitis B, hepatitis C, and HIV; and a complex of diseases with natural foci.

Methods of Antigen Detection in Diagnostic Material

The following methods are used for the early diagnosis of infections. IFA is used for express diagnosis of viral and bacterial infections. IHA is used for early detection of Ag in the patient and environmental objects. Hemagglutination reaction and HI are used for the express identification of viral infections (influenza, parainfluenza, mumps, poliomyelitis, adenoviruses, and viral encephalites) and a number of other diseases. Ag-neutralization assay is used to detect bacterial exotoxins (clostridia, corynebacteria, staphylococcus, etc.), as well as viruses in the case of diagnosis of measles, mumps, rubella, viral encephalites, Dengue fever, and Omsk and hemorrhagic fevers. Positive results can be obtained with the use of this assay several days (sometimes 2–3 weeks) after the start of infection. PR is the diagnostic technique in the case of meningococcus infection, trypanosomiasis, polyomyelitis, splenic fever, malaria, and viral hepatitis B, as well as enteric and toxicoinfection pathogens. RIA allows the detection of antigens of hepatitis B virus and other pathogens at early disease stages in 60–80% of patients (*Rukovodstvo po meditsinskoi*..., 2008).

Antibody Detection Methods

Antibodies can be detected in the case of later infection diagnosis, usually during the recuperation or remote periods. It is well-known that blood can contain Abs produced in the course of the previous disease or as a result of vaccination. They may mask the immunoresponse to a given infection and sometimes exert significant effects on the activity and level of response. It is well known that low antibody numbers stimulate the synthesis of homologous immunoglobulins in the organism after infection or vaccination, while high antibody numbers inhibit antibody production. In this view, it is not the mere fact of Ab detection in blood but Ab titer values characteristic of a given infection that possess diagnostic value. A fourfold increase in Ab titers in the dynamics of infection within a 7–14 day interval is even more indicative. It should also be taken into account that serological assays are not absolutely specific due to the presence of common Ags or individual specificity determinants in pathogens belonging to the same or even different species. In some cases, this may be misleading. For example, in the case of CFT or HI with anti-influenza Abs, seroconversion is possible when the Ab shows higher reactivity to the previously encountered virus than to the pathogen causing the current disease. The diagnostic value of serological assays may be enhanced by the differential identification of Abs belonging to different classes (IgM and IgG). IgM is produced at earlier stages of infection and therefore can serve as an indicator of the recent infection.

Abs in the blood serum are detected with the same serological assays used to detect Ags. The difference is that standard antigen diagnostic preparations are used to detect Abs. These include live and inactivated vaccines, soluble Ags, or erythrocyte antigen preparations. CFT is mostly used to detect streptococcus and meningococcus infections, pertussis, mycoplasmal pneumonia, influenza, mumps, measles, rubella, and cytomegalovirus infection. The limitations of CFT are its inconvenience, the requirement of the continuous availability of erythrocytes, complement, and antigen diagnostic preparations, the duration of the assay, and the relatively late detection of Abs in diagnostic titers (10–14 days of infection). IHA with erythrocytes sensitized with soluble Ags is used to diagnose pertussis, tuberculosis, mycoplasma infection, measles, cytomegalovirus infection, typhus fever, malaria, and plague. HI with standard viral diagnostic preparations is used to detect Abs against the influenza and mumps viruses and the measles and yellow fever viruses. The diagnostic Ab titers in blood serum increase slowly (to the 10tht–20th day of infection) and usually do not reach high levels (1 : 20–1 : 320). The Ab neutralization test is a very sensitive and specific method of Ab detection for staphylococcus infections, mumps, measles, chicken pox, viral encephalites, Dengue fever, Omsk hemorrhagic fever, and rabies. However, it requires the continuous availability of experimental laboratory animals, chicken embryos, or cell cultures, as well as long observations (from several days to several weeks). The PR variants described above are used to detect Abs against polyomyelitis, meningococcus infection, and trypanosomiasis pathogens (*Rukovodstvo po meditsinskoi*..., 2008).

