

Ministry of health care of Ukraine  
Highest state scientific institution of the Ukraine  
«Ukrainian medical stomatological academy»

"Approved"

at a meeting of the Department of Experimental  
and Clinical Pharmacology with Clinical  
Immunology and Allergology

**Head of the department**

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**Methodical guidance for students' self-directed  
work when preparing for practical session**

Academic subject	Clinical Immunology and Allergology
Semantic module №1	Immunological status. Immunodeficiency diseases and immune-pathology
Topic №8	<b>Fundamentals of transplantation immunity.</b>
Year of study	5
Faculty	medical

### 1. Relevance of the topic:

In developed countries organ transplantation is currently a common practice. Has become a routine kidney transplants, liver, heart. Hooks the unit transplant clinic heart-lung, pancreas cells. Very much attention is paid to a bone marrow transplant as treatment of hematological diseases (aplastic anemia, leukemia), and congenital diseases of metabolism and immune deficiencies (severe combined immune deficiency). Transplantation of organs and tissues attracts the attention of both specialists and stakeholders. The alluring prospect - the possibility of replacing nonfunctioning body - was difficult solvable problem. You must define two major problems of transplantation: a) technical aspect; b) Immunological aspects - connected mainly with the selection of a compatible donor. Histocompatibility donor and recipient, as well as a course immunosuppressive therapy can prevent transplant rejection.

### 2. Specific objectives:

1. Interpret the data phenotyping pair donor - recipient (histocompatibility definition index) in preparation for the transplantation of organs and cells.
2. Justify the use of immunosuppressive therapy in the post transplant period.
3. To determine the clinical and laboratory signs of hyperacute, acute and chronic rejection crises.
4. To conduct differential diagnostics between a crisis of rejection and infectious complications in patients after organ transplantation.
5. Identify the laboratory signs of systemic and local immunosuppressive mechanisms in normal pregnancy.
6. Determine the mechanisms of development of immune forms of infertility.
7. Interpret data phenotyping couple man-woman (the definition of histocompatibility index) at diagnosis immunedependent form fertility.

### 3. Basic knowledge, abilities, skills, necessary for a study themes (interdisciplinary integration)

The name of the previous disciplines	These skills
Anatomy	The structure of the thymus, lymph nodes, moat plaques, spleen, bone marrow and bronholung second system.
Normal physiology	The functioning of the central and peripheral organs of the immune and respiratory system.
Biochemistry	The action of cytokines. The action of different groups of biologically active substances.
Microbiology and Virology	Immune response, diagnostics of bacterial and viral infections
Therapy	Pathogenesis and clinical manifestations of allergic diseases and incendiary bronholung internal systems and secondary immunodeficiencies. Collection of immunological and allergological history. Setting immunologic diagnosis. The principles of treatment.
phthisiatry	The course and clinical manifestations of tuberculosis, as a cell-dependent immune response. Setting delayed type allergy testing.
Infectious diseases	The pathogenesis, clinical manifestations of bacterial and viral infections. To be able to diagnose bacterial and viral infections.
Obstetrics	Mechanisms childbirth, fundamentals of immunology of reproduction. The ability to diagnose and know the main methods of treatment of Rh incompatibility.

### 4. Tasks for independent work in preparation for the occupation.

**4.1. List of basic terms, parameters, characteristics which the student has to assimilate during preparation for classes.**

Term and n	Definition
<b>Placenta immunoregulatory function</b>	The synthesis of hormones with immunosuppressive activity necessary to support the immunological balance in the mother-fetus system.
<b>Zygote</b>	The fertilized egg
<b>Alotransplantation</b>	Transplantation of tissues
<b>Xenotransplantation</b>	Transplantation of organs and tissues within the various species.
<b>Acute rejection and graft</b>	Develops within the first 3 weeks after transplantation
<b>Chronic graft rejection</b>	There has been a few months or years after the transplant.

**4.2. Theoretical questions to the lesson:**

1. Transplant immunology. Immunological indications and contraindications to transplantation of organs and tissues.
2. Selection of donor-recipient pairs. Preexisting antilimfocytic antibodies, their predictive value.
3. Features of the pre- and post-transplant immunological monitoring.
4. Types crisis of rejection, their clinical and immunological characteristics and prognosis.
5. The immune status of pregnant women. Immunology lactation. Immunology fertilization.
6. Forms of immune infertility in marriage couples. The causes and mechanisms of formation of autoantibodies to gametes in both men and women.
7. Immunopatogenesis infertility, its diagnosis. Immunological approaches to the treatment of infertility.

