МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
Харківський національний медичний університет

Module 1.
Clinical immunology and allergology.
Theme 5.
ACQUIRED IMMUNODEFICIENTES

Manual for practical lessons students having higher Medical education in English

Модуль 1.
Клінічна імунологія та алергологія.
Тема 5.
НАБУТІ ІМУНОДЕФІЦИТНІ ЗАХВОРЮВАННЯ

Методичні вказівки до практичних занять студентів медичних вузів з англійською мовою навчання

Затверджено
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Compliers P. G. Kravchun,
V. D. Babadzhan,
O. I. Kadikova

Модуль 1. Клінічна імунологія та алергологія. Тема 5. Набуті імунодефіцитні захворювання : метод. вказ. до практ. занять студентів мед. вузів з англ. мовою навчання / упор. П. Г Кравчун, В. Д. Бабаджан, О. І. Кадикова. – Харків : ХНМУ, 2015. – 32 с.

Упорядники П. Г. Кравчун
В. Д. Бабаджан
О. І. Кадикова

Scientific-methodological study of the theme: Resistance to infection caused by the body's defense mechanisms. Acquired defects in immunological protection often lead to the emergence of secondary immunodeficiencies. Detection of acquired immunodeficiency should be thoroughly and promptly, as these patients have chronic bacterial, viral and fungal diseases, including opportunistic infections and lead to a high risk of death from acute infectious diseases on the background suppression of the immune system.

Study aim: To study the mechanisms of development, clinical features, features immunodiagnostics, approaches to the treatment of acquired T- and B-dependent immunodeficiency disease due to violation of phagocytes' immunity, and deficiency of complement proteins.

To acquaint students with the types of acquired immunodeficiency.

To know:

- Basic principles of classification of acquired immunodeficiency.
- Principles identify with acquired immunodeficiency.
- Types of acquired immunodeficiency combined immunodeficiency, and B- and T-cell links: mechanisms of development, clinical course, immune-diagnostics and treatment.
- Acquired immunodeficiency phagocyte component of the immune system and complement: mechanisms of development, clinical course, immune-diagnostics and treatment.
- Phases of clinical and immune-laboratory assessment of the patient with acquired immunodeficiency.

Be able to:

- Conduct medical history and physical examination of patients with acquired immunodeficiency states.
- Identify a plan for further clinical and immune - laboratory tests.
- Interpret data of laboratory tests in patients with acquired immunodeficiency.
- Report the results of an independent examination of the patient and outline a plan for further management of patients with acquired immunodeficiency.
- Explain the immunological diagnosis of the differential diagnosis.
- Assign Immunotropic therapy in treatment of infectious diseases.
- Conduct antiviral immunotherapy of administering interferon and interferon inducers.
- Evaluate the effectiveness of immunotherapy designed in dynamics.
- To make general recommendations for the treatment and prevention of disease in a patient with acquired immunodeficiency.

Educational aim:

● form the student responsible approach to the identification and subsequent referral to a specialized immunological treatment of patients with diseases of the immune system.

● develop the need for conscientious attitude to their professional duties, interest and encourage in-depth study of the problems of clinical immunology and cooperation.

Interdisciplinary integration

Discipline	To know	Be able to
Bases of immunology	Factors of nonspecific defense, immune response	Identify the basic principles of immunity
Normal and pathological physiology	Physiology of the immune system, the pathogenesis of allergic	Identify key signs of inflammation, pathogenesis of immune disorders
Pharmacology	Principles of immune therapy	Identify indications and contraindi-cations against the appointment
Therapy	Diseases of internal organs	Conduct medical history and physical examination of patients
Dermatology	Diseases of the skin	Identify abnormal skin elements impression
Resuscitation	Emergency Conditions	Provide first aid

The plans and organization of the lesson

Duration – 5 hours.

Place of employment – classrooms, allergy department of the Kharkiv City Clinical Hospital № 27.

Financial support classes: thematic tables, slides, presentations, laboratory equipment and utensils.