Allergological Methods

IgE synthesis is induced in cases of ARVI and CMV infections, helminthiases, pertussis, and mycoplasma infections; delayed-type hypersensitivity is observed with tuberculosis, leprosy, brucellosis, schistosomiasis, and measles. Importantly, immune complexes are formed in the case of many viral and bacterial infections, Lime borreliosis, brucellosis, and pseudotuberculosis (Zemskov et al., 2017).

Allergy Diagnostic Probes

The assays are based on the local or general response of an organism sensitized to a specific allergen. They are used in the case of bacterial infections: tuberculosis (tuberculin, the Mantoux test), leprosy, brucellosis (the Burnet probe), tularemia (tularin test), dysentery (Tsuverkalov probe); mycoses, namely, aspergillosis and candidosis (test with dermatophytin O); viral infections, mumps (test with inactivated vaccine against mumps), and helminthiases, namely, trichinellosis, echinococcosis (the Casoni test), filariasis, and paragonimiasis.

Skin Probe Interpretation

In the case of splenic fever, tularemia, and Q-fever skin probes using specific Ags become positive by the third to fifth day of infection and thus represent an early diagnosis technique. In the case of slow infections (ulcerating granuloma of the pudenda, leprosis, syphilis, and toxoplasmosis), the specific skin allergy can be detected 3–4 weeks after the onset of the disease and serve as an accessory index for diagnosis. In the case of tularemia, brucellosis, and toxoplasmosis, positive skin probes persist for many years and serve for retrospective diagnosis and the identification of susceptible individuals who need vaccination. Ag administration (tuberculin probes) to the sensitized organism sometimes has severe side effects complicating the infectious process. For example, strong skin probes may lead to the activation of infection foci in lungs, skin probes with toxoplasmin sometimes cause recrudescence of eye toxoplasmosis, and the administration of brucellin can enhance joint pain and pain along the nerves, recrudescence of inflammation foci, and swelling of the spleen and liver. In rare cases, severe anaphylaxis reactions may develop as a result of intracutaneous tests.

Methods for the Detection of Sensitized Cells

These methods detect certain oscillations of activity and the dynamics of demarcation changes in the nucleus and neutrophil index, leukocyte lysis (immunoleukocytosis), degranulation of basophilic leukocytes, leukergia (agglomeration of leukocytes), the reaction of the blast transformation of lymphocytes, and leukocyte migration inhibition reaction. The formation of a specific rosette with sheep erythrocytes in the presence of certain agents and other phenomena, which take place when sensitized cells make contact with the allergen, are also analyzed. The mentioned tests have a certain informative value and specificity level. The use of the named techniques is limited by their inconvenience, the required availability of specially prepared standard allergens, complex nutritive media used to perform the lymphocyte blast transformation reaction, and other components. The advantages of these tests include their simplicity, short test time, absolute safety for the patient, and the ability to carry out the test with many allergens and in a small blood volume (Zemskov et al., 2016).

PRINCIPLES OF INFECTION TREATMENT AT THE PRESENT STAGE

A complex array of pathogenetic processes forms in the course of infection. These include (1) the accumulation of foreign Ags and aggressive factors (endotoxins and acute phase proteins) and the suppression or stimulation of immune responsiveness; (2) competition between extracellular and intracellular pathogens for protective reaction regulators (cytokines); (3) inversion of the metabolic processes of free-radical substrate oxidation and the antioxidant system; and (4) dystrophic and other processes (Mikhailenko et al., 2005; Zemskov et al., 2018a, 2018b).

Antibiotics Therapy

Antibiotic therapy is the key method of infection treatment. The antibiotics may be broad-spectrum antibiotics, those acting on gram-positive or gram-negative microorganisms, or with specific activity, e.g., antituberculosis, antimycotic, or antiprotozoal. The antibiotic preparations are subdivided by the mode of action into bacteriostatic (capable of inhibiting the growth of microorganisms, tetracyclines) and bactericidal, which kill vegetative forms of microorganisms (penicillins and cephalosporins).