**4.3. Practical works (task) which are executed on employment:**

1. To learn the mechanisms of allograft rejection, recognition, immune response (cellular and humoral mechanisms), the relationship of coagulation.
2. Learn the differential diagnosis of a crisis of rejection and infectious complications.
3. Learn phenomenon second set - evidence of immunological nature of this reaction.
4. The reaction of "graft versus host" indication for transplantation.
5. Learn clinical transplantation: kidney, heart, liver, skin, lungs, bones, joints, cornea and bone marrow.
6. Learn remedies in transplantation: immunosuppression cyclophosphamide A, prednisolone, and azatoprinom.
7. Learn the techniques of oppression antigenspetsif nical response to the allograft.

**The contents of a class topic.**

**transplantation immunity**

Organ transplant the idea was prompted by the prospect of replacing the patient's body healthy. For the first time in the world of organ transplants (kidney) was performed by professor Y.Voronim in 1935 Kharkov: he carried out by donor kidney to the femoral vessels woman who poisoned mercuric chloride.

**The following types of transplants:**

- 1) *autologous transplantation* - the transplantation of own tissue;
- 2) *alotransplantation* - transplantation of organs and tissues within the same species;
- 3) *xenotransplantation* - the transplantation of organs and tissues within the different species;
- 4) *izotransplantation* - transplant between identical twins or between genetically identical animals.

Subjects who transplanted graft, is the recipient, and the one from which the organ or tissue is taken, - the donor.

**For breeding pairs of donor recipient must determine:**

1. The degree of histocompatibility, i.e. HLA phenotype of the donor and recipient.
2. The different temperatures preexisting antibodies in the recipient to donor antigens HLA system (anti-T and anti-B-antibodies).
3. antiendothelial antibodies of the recipient to donor antigens.
4. Starting the immune status of the recipient.

**MHC** - major histocompatibility complex, the system of JSC, which is transmitted hereditarily and provides tissue incompatibility between donor and recipient. Synthesis of AG provided by a group of closely linked genes. Also included are genes (Yr), which correspond to immune response. In humans, MHC is localized in chromosome 6 and HLA-called system because AG is well expressed on the surface of leukocytes.

**Transplant rejection:**

- **Primary response (first-set)** is the formation of specific T lymphocyte cytotoxicity of CEA that bind to target cells and lyse them. In addition to direct actions have been other mechanisms of damage of the target cells:

1. Indirect damage lymphokines;
2. Direct damage to the NK-target cells;
3. ADCC (antibody-dependent cellular cytotoxicity), which is caused by macrophages, polymorphonuclear leukocytes, K cells;
4. Phagocytosis of target loaded with hypertension;
5. By complement dependence cytotoxic antibodies.

- **A secondary response (second-set):** in the case after 2-3 weeks and more recipient re-transplanted organ or tissue, this leads to accelerated rejection of the transplant. On the fifth day to irreversible changes, resulting in tissue necrosis were recorded.

**The reaction of "graft versus host disease" (GVHD):**

If immunocompetent and transplanted cells that may be active against the recipient's body, developing GVHD. Tracking triad of skin lesions, gastrointestinal tract and liver. In severe collapse may come be with hypothermia. Regis trier joint disease, rheumatic heart disease. In the blood - anemia, leuko- and thrombocytopenia. There are acute and chronic GVHD. And immunosuppressive drugs are the main means of prevention and treatment of GVHD (cyclosporine + methotrexate), but the 30-35% of patients with transplanted bone marrow develops this reaction. In 2/3 of the cases it is possible to stop the use of high doses of globulin and antilimfo<sub>tic</sub> antitimid globulin.

