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Research Article

ACTUAL PRINCIPLES OF INFECTION TREATMENT

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ABSTRACT

Taking into account high variability of infection processes and, especially in latter days, predominance of suppressed clinical forms, immune- allergic disorders, and high mutability and antibiotic resistance of pathognomonic microflora etc., the treatment of infectious diseases should be multipurpose, including profile antibacterial and antiviral preparations, nitrofurans, deintoxication, antihistamine, anti-inflammatory non-steroid, antigenic, serum medications, sorbents, bacteriophages, eubiotics, metabolics, antioxidants, interferons, interferon inducers, thymomimetics, cytokines, nonspecific immunity stimulants, drug-free factors.

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INTRODUCTION

Under natural conditions, when infection develops, it forms a complicated pathogenic complex that includes accumulation of a large number of antigens, aggressive factors (endotoxins, acute-phase proteins, low-molecular nucleic acids etc.), and ultra boundary suppression and stimulation of immune reactivity, and also competition between extra- and intra-cellular parasites for defense reaction regulators, cytokines, distortion of metabolic processes (peroxidation of lipids and proteins), dystrophic and other processes. The main method of treatment of infectious diseases by antibacterial, antiviral and other drugs that lyse or limit their production of causative agents, haven't turned to account because these factors have a series of substantial weaknesses. Firstly, they have no physical ability completely eliminate pathogens; secondly, they stimulate the adaptation of the pathogens, for instance, to antibacterial drugs, and realize corruption distortion of defense reactions towards deficiency, allergization and autoaggression. At the same time, in case of repeated infection of larger causative agents (bacteria) by smaller ones (viruses), when the causative agents are destroyed, the etiology of infection changes, etc. All this requires additional comprehensive therapeutic influence on the

mentioned and other mechanisms (Vorobjev *et al.*, 2010; Pokrovsky *et al.*, 2013; Novikov D.K., Novikov P.D., 2009; Tsarev, 2010; Labinskaya, Volgina, 2008).

Antibiotics

The main factor of treatment of bacterial infections is antibiotics (AB), which are divided into 2 groups: AB that have a wide spectrum of influence on gram+ and gram-microorganisms and AB that have specific activity – antituberculosis, anti-fungal, antiprotozoal, antitumoral, immune-depressing etc. By the manner of activity, they are divided into 3 groups: bacteriostatic [microorganism's growth inhibition (tetracyclines)] and bactericides [that kill vegetative forms (penicillins, cephalosporins etc.)] (Pokrovsky, 2012; Pokrovsky, 2007; Vorobjev, 2008).

Classification of antibiotics by the mechanism of action (influence) on microorganisms

They are divided into: A – penicillins and cephalosporins that bind and inactivate transpeptidases that impede building an assembling of peptidoglycan molecules; B – vancomycin, cycloserine, bacitracin that inhibit the activity of intermediate precursors of cell wall synthesis; C – rifampicin and analogs that inhibit the activity of DNA-dependent RNA-polymerase; D – quinolones that inactivate DNA-polymerases; E – levomycetin and macrolides, interacting with ribosomes,

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which suppress the activity of peptidyl transferase and interrupt protein synthesis; F- sulfanilamides and tramoprin that block the formation of dihydropteroate synthetase and dihydrofolate reductase, which causes interruption of nucleotide synthesis.

General principles of antibiotic therapy

1. To make a correct patient's diagnosis, to detect localization of inflammation.
2. Defining the necessity to use antibiotics, because acute processes respond to treatment much better than chronic ones.
3. Preferred prescription of drugs of narrow spectrum of action taking into account flora's resistance to antibiotics, pharmacokinetics, age, body mass, allergological anamnesis, kidney and liver function, pregnancy, breast feeding, concomitant pathologies, administration of other medications.
4. Undesirable empiric prescription of drugs. When it is impossible to determine the antibiotic sensitivity, it is necessary to take account epidemiological data on microflora resistance to antibiotics in the region.
5. In case of life-threatening conditions, prescription of wide spectrum antibiotics without taking of pathogens' sensitivity to them.
6. Intensive and as early as possible prescription of bacterial infections' therapy during at least 5-7 days and more.
7. Assessment of efficiency of the prescribed preparation within 3-4 days (in case of absence of effect it is necessary to verify the presence of bacterial infection, correct choice of drugs, possibility of overlay of superinfection, formation of abscess, presence of foreign body, possibility of fever induction by the antibiotic itself).