Technological map of the practice lesson (table)

№ in the order	Stages of the lesson	Mastering level	Methods of control and studies	Time
1.	**Preparatory stage**			45 min
1.1.	Organizational issues		Register	5 min
1.2.	Educational goal setting and motivation	L – 0 (understanding of educational materials)	Manual for practical lessons for students	5 min
1.3	Verification of initial level of knowledge and abilities	L – 1 (recognition of educational material)	Test tasks for verifi-cation of initial level of knowledge (method. development), PC	35 min
2.	**Basic stage**			120 min
2.1	Discussion of thematic questions of employment	L – 1-2 (recognition and recreation of educational material)	Verbal control of acquired knowledge	45 min
2.2	Conducting Supervision case patients	L – 2-3 (reproduction and use of educational material)	Control of practical skills by the patient	15 min

№ in the order	Stages of the lesson	Mastering level	Methods of control and studies	Time
2.3	Analysis conducted Supervision	L – 3 (use of educational material)	Discussion of the results of surveys of patients	30 min
2.4	Break		Free time	20 min
3.	**Final stage**			60 min
3.1	Control and correction of abilities and skills	L – 2-3 (recreation and application of educational material)	Individual control of the acquired knowledge	10 min
3.2		L – 2-3 (recreation and application of educational material)	Test tasks are for final control of knowledge	30 min
		L – 4 (creative activity)	Decision of case studies	10 min
3.2	Results (theoretical, practical, organizational)			5 min
3.3	A task is on next employment			5 min
4	**All**			5 hours

The preparatory stage

At the beginning of class, the instructor reveals the importance of the subject, defines the main goals and objectives of the lesson, assess the initial level of knowledge by solving tests and oral interviews. Students are given a task to work with patients.

Literature

1. Practical immunology / C. Hay Frank, Olwyn M.R. Westwood ; with the assistance of Paul N. Nelson. – 6th ed. – 2012. – 400 p.

2. Manual of Allergy and Immunology: Diagnosis and Therapy Book / Jonathan Corren, Thomas B. Casale, Daniel C. Adelman. – 2011. – 528 p.

3. Clinical Immunology, 4th Edition / Robert R. Rich, Thomas A Fleisher, William T. Shearer, Harry Schroeder, Anthony J. Frew, Cornelia M. Weyand. – 2012. – 922 p.

4. Manual of Allergy and Immunology / Daniel C. Adelman, Thomas B. Casale, M.D., Jonathan Corren. – 4th ed. – Philadelphia : Lippincott Williams&Wilkins, 2010. – P. 528.

5. Essential Clinical Immunology / J. B. Zabriskie. – Cambridge University Press.- NY, 2012. – 352 p.

6. Spickett Gavin. Oxford Handbook of Clinical Immunology and Allergy / Gavin Spickett. – Oxford Medical, 2011. – 510 p.

7. Immunological techniques and their applications / K. S. Srikanth, Naveen Sharma, Rohini Garg and Ayub Qadri // National Institute of Immunology. – New Delhi, 2011. – P. 28

8. Massoud Mahmoudi / Challenging Cases in Allergy and Immunology // Springer Dordrecht Heidelberg London New York. – 2010. – P. 332.

Tests to check the initial level of knowledge

1. Enter the possible cause of recurrent purulent infections in patients with hypogammaglobulinemia:

A. Reduction of the number of B-Cell in the bone marrow
B. The absence of blood B-Cell with surface immunoglobulin's receptors
C. No indication of reasons

2. Do immunoglobulin's observed failure of one or several classes to children in normal circumstances?

A. Yes
B. No
C. In definite periods of life

3. What caused reduction in the level of physiological immunoglobulin are some classes of children in the norm?

A. Catabolism immunoglobulin obtained from the mother
B. Age-specific variation of fusion proteins

4. Which clinical signs are typical for patients with T-Cells immunodeficiency?

A. Increased sensitivity to viral infection
B. Attachment to tumors
C. The change of indices of T - Cells immunity
D. The change of indices of B - Cells immunity

5. Which factors can be cause the development of secondary immunedeficiency?

A. Nutritional factor
B. Severe infectious diseases
C. Long chronicle recurring infection
D. Irradiation
E. The introduction of a large dose of glucocorticosteroids preparations
F. Introduction of cytotoxic agents
G. None of these factors

6. The development of secondary immunodeficiency may be due to:

A. *Fermentopathy, including, caused by deficiency intake or impaired communication binding of iron ions in the organism*
B. Immunosuppressive action by viruses and their toxin
C. Reduction of functional activity of macrophages with chronic infection
D. Lesion of lymph vessels by microorganisms and their effects toxin
E. Appearance in the blood plasma factors, blocking lymphocyte blast transformation
F. Development lymphoproliferative diseases
G. No with these reasons can lead to the development of secondary immunodeficiency

7. Can a secondary immunodeficiency accept endemic?

A. Yes
B. No
C. Subject to certain conditions

8. Identify possible ways of distributing the acquired immunodeficiency caused by RNA-containing retrovirus that belongs to a group of lent virus?