Drug Prescription Guidelines

(1) The antibiotic sensitivity of the patient's microflora should be determined prior to the prescription of these drugs. In severe cases, broad spectrum antibiotics are used with consideration of the epidemiological data on drug resistance under health-threatening conditions. (2) The treatment of bacterial infections should be intensive, should start as early as possible, and should continue for no less than 5–7 days or longer. (3) The efficiency of the prescribed drug should be assessed in the course of 3–4 days. Further, the drug should be withdrawn or substituted. (4) Acute infections are more responsive to treatment than chronic ones. (5) In the selection of an antibiotic for therapy, preference should be given to narrow spectrum antibiotics. Drug pharmacokinetics and the individual patient characteristics (age, body weight, allergies, kidney and liver function, pregnancy, lactation, concurrent diseases, and use of other drugs) should be taken into account. (6) Bactericidal drugs are more preferable for the treatment of infections involving organs and tissues with poor vascularization, while longer treatment courses are required for diseases caused by intracellular pathogens. (7) In the case of immunodeficiencies, not only efficiency but also the immunotropic activity of antibiotics should be considered. In the case of abscess development, antibiotic therapy should be accompanied by operative treatment. (8) Prolonged therapy with broad spectrum antibiotics requires monitoring of the risk of superinfection development.

Drawbacks and Side Effects of Antibiotic Treatment

These consist of the impossibility of complete pathogen elimination, the shift in protective responses towards deficiency, allergization, autoaggression, etc., and the accumulation of microflora with polyvalent resistance to antibiotics, mostly in the case of healthcare-associated (nosocomial) infections. The acro-

nym ESKAPE stands for the "run for your lives" group: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species. It should be taken into account that the frequency of pregnancy abortion increases by 67% upon the treatment of pregnant women with macrolides, by 65% upon treatment with quinolones, and by 71% upon treatment with metronidazole. Broad-range antibiotics administered to women in the third trimester of pregnancy cause frequent acute respiratory disease (ARD), bronchial asthma, dysbacteriosis, obesity, hypertension, and diabetes in children for 18 months.

Mechanisms of Immunotropic Activity of Antibacterial Preparations

Sulfanilamides. The mechanism of action of these drugs is based on disruption of the synthesis of folic and dihydrofolic acids, which are essential for microorganisms. Sulfanilamides may be subdivided into four groups by the duration of their action: (1) short-acting drugs (norsulfazolum, aethazolum, and sulfadimezinum); (2) drugs with medium duration of action (sulfazine); (3) long-acting drugs (sulfapyridazinum, sulfamonomethoxine, and sulfadimethoxine); and (4) super-long-acting drugs (sulfalene).

Bacteriophages are used (1) for the treatment of infections (cholera, staphylococci, anaerobic bacteria, etc.); (2) for clinical purposes in the case of the identification of the microorganism species; (3) for infection prophylaxis; (4) for environment sterilization; (5) for food preservation; (6) for the targeted transfer of the genetic material of bacteria in genetic-engineering studies; (7) for implementation of the immunomodulation phenomenon via lysis of microflora with the release of endogenous stimulators (endotoxins, low-molecular nucleic acids, etc.), and (8) for a reduction in the antigen load via the lysis mechanisms mentioned above. The following phages are approved for clinical use in Russia: staphylophage, streptophage, dysphage, typhoid fever phage, clebsiphage, coliphage, proteophage, salmonella phage, blue pus bacillus phage, pyopolyphage, intestiphage, and sextaphage.

Antiviral treatment is carried out in order to suppress the viral infection itself, to eliminate the consequences of infection, including bacterial complications, and to provide conditions for the development of immunity. The patients need to take drugs that prevent viral adsorption on target cells (dextransulfate and antibodies against cellular receptors), drugs that suppress replication of the infectious agent (azidothymidine and videx), interferons, antiviral drugs (amixin, arbidol, and zovirax) and interferonogens (glutoxim, derinat, and ridostin), T stimulators of protective responses (hepon and thymus derivatives), and polypotent stimulators (sodium nucleinate and immunomax). Broad-spectrum antibiotics are used in special cases (age groups and chronic patients), and specific immunoglobulins and other serum products are used in the case of severe infections.