Side effects of antibacterial therapy

The most common are (1) allergic reactions (to penicillin, cephalosporins); (2) intestinal dysbacteriosis (using of wide spectrum AB); (3) oto- and nephrotoxic damages (caused by aminoglycosides, macrolides); (4) suppression of bone marrow hemopoiesis (when using laevomycetin, sulfanilamides, nitrofurans); (5) liver injury (caused by tetracycline, erythromycin etc.); (6) predominant action of some antibiotics stronger on macroorganisms than on microorganisms (for example, antitumor AB), which causes immunosuppression and cytotoxic, teratogenic and mutagenic effect (Zemskov et al., 2013).

Other Drugs

Sulfanilamides

Their mechanism of action connected with disturbance of synthesis of folic and dehydrofolic acids required for microorganism's activity. By the duration of action, the drugs divide into 4 groups: 1) short-term (norsulfazole, etazole, sulfadimine); 2) medium-term (sulfazine); 3) long-term (sulfapyridazine, sulfamonomethoxine, sulfadimethoxine); 4) extra-long-term (sulfalene). Sulfanil amides have bacteriostatic effect. Note that apart from AB and sulfanilamides, for treatment of infections are used also nitrofurantoin derivatives (furaginum, metronidazole, flagyl, trichopol).

Desintoxication drugs

An important role in treatment of infections proceeding with intoxication occurrences play desintoxication medications contributing to reduction of toxicoses, improvement of microcirculation, elevation of organism's protection capabilities. Presently, hemodez, rheopolyglukin, gelatinolum, hydrolysine, aminopeptide etc. are being use as antitoxic preparations [(drugs)] (Zemskov et al., 2015).

Non-steroidal anti-inflammatory drugs

An integral part of infection treatment is non-steroidal anti-inflammatory drugs (NSAID). They include derivatives of salicylic acid (acetylsalicylic acid etc.), propionic acid (ibuprofen etc.), acetic acid (indomethacin etc.), pyrazolones (butadion etc.), derivatives of anthranilic acid and its analogs (mefenamic acid etc.), nicotinic acid (niflumic acid etc.), indole and indazole (indoxol), oxicams (piroxicam etc.), various compounds (surgam etc.). Prescription of NSAID allows reducing or removing inflammatory edema. It should be remember that many NSAID have pronounced effect on immune system, this is why their long-term use is not always reasonable. Among side effects of NSAID most common are abdominal pains, nausea, vomiting, anorexia, gastric ulcer. There is a possibility of hemopathy (anemia, agranulocytosis, and thrombocytopenia), toxic kidney injury, immediate type allergic reactions (Quincke's edema, anaphylactic shock), bronchial asthma exacerbation, vertigo, headache, seldom seizures, hallucinations. Contraindications are gastric and duodenum ulcer, decreased kidney and liver function, pregnancy (first 3 months), hematopoietic system diseases, bronchial asthma etc.