A. Sexually
B. Parenteral own way
C. Transplacental from mother to fetus
D. None of these paths

9. Which Cells of cells immunity system selectively affected in the syndrome of acquired immunodeficiency?

A. T-helper
B. T-suppressors
C. T-killers
D. Cytotoxic T-lymphocytes

10. Is it typical that viral infection of lungs, gastrointestinal tract and central nervous system in HIV infection caused halovirus, herpes simplex virus 1 st and 2-types and papova-virus?

A. Yes
B. No
C. In rare cases

11. What are the symptoms of HIV?

A. Reduction of body weight by 10 % and more
B. Chronic diarrhea duration of more than 1 month
C. Fever, duration of more than 1 month
D. Lymphadenopathy

12. What are chemo taxis and chemo kinesis?

A. Chemo taxis – is a direct migration of granulocytes to the concentration gradient of mediators and chemo kinesis - is the mobility of these cells.
B. Chemo taxis and chemo kinesis provided under the supervision of chemo kinetic factor of eosinophils.
C. Chemo kinesis - is under the control of migration of granulocytes chemo kinetic factor of eosinophils.
D. Chemo taxis and chemo kinesis is a process of spontaneous activation of mast cells.

13. Patient that was 5 years ago over the course of treatment of focal pulmonary tuberculosis, turned to clinic for removal of accounting. At the control examination found that previously positive Mantua reaction was negative. Consider...

A. The patient is cured of tuberculosis.
B. Conserved active tuberculosis.
C. Patients should be vaccinated with BCG
D. There is a state of immunodeficiency (possibly AIDS).

14. Effectiveness of treatment with interferon above...

A. Combined treatment
B. Isolated using the drug
C. No significantly difference

15. There is a synergistic effect of interferon and chemotherapy?

A. Yes.

B. No.

C. No specific regularities.

16. There is a synergistic effect of interferon and tumor necrosis factor?

A. Yes.

B. No.

C. No specific regularities.

17. Normally, immunocompetent cells have completed differentiation...

A. Capable of self-replication.

B. Lose their ability to reproduce.

18. Which pathological states and diseases associated with immunosuppressant should differentiate with AIDS?

A. With congenital immunodeficiency

B. From the malignant tumor lymphoreticular system

C. With severe protein - energy deficiency

D. With any of these pathological states

19. What are the symptoms of HIV?

A. Reduction of body weight by 10 % and more

B. Chronic diarrhea duration of more than 1 month

C. Fever, duration of more than 1 month

D. Lymphadenopathy

20. What is the systemic response to sepsis?

A. The fugitive emissions of a set of mediators

B. The reduced number of lymphocytes

C. The release of a set of prose consumption and anti-inflammatory cytokines

D. In the inactivation of compliment

E. The activation of macrophages, lymphocytes and endothelial

Correct answers: 1 – A, B. **2** – C. **3** – A. **4** – A, B, C. **5** – A, B, C, D, E, F. **6** – A, B, C, D, E, F. **7** – C. **8** – A, B, C. **9** – A. **10** – A. **11** – A, B, C, D. **12** – A. **13** – D. **14** – A. **15** – A. **16** – A. **17** – B. **18** – A, B, C. **19** – A, B, C, D. **20** – A.

BASIC CONTENT OF THEME

Analysis of theoretical material and interesting, complex patients and their medical records.

List of theoretical questions

1. Congenital immunodeficiency disease: definition, classification, mechanisms of development.

2. Clinical signs, immune-diagnostics, medical tactic, treatment approaches: combined, T- and B-dependent immunodeficiency's caused by disturbance immunity and phagocytes' deficiency of complement proteins.

3. Principles immunotropic clinical use of drugs.

4. Indications and contraindications for the purpose, dose selection, immunological monitoring of therapeutic efficacy.

8. Replacement therapy.

9. Cytokinotherapy, antireceptors drugs and others.

10. Basic principles of immunization bacterial and viral infections.

11. The main types immunorehabilitation, its strategy, tactics and the basic principles.

12. Rapid fatigue syndrome, chronic fatigue syndrome.

13. Immunopathogenesis, stage of development, the classification of HIV-infection/AIDS.

14. Clinical and laboratory criteria for diagnosis, principles of treatment of AIDS.

15. Basic principles of prevention of AIDS in Ukraine. Health professionals as individuals "at risk" high risk of morbidity from AIDS.