The treatment of Chlamydia involves the use of (1) tetracycline group antibiotics, including doxycycline (vibramycine), lymecycline, unidox, and metacyclinum (rondomycine); (2) macrolides, including erythromycin, rovamycine (spiramycinum), rulide (roxithromycin), sumamed (azithromycin), midecamycin, eracin, josamycin (Wilprafen), pristinamycin, and klacid (clarithromycin); (3) antibiotics of the rifampicin group, including rifampicin, rifampin, Benemycin, Rimactan, and Rifacol; (4) fluoroquinolones, including ofloxacin (Tarivid and Zanocin), levofloxacin (Tavanic), lomefloxacin (maxaquin), pefloxacin (Abaktal and peflacine), and ciprofloxacin (Ciprobay, Cifran, Ciprolet, etc.); (5) efficient drug combinations, e.g., rifampicin/erythromycin, doxycycline/sulfapyridazinum, etc.; (6) nystatin, ketoconazole, and bactisubtil for candidamycosis prophylaxis; (7) adjunctive therapy with enzymatic preparations with hyaluronidase activity (trypsin and Wobenzym), biogenic stimulators (aloe, Fibs, ascorbic acid, and folic acid), desensitizing drugs (clemastin, loratadine, and aerius), nonsteroid anti-inflammatory drugs (ibuprofen, indomethacin, and Voltaren), eubiotics (Acilact, Bificol, Bifidumbacterin, and Lactobacterin), Hylak forte, hepatoprotectors, and food additives (Milife, Preventan, Cygapan, Panangin, and vitamin E); and (8) immunocorrection therapy with sodium nucleinate, Ridostin, Derinat, Imunofan, Thymogen, Thymalin, Tactivin, Myelopid, and complex immune preparation, which proved to be efficient.

Immunotherapy of Infections

Immunotherapy implies the use of vaccines, anatoxins, and immunoglobulins, which are etiotropic drugs, to treat chronic and slow infections and diseases that react slowly to conventional treatment and pathogenetic treatment via the administration of blood, blood substitutes, blood plasma, eubiotics, nonspecific immunity stimulators, and interferons, which block viral replication in the infected cell and participate in the interactions between cells of the immune system. Interferonogens are inducers of endogenous interferon production. They include complexes of high and low-molecular compounds that are able to stimulate the production of patient's own (endogenous) interferons: nucleic acids, viruses, bacteria, and synthetic preparations. Therefore, interferon-inducers possess antiviral, immunomodulating, antitumor, and other properties. Some preparations simultaneously exert antimicrobial and immunostimulatory effects. These include specific immunoglobulins and plant extracts.

Immunotherapeutic drugs are subdivided into four groups by origin: (1) those obtained from human and

animal blood and organs (plasma, immunoglobulins, thymus preparations, myelopeptides, interferons, splenin, placenta extracts, antilymphocyte serum, etc.); (2) those obtained from plants (eleutherococcus, Schisandra chinensis, imania tinctures, etc.); (3) stimulators of microbial origin (pyrogenic, prodigiosan, zymosan, sodium nucleinate, bificol, bacteriophages, etc.); and (4) synthetic preparations (levamisole, pentoxylum, methyluracil, Hemodez, Polyoxydonium, Licopid, diuciphon, etc.).

The indicated drugs are subdivided by their mechanism of action into specific active (vaccines and anatoxins) and specific passive (sera and immunoglobulins) drugs.

Principles of Immunotherapy of Infections

Immunotherapy is used together with other drugs (antibiotics, sulfanilamides, and corticosteroids). The efficiency of the therapy depends on the validity of the assessment of the initial status of the patient's immunoreactivity, the type and degree of pathological changes, and the selection of the right therapeutic compound and the treatment regimen (*Natsional'naya*..., 2012). It is also important to understand the mechanism of action of the prescribed drugs, their side effects, their compatibility with other treatment approaches, their allergenicity, etc. The used vaccine therapy for immune tolerance to certain Ags may not exert any positive clinical effect in some cases and may even aggravate immune depression with possible risks of anaphylactic shock and the induction of autoimmune conditions. There are known cases in which the administration of vaccines with therapeutic purposes led to severe complications associated with massive disruption of microbial cells and the development of toxic shock. Blood and plasma transfusion is an efficient means of stimulation of patient's immunoreactivity. However, this treatment approach should be used only in the case of strong indications and under the strict control of its effects on the disease progression and immunity and allergy indices. Etiotropic treatment (immune sera, immunoglobulins, bacteriophages, and interferon) and detoxication treatment (blood, plasma, and blood substitutes) should be prescribed as soon as possible after the onset of infection. A number of nonspecific stimulators are used at the height of disease and during the recuperation phase (pentoxyl, vitamins, and methyluracil) or for the treatment of complications (Ferrochel, Phytin, and levamisole). Therapeutic vaccines are administered to patients with protracted and chronic diseases. The use of polysaccharide drugs is prohibited in the febrile state. Eubiotics should not be prescribed together with antibiotics or other preparations of this kind.