Antihistamine drugs

Among antihistamine drugs are preparations having antiallergic activity due to blockade of one of the main allergy mediator – histamine. In infectology, most frequently used are blockers of H1- receptors of histamine, unlike gastroenterology, where application of H2-blockers is in general use. By the chemical structure, there are distinguished antihistamine drugs of first, second and third generation, which can be administered intramuscularly, intravenously, orally, locally, intrarectal. They are mainly metabolize in liver and excreted renally. Side effects: drymouth, nausea, vomiting, diarrhea, headache, vertigo, general weakness, drowsiness, skin photosensitization, agranulocytosis, immunodepression etc. Contraindications to use of antihistamine drugs: idiosyncrasy, dysuria, myasthenia, pregnancy (especially in the first 3 months), prostate adenoma, closed-angle glaucoma. Among antihistamine drugs of the first generation the most widely used are diphenhydramine (benadryl, diphenhydramine), promethazine (phenargan, promethazine, pipolphen), diazolin (mebhydrolin), phencarol (quifenadine), clemastine (tavegil), trimепразин (theralene), hydroxyzine (atarax), cyproheptadine (peritol). These drugs are prescribe per os, intramuscularly, intravenously. Among antihistamine drugs of the second generation, presently the most widely used are terfenadine (terfen, triludan, teldan), astemizole (hismanal), loratidine (claritin, rinoral), acrivastine (semprex), levocabastine (livostin), azelastine (allergodil, rinoplast, radetizine, aflun). Characteristic of these drugs are selectivity of action and lower risk of side effects. The drugs should be carefully combine with tranquilizers, neuroleptics,

central analgesics, taking into account the possibility of sedative effect potentiation. Moreover, they have alkaline pH and therefore are incompatible with dedications having acidic reaction (laevomyctin, hydrocortisone hemisuccinate etc.). It is well known that antihistamine drugs have immunosuppressing properties, “erase” immune memory, and these effects increase in combination with antibiotics. It should be note that presently clinical practice increasingly uses antihistamine drugs of the third generation, for example such as kestine (ebastine) and cetirizine (zyrtec), fexofenadine [telfast] (Zemskov *et al.*, 2016).

Bacteriophages

Practical application of this group of drugs is used in treatment of infections (cholera, staphylococcal, anaerobic etc.), for diagnostic purposes when determining the type of microorganisms. Moreover, they are used for directional transport (vector) of genetic information between bacterial cells in genetic engineering researches and for implementation of immunomodulation phenomenon during lysing of microflora accompanied by release of endogenous stimulators (endotoxins, low-molecular nucleic acids etc.) and lowering of antigen load. For clinical use in Russia are allowed staphylophage, streptophage, dizphage, typhoid phage, klebsiphage, koliphage, proteophage, salmonella phage, pseudomonas phage, pyopolyphage, intestiphage, sextaphage etc.

Sorption methods and eubiotics

The method of reducing the concentration of infectious agents and their wasteproducts in the organism is the use of sorption methods– hemo-, immuno-, entero-, liquorosorption, xenoperfusion; in a sense – classical and membrane plasmapheresis, cytopheresis etc. In as much as the infectious processes, especially into dermal canal, cause disturbance of normal microflora, respectively, as pathogenetic action are used bacterial drugs and fungal drugs (eubiotics). Distinguished are probiotics – drugs of normal microflora and its derivatives; prebiotics – factors that stimulate acceptance and reproduction of flora, and synbiotics – a complex of pro- and prebiotics. Among recommended drugs are acipol, acilact, bactisubtil, bactobacterin, biotorin, bifacid, bifidin, bifilong, bifiliz, bifinormalizer, bifidum bacterin, bificol, vitanar, vitaflor, colibacterin, lactobacterin, lactofiltrum, linex, propermil, sanafiron, sporobacterin, enteral etc.

Serum Drugs

In infectology, serum drugs are used for immunodiagnostics, passive immunoprophylaxis, pathogenetic serologic therapy of infections, immune substitution of insufficiency of humoral defense factors, immunotropic treatment of non-infectious diseases, regulation of immune homeostasis, immunotherapeutic clinical support in case of immune-dependent and immune-associated pathological processes (Petrov, Khaitov, 2011; Zverev, Khaitov, 2014).

Classification of serum drugs

These drugs are subdivided into antitoxic serums (antitetanic, antitubulinic, antidiphtheritic, antigangrenous etc.) and antibacterial serums (antimeningococcal, antistreptococcal, antipneumococcal etc.), immune globulins (IG) – antiviral

(antirabic, against tick-borne encephalitis, against Crimean hemorrhagic fever etc.), and medicinal ones, of directed action, made from blood of volunteers vaccinated with various preparations (against tetanus, staphylococcal infections, hydrophobia, chicken pox, influenza, hepatitis B etc.). The compositional so includes plasma and IG of healthy donors and diagnostic serums.