The practical works (tasks) to be performed in class

Secondary (acquired) immunodeficiency – is a clinical and laboratory immunological syndrome that develops in the normal function of this immune response, characterized by clinical symptoms, persistent marked changes in quantitative and functional parameters of adaptive immunity and/or congenital factors immune resistance and is an area of risk for chronic infectious diseases and complications, autoimmune diseases, allergic diseases and tumor growth.

This definition emphasizes its secondary immunodeficiency following features:

• disturbances in the immune system works really secondary as in clinical and in immun - laboratory respect (you can find out in an interview with the patient);

• clinical manifestations characterized by certain dependent immune prolonged symptoms: subfebrile, lymphadenopathy, fatigue syndrome, polyart-hralgias, fibromyalgia, not healing of wounds, skin rashes, and other symptoms characteristic clinical syndromes. The symptoms are protracted course.

• violations of the immune system have steady and pronounced character. Transient, temporary changes in immune parameters may be due to the peculiarities of the situation response;

• violations of the immune system should be not only qualitative character, estimate a function of certain cells of the immune system;

• violations in the immune system can touch the figures as specific (adaptive) immunity and nonspecific resistance.

It is important to target doctors that some so-called healthy individuals can be identified laboratory signs of secondary immunodeficiency, accompanied by only a few nonspecific symptoms, such as chronic fatigue. This person can be attributed to the risk of their or other diseases associated with secondary immunodeficiency, infectious, autoimmune, allergic disease, tumor process, and so on.

Causes of secondary immunodeficiency's:

I. Infectious
1. Viral infection:
   a) acute – measles, rubella, influenza, mumps virus disease (mumps), chicken pox, hepatitis, herpes etc.
   b) persistent – chronic hepatitis B, AIDS etc.
   c) birth – cytomegalovirus, rubella (TORCH- complex).
2. Bacterial infections: staphylococcal, pneumococcal, meningococcal, tuberculosis and others.
3. Helminthiasis and protozoan infestations (malaria, toxoplasmosis, leishmaniasis, tryhiniloz, ascariasis etc.).

II. Nutritional (malnutrition):
1. protein- energy malnutrition ;
2. deficiency of micronutrients (Zn, Cu, Fe), vitamins - retinol (A), ascorbic acid (C), alpha tocopherol (E), folic acid;
3. malnutrition, cachexia, loss of protein through the intestines, kidneys;
4. inborn errors of metabolism ;
5. excessive nutrition obesity;
6. syndrome of malabsorption in the intestines.

III. Metabolic:
1. chronic renal failure, uremia, nephrotic syndrome;
2. chronic liver disease,
3. diabetes,
4. hiperkatabolizm immunoglobulins.

IV. Conditions that result in the loss of immune cells and immunoglobulins (bleeding chylorrhea, burns, nephritis).

V. Malignant neoplasm's, particularly lymph proliferative.

VI. Autoimmune disease.

VII. Exogenous and endogenous intoxication (poisoning, thyrotoxicosis, decompensate diabetes).

VIII. Immunodeficiency after various influences:
1. Physical (ionizing radiation, ZVCH et al.)
2. Chemicals (imunosupressory, cytostatics, corticosteroids, drugs, herbicides, pesticides, etc.)
3. Adverse environmental factors;
4. Measures immunosuppressive treatment: medicines (immunosuppressant's, steroids, cytostatics, antibiotics, non-steroidal anti-inflammatory drugs).
5. Occupational hazard, including X-ray radiation, radioactive impact biologically active and chemically aggressive substances.
6. Different types of stress (emotional, psychological trauma, physical, athletic handling, etc.).

IX. Various serious illness, surgery, anesthesia care.

X. Violation of neurohormonal regulation.

XI. Age-related factors: early childhood, old age, pregnancy.

It should again be emphasized that the clinical features and laboratory data of secondary and primary immunodeficiency's very similar, even to the existence of the relationship between the nature of immune disorders and the type of pathogen. The fundamental difference is the reason underlying immune disorders: the primary is a birth defect in secondary - purchased.