Serum Preparations

Serum preparations are used for the specific treatment, emergency and passive immunoprophylaxis, and elimination of certain immunodeficiencies.

Serum preparations may have different origins: (1) antitoxic sera are obtained via cattle immunization (antidiphtheria, antitetanus, antigangrene, polyvalent antibotulin, etc.; (2) antibacterial and antiviral sera are obtained via animal hyperimmunization with killed bacteria or Ags (antisplenic fever, and rabies, etc.) with the production of gamma-globulins as a result of serum concentration and purification; and (3) homologous globulins are obtained from human blood. There are targeted drugs that are obtained from the blood of volunteers vaccinated with different preparations (against tetanus, staphylococcus infections, etc.). Plasma is also a serum preparation. The therapeutic effect is achieved in several minutes with intravenous administration and in several hours with intramuscular administration. The duration of the effect is 21–22 days for homologous preparations and 10–12 days for heterologous preparations.

Possible Complications and Necessary Precautions with the Use of Serum Preparations

(1) The transmission of "syringe" infections cannot be totally excluded (malaria, hepatitis B and C, etc.). (2) An allergic response, including anaphylactic shock and serum disease, may be induced. (3) The development of endocrine disorders following the administration of high doses of placental gamma-globulin to boys younger than three years old was observed. (4) Recurrent pregnancy loss was described in women who received high doses of serum preparations in infancy (younger than three years old). (5) Inhibition of antibody formation and a decrease in the level of vaccinal immunity with concurrent administration of serum preparations is likely. (6) The conventionally used passive immunotherapy regimen, intermittent administration with a 1- to 5-day interval, may produce Abs against the used preparation, neutralizing its effect. Therefore, a limited number of higher-dose injections is more preferable.

It should be noted that any gamma-globulin contains up to 180–250 different Abs against multiple Ags. Therefore, any available serum preparation may be used for an infection in the absence of the specific gamma-globulin (Zemskov, 1977).

The injection of gamma-globulins appears to be more advantageous during the acute period of infection and less advantageous during remission or convalescence.

At the same time, the injection of gamma-globulins to patients with a complete absence of any class of immunoglobulins is prohibited.

Nonspecific Immunomodulation

The modulation of immunoreactivity in the case of infectious pathology has become more important due to the decrease in the collective immunity of the human population, the significant increase in the incidence and chronicity of infectious diseases, and the uncontrolled, irrational use of antibacterial drugs. It is well known that immunotropic drugs are broadly used in applied medicine to increase treatment efficiency. The diagnostic criteria for the prescription of immunotropic drugs are based on the patient's immunogram data, interferon status, and local immunity data. The clinical and immune criteria of treatment efficiency are determined by medical experts, who must consider the preliminary assessment of the recommended effects.

Types of Immunomodulation

Systemic immunodmodulation affects the main elements of the immune system (T, B, and phagocytes), and may be implemented with the use of one universal or several different drugs or nondrug factors, including thymus preparations, myelopeptides, synthetic preparations, including levamisole, Polyoxidonium, Licopid, combinations of immune stimulators and suppressors, etc.

Local immunomodulation is the activation of local resistance in organs that communicate with the environment (urogenital, respiratory, and digestive tracts) with Kipferon, complex immunoglobulin protein, Viferon, Superlimf, Vilosen, and other preparations administered in the form of aerosols, drops, collyria, suppositories, etc.