Side reactions and complications of serum drugs

1. Addition of IG may cause headache, vertigo, migraine, nausea, vomiting, abdominal pains, diarrhea, increase/decrease in arterial pressure, tachycardia, cyanosis, dyspnea, chest pains. Rarely occurs hypotonia, collapse, faintness, hyperthermia, chill, hyperhidrosis, myalgia, renal tubules necrosis.
2. Native drugs also do not exclude transfer of «syringe infections» (syphilis, malaria, hepatitis, HIV/AIDS). Temporary increase of antibodies in blood after addition of nonspecific IG can result in false-positive results of serologic investigation methods. In the interval from several hours to several days, signs of aseptic meningitis may appear and disappear without a trace.
3. IG can induce allergic reactions, including even anaphylactic shock. In order to rule the mout, Bezredko’s method is used: 30 minute sprior to intramuscular or intravenous addition of a serum drug, an intradermal testis performed via injecting 0.1 ml of 1:100 diluted preparation, and the remaining dose is only administered in case of complete absence of any reaction. Effectiveness of antihistamine drugs as preventive measures is low.
4. IG addition for 1.5-3 months weakens the efficiency of live-virus vaccines against measles, rubella, epidemic parotitis, poliomyelitis, chicken pox. The same happens in case of simultaneous administration of killed vaccines and anatoxins with antisera.
5. There are described cases of phenomenon of induction of endocrine disorders in case of addition to up to 3-year old boys of large doses of placental immunoglobulin containing considerable concentrations of female sex hormones, and of miscarriage by women who received in the age of up to 3 years large doses of serum preparations (3 - 6 ml).
6. In case of organism’s overload with IG, as a result of dehydration, there is a theoretical possibility of decrease of liver detoxication, cachexia etc., suppression of formation of active immunity against pathogens in case of acute infectious processes, induction of toxic shocks resulting from mass breakdown of microorganisms with release of endotoxins, acute phase proteins etc.
7. Serum disease occurs when addition into an organism of antitetanic, anti-influenza, antidiphtheritic, antitubulinic, antirabic, antigangrenous etc. serums, antilymphocytic and other immunoglobulines, as well as foreign hormones (insulin, adrenocorticotrophic hormones), vaccines, anatoxins etc. (Zemskov *et al.*, 1977; 2015).

Additional infection treatment methods

In some cases, according to a patient’s indications, it is necessary to decrease the capillary permeability (by corticosteroid drugs, derivatives of salicylic acid,

indomethacin) and stabilize the permeability of lysosomal membranes, and prevent egress of lysosomal hydrolases (by mefenamic acid, chingamin, hydroxychloroquine). It is also appropriate to inhibit the synthesis of high-energy compounds (by salicylates, indomethacin, and derivatives of pyrazolone) and to increase the formation or releasing of inflammation mediators (by anti-inflammation, anti-serotonin, anti-bradykinine, anti-prostaglandin drugs, and protease inhibitors). It is equally important to block the structure of tissue inflammation components (by ibuprofen, ketotifen, naproxen, diclofenac) and influence the metabolic immunity (by methyluracil, pentoxyl, orotic acid, riboxine, asparcam, panangin). In case of presence of anallergic component and a risk of formation of pseudoallergy, it is necessary to use choleric and spasmolytic drugs, enterosorbents (activated carbon, polyhepan, polysorb MP) and hepatoprotectors (lipoic acid, carsil, essential). All these medical drugs cause additional and often unpredictable load on the immune system, thus aggravating the disturbance of its functions.