Similarly, as the primary and secondary immunodeficiency's may be due to dysfunction of one of the major systems of immunity: humoral (B-system), cellular (T-System), a system of phagocytes, complement system or more (combined defects).

Among secondary immunodeficiency's are three forms: acquired, induced, spontaneous (ICD-10 code D.84.9).

Acquired form of secondary immunodeficiency are acquired immunodeficiency syndrome (AIDS), which develops as a result of destruction of the immune system of the human immunodeficiency virus (HIV).

Induced form (codes ICD-10 D.84.8) secondary immunodeficiency occurs as a result of specific causes of its appearance: X-rays, cytostatic therapy, corticosteroid use, trauma and surgery, as well as violations of immune re- emerging in relation to underlying disease (diabetes, liver disease, kidney disease, malignant neoplasms).

Spontaneous form (codes ICD-10 D.84.9) secondary immunodeficiency characterized by the lack of obvious reasons that caused impaired immune responsiveness. Clinically, it manifests as a chronic, often relapsing infectious and inflammatory broncho-pulmonary system, sinuses, urogenital and gastrointestinal tract, eyes, skin and soft tissue caused by opportunistic (opportunistic) microorganisms. Therefore, chronic, often recurrent, slow, such that it is difficult to treat with traditional means inflammation of any location in adults treated as clinical manifestations of secondary immunodeficiency state.

In quantitative terms, spontaneous form is the dominant form of secondary immunodeficiency.

Types of immunodeficiency

Types of immunodeficiency depending on the etiological factor:

– Specified (infectious, toxic, metabolic, physical, psychogenic, traumatic, indicating a specific diagnosis - a disease it caused) (ICD-10 code D.84.8);

– Unspecified (or essential or idiopathic, or spontaneous - exposed in the absence of any etiological factor) (ICD-10 code D.84.9).

Types specified immunodeficiency:

- Infectious immunodeficiency formed as a result of the infectious agent, including pathogenic (viral, bacterial, protozoal and fungal).
- Toxic immunodeficiency develops under conditions of prolonged exposure to exo- and endotoxins, xenobiotics etc. (exogenous, medical, professional, endogenous, burn, etc.).

• Metabolic immunodeficiency develops under conditions of prolonged metabolic disorders, including disorders of acid- base balance (food, exchange, due to lack of protein malabsorption, etc.).

• Physical immunodeficiency develops as a result of long-term effects on the human body ionizing and ultraviolet radiation of high frequency fields and so on.

• Psychogenic immunodeficiency develops under conditions of long-lasting emotional overload, stress, diseases of the central nervous system and so on.

• Posttraumatic immunodeficiency (including operational) develops under conditions of severe extensive injuries, burns, volume and prolonged surgery, blood loss more.

Types of defects in the immune system:

• Lymphocytic immunodeficiency characterized by robust quantitative and/or functional changes in T-cell component of the immune system.

• Humoral immunodeficiency characterized by robust quantitative and/or functional changes in B-cell component of the immune system, including the production of antibodies.

• Phagocytic immunodeficiency characterized by robust quantitative and/or functional changes of phagocytic cells (monocytes/macrophages, granulocytes) immune system.

• Complementary immunodeficiency characterized by persistent changes in the level and activity of components of complement.

• Combined immunodeficiency characterized by robust quantitative and/or functional changes in performance multiple (two or more) parts of the immune system. It is advisable to allocate the leading defect of the immune system (for example, a combined defect of lymphocyte overload).

Variants of immunodeficiency's:

Acute – clinical and laboratory signs of immunodeficiency develop and persist for 1 month.

Subacute – clinical and laboratory signs of immunodeficiency develop and persist for 3 months.

Chronic – clinical and laboratory signs of immunodeficiency develop and persist for 6 months.

Recurrent – clinical and laboratory signs of immune re- formed earlier than 6 months after successful treatment.

The degree of immune deficiency

(depending on the absolute lymphocyte count, absolute lymphocyte count rate – 1,4–3,2×10^9/l):

1. degree of immune deficiency – minimum (ID-1) – the absolute number of lymphocytes is 1,4–1,2×10^9/l laboratory parameters reduced by 15–30 % of the average normal value. Clinically immune deficiency may not manifest (offset form).

2. degree of immune deficiency – medium (ID-2) – the absolute number of lymphocytes is $1,1–0,9\times10^9$/l laboratory parameters reduced by 35–55 % of the average normal value. Clinically immunodeficiency may present one or a combination of several clinical syndromes, subacute or chronic clinical course.