Adjunctive immunomodulation uses membrane protectors and energizers, normalizing oxidation phosphorylation processes (riboflavin and nicotinamide), glycolysis and pentose phosphate pathway activators (thiamine and Riboxinum), free fatty-acid oxidizing agents (pantothenate and carnitine), tricarboxylicacid cycle stimulators (biotin and lipoate), and the rational combination of conventional drugs with stimulating and suppressor properties.

Immunomodulation Variants (Blocks)

Pharmacological monoimmunocorrection is prescribed based on the clinical laboratory parameters for a single modulator (Zemskov et al., 1994). Its induce interferon synthesis via the administration of interferonogens or α-, β-, and γ-interferons in order to regulate immune responses and eliminate intracellular pathogens (viruses, Chlamidia, etc.) and involves the use of natural and synthetic nucleic acid preparations (sodium nucleinate, Ridostin, Derinat, Poludanum, poly(I:C), and Isoprinosine) as preparations with multipotent properties (detoxicating, reparatory, radioprotection, immunomodulating, and other). Active or passive (substitution) immunotherapy is also carried via the administration of vaccines, anatoxins, and serum preparations to stimulate or compensate for the lack of protection response factors.

Nondrug monoimmunocorrection is carried out with nondrug factors, including ozonized solutions, low-intensity laser radiation, sorption methods, hyperbaric oxygenation, acupuncture, plasmapheresis, ultraviolet blood irradiation, extracorporeal blood cell activation, etc.

Combined immunocorrection is the successive or simultaneous administration of drugs and nondrug factors with different mechanisms of action (Zemskov et al., 1994): (1) active adjuvant—the use of vaccines together with adjuvants/stimulators (Zemskov et al., 2008); (2) passive adjuvant—the administration of immunoglobulins/sera together with adjuvants/stimulators (Zemskov et al., 2008), and (3) rational systemic—the combined use of local and systemic immunity stimulators (Zemskov et al., 2008).

Alternative immunocorrection is the simultaneous or successive use of stimulators and suppressors of protective responses (Zemskov et al., 1994), including corticosteroids, cytostatic agents, chemotherapeutic agents, radioactive irradiation in the presence of sodium nucleinate, thymus derivatives, interferonogens, interferons, myelopeptides, etc.

Complex (multicomponent) immunocorrection is the combination of more than two pharmacological and nondrug preparations, antigenic, modulating, metabolic, and other preparations of various origins and with different mechanisms of action.

Immunometabolic correction implies the combination of pharmacological modulators of immunoresponse with metabolic agents/antioxidants (Zemskov et al., 2008).

Pharmacological and nondrug immunocorrection is the simultaneous prescription of pharmacological and nondrug modulators (Zemskov et al., 2007, 2008): plasmapheresis, ultraviolet blood irradiation, low-intensity laser irradiation, natural and synthetic nucleic acid preparations, thymomimetic preparations, etc.

The combined use of several of the aforementioned blocks is required to reproduce the natural mechanisms of immune homeostasis restoration in the case of infections.

Adjunctive Infection Treatment

Detoxicating preparations. Hemodez, Rheopolyglukin, Gelatinol, Hydrolysine, Amino Peptide and other drugs are currently used for detoxication.

Nonsteroid antiinflammation drugs include derivatives of salicylic acid (acetyl salicylic acid, etc.), propionic acid (ibuprofen, etc.), acetic acid (indomethacin), pyrazolones (butadione, etc.), derivatives of anthranilic acid and its analogs (mefenamic acid,

etc.), nicotinic acid (niflimic acid, etc.), indole and indazole (indoxyl), oxycam (pyroxycam, etc.), and other compounds (surgam, etc.). The administration of these preparations makes it possible to decrease or eliminate inflammatory edema.

Antihistaminic drugs include preparations with antiallergy activity, which is achieved via the blocking of histamine, a key allergy mediator. The following antihistaminic drugs are currently known: (1) ethanolamines (Dimedrol); (2) ethylenediamines (Suprastin); (3) alkilamine derivatives (Actidil); (4) phenothiazines (Diprazinum); (5) dihydrocarbomines (Diasolin); (6) piperazines (Stugeron and Cyclizine); (7) benzhydryl ester derivatives (Tavegyl), and (8) piperidines (cyproheptadine). Key indications for the prescription of the antihistaminic drugs are pollen diseases, Quincke's edema, acute and chronic urticaria fever, hay fever, vasomotor rhinithis, serum disease, bronchial asthma, eczematous dermatitis, etc. Antihistaminic drugs can be administered intramuscularly, intravenously, orally, locally, and intrarectally.