Antiviral treatment

It is well known that viral infection creates conditions for development of bacterial or other pathology, since it damages the mechanical barriers (mucous membranes), «intercepts» cytokines and other regulators of the basic functions of organism causing mass destruction of tissues, releases toxic products, immunoactive factors making for allergies, autoaggressive reactions and immune paralysis. Implementation of the principles of treatment of viral infections depends on the type of pathogen, nature and morbidity of pathological process, patient's age, conditions of his or her immune reactivity, presence of associated complications and other circumstances. The treatment is conducted in order to inhibit the development of the viral infection proper, eliminate its post-effects, including bacterial and other complications, and create conditions for immunity formation. Symptomatic therapy by antipyretic, antihistamine, vitamin drugs is ambiguous. Therefore, fever, on the one hand, inhibits replication of viruses; on the other hand, it decreases antiviral activity of natural killers, and finally it may cause fatal consequences in aged groups and chronic patients. Antihistamine drugs, when they eliminate allergic reactions, also inhibit the degree of irresponsiveness and immune memory. Antiviral effect to ascorbic acid is an exaggeration; it requires prescription of large doses, up to 10 g per day, what is unreal. Patients with viral infections need prescription of drugs that prevent virus adsorption on target cells (dextran sulfate, trovilol, antibodies against cell receptors), as well as drugs that inhibit replication of infectious agent (azidothymidine, videx, antisense oligonucleotide, viral protease inhibitors). It is extremely important to use interferons – fibroblast and leukocytal, realizing antiproliferative (recognition, elimination of foreign nucleic acids, virions, and neoplasms) and immunotropic effects (stimulation of phagocytosis, natural killers, autoantibodies, class E immune globulins). Such antiviral drugs are widespread: amixin, arbidol, zovirax, valtrex, famvir and interferon inducers, glutoxim, derinat, ridostin, cycloferon,

neovir, sodium nucleinate. In addition, they use stimulators of cell defense reactions: hepon, thymomimetics (tactivin, thymalin, thymogen, vilosen, imunofan); polypotent immunity stimulators: sodium nucleinate, derinat, immunomax, myelopeptides and drug-free factors – low level laser therapy, blood ultraviolet radiation. They use also metabolics and antioxidants: hypoxen, cigapan, tocopherol acetate, selenium preparations. In special cases (elderly people and weakened groups, chronic patients etc.) are prescribed wide spectrum antibiotics, and in case of severe infection – specialized immunoglobulins and other serum drugs. In some cases of lingering and flaccid, chronic course of infection process, for example, with viral hepatitis or carriage of HBs antigen, it is prescribed to carry out active immunotherapy by antiviral vaccines. In cases of acute respiratory viral infections, where, because of wide polyetiology of pathogens, postinfectious resistance almost does not develop, the problem of nonspecific activation of antiviral resistance of patients becomes especially relevant (Zemskov et al., 2015).

An important component of infectious process is metabolic disorders, that include accumulation of toxic, immunosuppressing products of free-radical lipid and protein oxidation against the background of weakened activity of the antioxidant system. For correction of this pathology, it is expedient to prescribe antioxidants (hypoxen), keratinoids (retinol, tocopherol), phospholipids, hepatoprotectors (essential, lipostabil), ascorbic acid, and food additives: limontar, cigapan, preventan, tycveolum etc. (Zemskov et al., 2016).

Immunotherapy of infections

It implies that in treatment of chronic and poorly responding to conventional therapy diseases, they use vaccines, anatoxins, immunoglobulins, i.e. etiotropic drugs and pathogenetic treatment with use of blood, blood substitutes, plasma, nonspecific immunity stimulators etc. A series of drugs simultaneously have antimicrobial and immune stimulating actions (immunoglobulins, plant extracts etc.). Presently, because of changes in the natures of the course of infectious diseases, extensive clinical use of drugs that suppress immune reactions (corticosteroids, wide spectrum antibiotics) and increased allergization, it is necessary to free the organism from infectious agents extremely quickly and restore its destroyed homeostasis.

By origin, immunotherapeutic drugs subdivide into 4 groups

1. obtained from blood of various organs of humans and animals (plasma, immunoglobulins, thymus drugs, myelopeptides, interferons, splenin, placenta extract, antilymphocytic serum etc.),
2. obtained from plants (tinctures of eleuterococcus, schizandra, imanium etc.),
3. stimulators of microbial origin (pyrogenal, prodigiosan, zymosan, sodium nucleinate, bificol, bacteriophages etc.),
4. synthetic drugs (levamisole, pentoxyl, methyluracil, hemodez, polyoxidonium, licopid, diuciphonum etc.).