**Immunosuppressive when allograft therapy**

Agents	Mechanism of action
Corticosteroids (prednisone and other drugs)	Suppression inflammation, phagocytosis, free-Suppress lysosomal enzymes, express-these molecules MNSII class, the secretion of IL-1
Cyclosporin A, tacrolimus (FK506), rapamycin	Prevent activation of T cells, influencing the effect of IL-2
Antimetabolites: azathioprine, chlorambucil, cyclophosphamide	Oppression nucleic acid synthesis due suppression inosinic acid or alkylating DNA
Monoclonal antibodies T-marker for cell	The elimination of cells that mediate transplant rejection
The total exposure of lymphocytes	Elimination of mature T-cells able to reject the transplant; thanks gemopoez and these cells deputy on tolerant cells
Active enhancement of survival transplanted	Education protective blocking antibodies to the antigens on the transplant ABO surface. Stimulation of T-suppressors

For immunosuppressive therapy is widely used **antilymphocytic serum** (ALS), in particular its globulins - ALG, due to the pronounced influence of immuno-depressive. Today, transplant centers in the West use the ATC - anti-thymocyte globulin. Positive results in the treatment of acute rejection crisis caused by the fact that anti-thymocyte antibody create cytolytic complement-dependent effect on T-lymphocytes from the recipient. In most known applications ALS transplant centers and GAT was limited due to the fact that the resulting protein material retention agents predetermined severe allergic reactions. In addition, during the experiment, it was found that the effect on ALS retrosternal gland - central body immunity, causing its destruction. It requires to be very careful while using ALS and ATG in transplantation.

### **Materials for self-control:**

#### **A. Tasks for self-control:**

1. What is the major histocompatibility complex in humans?
  - a) HLD;
  - b) HNA;
  - a) HLA;
  - g) Ministry of Emergency Situations.
2. Where are the genes that encode the HLA system in humans?
  - a) on chromosome 12;
  - b) on chromosome 6;
  - c) on chromosome 4.
3. The main body proteins that recognize antigen have,:
  - A. Albumins
  - B. Immunoglobulins
  - C. The glycoproteins
  - D.  $\beta$ -globulins
  - E.  $\alpha$ -fetoprotein
4. The most strongly activates complement:
  - A. Ig G
  - B. IgE
  - C. IgM
  - D. IgA
5. The immediate immunological mechanisms of T-dependent reactions is:
  - a) the sensitization of T lymphocytes;
  - b) the formation of reagenic antibodies;
  - c) formation of immune complexes;
  - d) formation of cytotoxic antibodies.
6. At the stage of immunological T-dependent reactions involving everything EXCEPT
  - a) plasma cells;
  - b) macrophages;
  - c) T-suppressors
7. Which cells of the immune system only recognize antigen in complex with major histocompatibility complex molecule
  1. T cells
  2. clara cell
  3. Langerhans cells
  4. Monocytes
8. Using a processing system is an antigen for T-dependent antibody production?
  1. receptors
  2. HLA - I
  3. HLA - II
  4. Toll -like receptors
9. Self in normal conditions of recognizing an antigen can:

1. T - Lymphocytes
2. B lymphocytes
3. Only CD4 lymphocytes
4. Only CD8 lymphocytes

10. The patient of 38 years flowed native plasma. At the end of the infusion condition deteriorated: patient disoriented, agitated. Respiratory rate (36 for 1 min., AO (70/40 mm Hg. Art., Breath difficulties, whistling dry rales. Which of the following drugs should be introduced in the first place?

- A. Adrenaline.
- B Eufilin.
- C. Suprastin.
- D Adrenalin.
- E Kardiamin

#### **Tests of the second level**

11. Patient for 28 appealed to the antenatal clinic because of primary infertility. Married for 6. For medical assistance due to infertility refers for the first time. What research is needed in the first place ?

- A Semen, basal temperature, metrosalpingography
- B The basal temperature, hormonal mirror
- C Metrosalpingography, basal temperature, colpocitogramma
- D basal temperature, diagnostic laparoscopy
- E basal temperature, ultrasound, diagnostic curettage

12. Patient 32 over there because of infertility for the past four. The study included: male - fertile, fallopian tubes - walkable, two-phase menstrual cycle. Objectively: revealed an increase in ovaries. What additional research mostly shown in this situation?

- A Hysteroscopy
- B. Diagnostic curettage
- D Diagnostic laparoscopy
- E metrosalpingography

13. In women over 30, when the second child was born with a birth-anemic jaundiced form of hemolytic disease blood in a woman A (II) Rh - blood group In newborn (III) Rh +, in the newborn and his father B (III) Rh +. Which The most likely reasons immunoconflict?