3. degree of immune deficiency – high (ID-3) – the absolute number of lymphocytes is less than $0,9\times10^9$/l laboratory parameters decreased by more than 55 % of the average normal value. Clinically severe immunodeficiency manifested clinical symptoms.

Classification of secondary immunodeficiency's by functional impairment:

• FI I – the patient retains capacity needs outpatient treatment without issuing medical certificate;

• FI II – patient temporarily loses capacity or limited capacity, needs outpatient treatment with the issuance medical certificate;

• FI III – the patient loses capacity is temporarily or permanent disability, require hospital treatment and/or examination performance.

Principles of treatment of secondary immunodeficiencies

Stages of treatment and immunorehabilitation patients with secondary immunodeficiency: 1) elimination of etiological factors; 2) antimicrobial therapy; 3) replacement immunotherapy; 4) preventing infection; 5) immunocorrection; 6) preventive immunotherapy and immunorehabilitation.

Reference points treatment of secondary immunodeficiencies are relevant protocols.

When damage of the cells of monocyte-macrophage system presents used Polyoxidonium at a dose of 6 to 12 mg, Likopid at a dose of 1 mg, 10 mg. In the most severe lesions used granulocyte-macrophage colony-stimulating factors: molhramostym (leycomaks) 150 mcg, 300 mcg, 400 mcg, fylhrastym (neypohen) 300 mcg, 480 mcg. For replacement therapy used leycomass.

When defects of cellular immunity present applies one of the following drugs: Polyoxidonium at a dose of 6 to 12 mg, Tactyvin at a dose of 0.01 % solution – 1 ml subcutaneously, tymoptyn at a dose 100 mkg ; thymogen 0.01 % solution – 1 ml, timalin 10 mg 1 times daily.

When defects of antibody synthesis of B-lymphocytes present are indicated - miyelopyd 0.003 g, Polyoxidonium at a dose of 6 to 12 mg.

When defects of humoral immunity (and or hypogammaglobulinemia) present apply replacement therapy with immunoglobulin: sandoglobulin 1.0, 3.0, 6.0 and 12 g per day; octagam 50,100, 200 ml daily ; intraglobin 2.5 g, 5,0 g, normal human immunoglobulin 200 ml, biaven 50–250 ml. Preparations containing IgM, pentaglobin 5% – 10.0 ml, 20.0 ml, 50.0 ml. Replacement therapy is conducted in the saturation regime (level of immunoglobulin G at least 400 mg/ml), supportive therapy – under medical supervision – immunologist.

Basics immunotherapy of viral infections:

1. Activation of intracellular antiviral defense (interferon).

2. Activation of phagocytosisof killer cells (Polyoxidonium).

3. Binding of virus after the destruction of infected cells and release of viral particles in the peripheral blood (specific gamma globulin, blood plasma in conjunction with antibiotics and antiviral drugs - Tamiflu).

4. Increased synthesis of antiviral antibodies (isoprinozin).

Length of stay from 20 to 30 days.

Additional Therapy – methods of extracorporeal immune – plasmapheresis, immunosorbtion, extracorporeal immunotherapy.

Requirements for treatment outcomes – termination of clinical manifestations of immune deficiency, reducing the frequency of relapses, or a tendency to normalization, normalization initial parameters altered immunity.

Duration eliminate immunological disorders ranges from 30 days to 6–9 months and depends on the properties of the drug marker parameter and the nature of the disease.

The Centers for Disease Control and Prevention (CDC) classification system for HIV-infected adolescents and adults categorizes persons on the basis of clinical conditions associated with human immunodeficiency virus (HIV) infection and CD4+ T lymphocyte counts. The system is based on three ranges of CD4+ T lymphocyte counts and three clinical categories and is represented by a matrix of nine categories. Using this system, any HIV-infected individual with a CD4+ T cell count of <200/μL has acquired immune deficiency syndrome (AIDS) by definition, regardless of the presence of symptoms or opportunistic diseases.

The clinical conditions in clinical category C now include *pulmonary tuberculosis, recurrent pneumonia, and invasive cervical cancer*.

Clinical categories of HIV infection

Category A: *Consists of one or more of the conditions listed below in an adolescent or adult (>13 years) with documented HIV infection.*

Asymptomatic HIV infection

Persistent generalized lymphadenopathy

Acute (primary) HIV infection with accompanying illness or history of acute HIV infection.