By the nature of immunotherapeutic action, immunotherapeutic drugs subdivide into drugs with specific (directed) action – vaccines, anatoxins, immune serums, immunoglobulins, and

nonspecific organism resistance stimulators – blood and its preparations, plasma, bificol etc.).

Indications for prescription of immune stimulators are flaccid course of infectious process, its chronization and recurring, sharp long-term suppression of the indices of non specific anti infection resistance and specific immunity in patients. It may also include changes in the nature and increased intensity of pathological changes, threat of development of secondary infection and curative use of drugs with immunosuppressing properties (Zueva, Yafaev, 2008). Immunotherapy prescribed in a complex with other medical drugs (antibiotics, sulfanilamides, corticosteroids). Its efficiency depends on the correct assessment of the initial condition of the patient's immune reactivity, the nature and intensity of pathological changes, the choice of optimal drug and dosing schedule. It is also necessary to have an idea about the action mechanisms of prescribed drugs, their side effects, compatibility with other infection treatment methods, allergic properties etc. Sometimes, vaccine therapy prescribed in case of immune tolerance to a certain AB, may render no positive clinical effect and even aggravate the condition of immune depression; simultaneously, there risk of anaphylactic shock is possible, as well as induction of autoimmune diseases and toxic shock. Blood and plasma transfusion is a good means instrument for stimulation of the patient's reactivity. However, this method of treatment is constrained by stable indications and should be performed only under a control of its influence on the course of disease, immunity indices and possibility of allergy. Drugs of etiotropic (immune serums, immunoglobulins, bacteriophages, interferon) and desintoxication action (drugs of blood, plasma, blood substitutes) should be prescribed as early as possible after the onset of the disease. A series of nonspecific stimulators are used at the height of disease and in the convalescence period (pentoxyl, vitamins, methyluracil) or for treatment of complications (ferrocalum, phytin, levamisole). Curative vaccines are added to patients with lingering and chronic forms of disease. The use of polysaccharide preparations is contraindicated for fever conditions. Eubiotics are not prescribed simultaneously with antibiotics and other similar drugs (Khaitov *et al.*, 2012).

Nonspecific immunomodulation (immunotherapeutic support) of infections

It implies not only correction of immune, but also normalization of hematological, bacteriological, clinical and other indices in patients. Under today's conditions of decrease of collective immunity of the humanity, substantial growth of infectious diseases rate, chronization, uncontrolled and irrational use of antibacterial drugs, the problem of immune reactivity modulation acquires special relevance. Diagnostic criteria of control overprescription of immunotropic drugs are implemented through assessment of the complex of clinical and laboratory indices in patients (Zemskov *et al.*, 2016). Clinical and immune criteria of effectiveness are determined by respective specialists with due account for preliminary approbation of the recommended actions. Immunotropic drugs, according to some classifications, divide into groups (Khaitov *et al.*, 2012) that induce various effects. These effects are quite numerous and are presented in the text:

1. Stimulation of formation of immune cells due to the influence on the hemopoiesis system (colony-stimulating factors).
2. Interaction with specific receptors of immunocompetent cells.
3. Stimulation or suppression of cytokines' release.
4. Formation of active (vaccine) or passive (serum) anti-infective immunity.
5. Normalization of microecological status of organism (eubiotics).
6. Provision of energy needs and essential components for immune reactions (macro-, microelement, vitamins, biological additives, antihypoxic drugs).
7. Activation of the processes of detoxification of immune reaction products (hepatoprotectors, enteral sorbents, afferent methods).
8. Elimination of antigens (adsorbents) from organism.
9. Substitution therapy (thymus drugs, immunoglobulins, white-cell- rich suspension).
10. Direct action on antigens (antiviral drugs).

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