- A Rhesus conflict
- B Conflict antigen A.
- C Conflict of antigen B.
- D Conflict antigen AB.
- E Conflict ABO

14. Woman over 25 appealed to the antenatal clinic with complaints of infertility. Married 1 year, contraceptives does not use. with anamnesis that often treated in gynecological department because of acute exacerbations of chronic adnexitis. What is the diagnosis?

- A ovarian apoplexy
- B Chronic adnexitis
- C Primary infertility
- D Secondary infertility
- E pelvioperitonit

15. Patient 30 for complaining of infertility for 3 over. In history – behind uterus pregnancy (surgery salpingoektomia left because 1 year ago) and a cyst of the right ovary (operative treatment - with the right adnecectomia , the volume). Husband surveyed, pathology is not revealed. What tactics infertility treatment shows that a married couple?

- A Vitro Fertilization
- B Laparoscopy
- C hysteroscopy
- D Gidrotubation

### **Problem number 1**

It is known that the class II molecules MHC express primarily B cells, dendritic cells and thymus epithelial cells. The expression of these molecules is induced on other cells? What are the main loci HLA class -II.

### **task №2**

Patient M, 49 years old kidney allotransplantation. Histocompatibility Index 75%. After a kidney transplant patient was assigned immunosuppressive therapy. On the 16 th day after the operation has opened the abscess with a greenish allocation and suddenly showed signs of acute renal failure. In immunogram: a significant reduction in the total number of CD4+ T cells with an increase in the number of CD8+ T lymphocytes, the Graft 0.8. Suspected acute crisis of rejection, infectious complications, hyperacute rejection crisis, chronic crisis of rejection, medical glomerulonephritis Your diagnosis, treatment strategy?

### **Answers**

1-b ; 2. - c; 3 - e; 4 - c; 5 - a; 6 - a; 7 - 3; 8 - 3; 9 - 2; 10 - D; -A 11; C12; -A 13; 14 C; -A 15;

Task number: 1 Gamma INF th. Locus - DR, DP, DQ

task №2 Infectious complications, antibiotic therapy should be assigned a wide range of actions under the control of immune parameters may stimulants phagocytosis (likopid)

### **Control of the final level of knowledge**

#### ***Tests of the first level***

1. What are the main loci that encode molecules MHC Class 1:

a) -15-ligand CD8, CD16 - 15 ligand, CD95 - 4 ligand;

b) HLA - B, HLA - A , HLA - C;

in) HLA - DP, HLA - DQ , HLA - DR.

2) .Pregnant woman suffered flu. What do you call a baby developed influenza immunity?

1.natural active;

2.artificial passive;

3.natural passive.

4.artificial active

3) .Antigena major histocompatibility complex does not take part in:

1.Reaction of transplantation immunity

2.Anti virus protection

4.Regulation of immune response

5.Made by phagocytosis

4) Referring immunoregulatory index layer should be OK after transplantation and in the normal course of pregnancy?

1.0,5 - 1.0

2.1,0 - 1.5

3.1,3 - 1.8

4.1,8 - 2.4

5) .When and where for the first time conducted a kidney transplant allogeneic living person?

1.1906, Jaboulay, France

2.1933, Crow, Ukraine

3.1934, Michchou, USA

4.1937, Santa, England

6) .What different function of dendritic cells from other species antigenpresent their cells (macrophages)?

1.structural modifications of the cell membrane

2. permanent separation and re-synthesis HLA II

3. permanent separation and HLA I resynthesis

4. immediately include HLA synthesis immediately after phagocytosis object

7. What are the main locus of that encode the class II molecules MHC

a) CD8 -15-ligand, CD16 - 15 ligand, CD95 - 4 ligand;

- b) HLA - B HLA - A HLA - C;
- c) HLA - DP HLA - DQ HLA - DR.

8) .What is not a direct indication for bone marrow transplantation?

- 1.Acute chronic leukemia
- 2.Hard, mostly in due pendent immunodeficiencies
- 3.Hard predominantly T-dependent immunodeficiency
- 4.Aplastic anemia

9) Referring cells can recognize an antigen alone, without the interaction of HLA system ?