Sorption Methods and Nondrug Immunotherapy

Sorption treatment methods including hemo, immuno, entero, and liquorosorption, xenoperfusion, classical and membrane plasmapheresis, cytopheresis, splenoperfusion, etc., are used to cleanse toxic products (medium weight molecules, endotoxins, acute phase proteins, etc.) from the patient.

Nondrug factors with an immunocorrecting effect include low-intensity laser radiation, ultraviolet irradiation and magnetic treatment of autologous blood, extracorporeal (extraorganismal) treatment of lymphocytes and leukocytes with modulators, ultrasound treatment of the organs of the central immune system, acupuncture, hyperbaric oxygenations, thermal therapy and diet therapy, health resort treatment, and blood and plasma transfusion.

Eubiotics

Since infection processes, especially in the intestinal tract, disrupt normal microflora, bacterial and fungi preparations (eubiotics) are used as pathogenetic agents. These include probiotics, preparations of normal microflora and its derivatives, prebiotics, factors stimulating the adaptation and reproduction of microflora ("fertilizers"), and synbiotics, the combination of pro- and prebiotics.

The recommended preparations are Acilact, Acipol, Bactisubtil, Bactobacterin, Biotorin, Bifacid, Bifidin, Bifidumbacterin, Bificol, Bifilys, Bifilong, Bifinormalizer, Vitanar, Vitaflor, , Colibacterin, Lactobacterin, Lactoglobulin, Lactofiltrum, Linex, Propermil, Sanafiron, Sporobacterin, Tramelan, and Enterol.

Antioxidant Treatment of Infections

Antioxidant therapy implies the administration of preparations that normalize the free-radical oxidation of lipids and proteins and enzymatic and nonenzymatic mechanisms of the antioxidant system such as Hypoxen, Wobenzym, Tsygapan, Limontar, sodium nucleinate, Derinat, Milife, Tycveol, etc.

Other Types of Drugs and Treatment

In certain cases, if medically required, it is necessary (1) to decrease capillary permeability with the use of corticosteroid drugs, salicylic acid derivatives, and indomethacin; (2) to stabilize the permeability of lysosomal membranes and prevent release of lysosomal hydrolases with mefenamic acid, chingamic, and hydroxychloroquine; (3) to inhibit the synthesis of macroergic compounds with salicylates, indomethacin, and pyrazolone derivatives; (4) to decrease the formation or release of inflammation mediators with anti-inflammatory, antiserotonin, antibradykinin, and antiprostaglandin drugs and protease inhibitors; (5) to block the structure of tissue-inflammation components with ibuprofen, Ketotifen, Naproxen, and Diclofenac; and (6) to modulate metabolic immunity with methyluracyl, pentoxyl, orotic acid, Riboxin, Asparcam, and Panangin. Choleretic and spasmolytic preparations, intestinal sorbents (activated carbon, Polyphepan, and Polysorb MP), and hepatoprotectors (lipoic acid, Carsil, and Essentiale) should be used in the case of the presence of the allergic component in patients and the risk for the development of pseudoallergy.

It is important to consider that all of these medications can put additional, often unpredictable, stress on the immune system, deepening its malfunction.

CONCLUSIONS

Nonspecific and specific interpretations of laboratory diagnosis was discussed. The modern laboratory panel in its different variants, including allergological methods, was described in detail. The algorithm for the use of antibacterial and antiviral drugs in the case of infectious diseases, their side effects (including adventitious immunotropic effects), different types of immunomodulators, their existing variants, and the efficiency of adjuvant non-anti-infectious drugs were considered.

COMPLIANCE WITH ETHICAL STANDARDS

Statement on the welfare of animals and humans. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All applicable international,

national, and/or institutional guidelines for laboratory animal treatment were followed.

Conflict of interest. The authors declare no conflict of interest.

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