- 1.T lymphocytes helpers
- 2.T-suppressor lymphocytes
- 3.B lymphocytes
- 4.citotoxic lymphocytes

***Tests of the second level***

10. When blood transfusions at 8-year-old boy with hemophilia A, suddenly appeared pain for chest and in the back, shortness of breath, cold sweat. Objectively: pale skin, CHSS- 100 / min, AT-60/40 mmHg. Oliguria, urine brown. In the treatment of this complication is the priority purpose:

- A Eufilina
- B Lasix
- C Adrenaline
- D prednisolone
- E analgin

11. A pregnant 26-year-during, pregnancy 2, 14-15 weeks. 1 pregnancy ended in abortion in 11-12 weeks. The woman - (0) Rh <sup>-</sup>, husband - (0) Rh <sup>+</sup> blood group. What the survey is necessary to the woman?

- A biochemical analysis of blood
- B Identification antirhesus antibodies
- C coagulation
- D Definition of group antibodies
- E cordocentesis

12. The child was born on the 8th month of pregnancy. It found: microcephaly, cataracts, heart disease. The child's mother at the 2nd month of pregnancy was sick: it was not long raising the temperature to 37.5 C, the increase in the lymph nodes rash on the face, body and limbs, which took place without residual submitted. What is the most likely diagnosis in the mother of the child?

- A Rubella
- B cytomegalovirus infection
- C Herpetic infection
- D Hlamidna infection
- E toxoplasmosis

13. Woman 22 during appealed to the antenatal clinic because of pregnancy 11 to 12 weeks. The examination is definitely a positive Wasserman, a dermatologist diagnosed the secondary latent syphilis. Your tactics are.

- A. The prolongation of pregnancy after 1 year antisyphilis second therapy.
- B. Boxed abortion rate to antisyphilis second therapy.
- C. Emergency abortion.
- D. An artificial termination of pregnancy after the course antisyphilis therapy.
- E Antisyphyllitic treatment three times during pregnancy

14. The patient was a 28-over, turned to the gynecologist with complaints of infertility for 3 over. Menstrual function - is not broken. In history - one artificial abortion, chronic oophoritis. Contraceptives are not used. Semen husband without pathology. With a method, you must start a survey to establish the diagnosis of infertility?

- A. Diagnostic uterine cavity curettage
- B Hysterosalpingography
- C Laparoscopy



D hormone study

E. Hysteroscopy

15. Women over 33 in the past underwent 2 operations due to an ectopic pregnancy STI, two fallopian tubes removed. Addressed for consultation with the question, what can be done to get pregnant?

A Artificial insemination with donor sperm

B. Artificial Insemination by Husband

C In Vitro Fertilization

D. Surrogate motherhood

E. Induction of ovulation

### **Task №1.**

Name any feature antigen receptors of B-lymphocytes (structure, location) and what sequence of production of immunoglobulins by plasma cells as T-independent antibody production scheme?

### **Task №2.**

The patient was 47 years old had transplantation of liver. Histocompatibility index of 65%. On the 4th day of the postoperative period, there was a pain in the right upper quadrant, nausea, increase and up to 38 degrees C. Immunogram: increasing the number of SDZ - and CD4 -cells against the background of reduction of CD8 - lymphocytes IRI- 2.2. The needle aspirate: dominated by T-helper cells, high levels of IL-2 Suspected acute crisis of rejection, infectious complications, hyperacute rejection crisis, chronic crisis of rejection, drug-induced glomerulonephritis your diagnosis, what name the cells infiltrated inflammation area and name the main directions of tactics of treatment?

### **Task №3.**

What types of cells are used in the test with the type of lymphocyte antigens for MOE 1 and II classes

Answers: 1 - would be; 2 -3; 3 - 4; 4 -2; 5 -2; 6 -2; 7 -to; 8 -4; 9 -3; -A 10; -In 11; C12; -A 13; -In 14; -A 15;

Task №1 placed on the surface of B-lymphocytes, have the structure of a monomeric IgM.; a quick way to increase the number of antigen-specific natural antibodies and they are represented by only one class of Ig - IgM

Task №2. Acute crisis of rejection, the infiltration area is filled mainly mature lymphocytes (CD 8, CD 4); the treatment is necessary to adjust the immunosuppressive therapy

Task №3. For MOE class 1 - ordinary cells of the peripheral blood for MOE Class 2 - lymphocytes of the peripheral blood, enriched with B-lymphocytes.

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