Category B: Consists of symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in clinical category C and that meet at least one of the following criteria: (1) The conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or (2) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection.

Examples include, the following:

Bacillary angiomatosis

Candtdiasis, oropharyngeal (thrush), vulvovaginal;

Cervical dysplasia (moderate or severe)/cervical carcinoma in situ;

Constitutional symptoms, such as fever (38.5°C) or diarrhea lasting >1 month, Hairy leukoplakia, oral;

Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome;

Idiopathic thrombocytopenic purpura,

Listeriosis, Peripheral neuropathy;

Pelvic inflammatory disease, particularly if complicated by tuboovarian abscess.

Category C: Conditions listed in the AIDS surveillance case definition.

Candidiasis of bronchi, trachea, lungs or esophageal;

Cervical cancer, invasive,

Coccidioidomycosis, disseminated or extrapulmonary;

Cryptococcosis, extrapulmonary,

Cryptosporidiosis, chronic intestinal (>1 month's duration);

Cytomegalovirus disease (other than liver, spleen, or nodes), retinitis

Encephalopathy, HIV-related;

Herpes simplex: chronic ulcer(s) (>1 month's duration); or bronchitis, pneumonia, or esophagitis;

Histoplasmosis, disseminated or extrapulmonary;

Isosporiasis, chronic intestinal (>1 month's duration);

Kaposi's sarcoma; Lymphoma, Burkitt's lymphoma;

Mc. avium complex, Mc. Tuberculosis;

Pneumocystis carinii pneumonia, Pneumonia, recurrenta;

Salmonella septicemia, recurrent;

Toxoplasmosis of brain;

Wasting syndrome due to HIV.

HIV disease is a spectrum ranging from primary infection, with or without the acute syndrome, to the asymptomatic stage, to advanced disease.

The etiologic agent of AIDS is HIV (HIV-1,2).

HIV is an RNA virus. The life cycle of HIV begins with the high-affinity binding of the gp120 protein via a portion of its V1 region near the N terminus to its receptor on the host cell surface, the CD4 molecule of T lymphocytes. It is also expressed on the surface of monocytes/macrophages and dendritic/Langerhans cells. Following binding, fusion with the host cell membrane occurs via the gp41 molecule, and the HIV genomic RNA is uncoated and internalized into the target cell. The reverse transcriptase enzyme, which is contained in the virion, catalyzes the reverse transcription of the genomic RNA into double-stranded DNA. The DNA translocates to the nucleus, where it is integrated into the host cell chromosomes through the action of virally enzyme, integrase. This provirus may remain transcriptionally inactive (latent), or it may manifest varying levels of gene expression, up to active production of virus.

Activation of the host cell is required for the initiation of transcription of the integrated proviral DNA into genomic RNA or mRNA. Following transcription, HIV mRNA is translated into proteins that undergo modification through glycosylation, phosphorylation, and cleavage. The viral core is formed by the assembly of HIV proteins, enzymes, and genomic RNA at the plasma membrane of the cells. HIV incorporates a variety of host proteins, including major histocompatibility complex (MHC) class I and II antigens, into its lipid bilayer. Budding of the progeny virion occurs through the host cell membrane, where the core acquires its external envelope.

Transmission HIV is transmitted by both homosexual and heterosexual contact; by blood and blood products; and by infected mothers to infants either intrapartum, perinatally, or via breast milk. After more than 15 years of scrutiny, there is no evidence that HIV is transmitted by casual contact or that the virus can be spread by insects, such as by a mosquito bite.

There is a small, but definite, occupational risk of HIV transmission among health care workers, laboratory personnel, and potentially others who work with HIV-infected specimens, particularly when sharp objects are used. An increased risk for HIV infection following percutaneous exposures to HIV-infected blood is associated with exposures involving a relatively large quantity of blood, as in the case of a device visibly contaminated with the patient's blood, a procedure that involves a needle placed directly in a vein or artery, or a deep injury.

Epidemiology HIV infection/AIDS is a global pandemic, with cases reported from every country. Figure illustrates the beginnings, real and projected peaks, plateaus, and declines of the epidemic in different regions of the world.

Pathophysiology and pathogenesis The hallmark of HIV disease is a profound immunodeficiency resulting primarily from a progressive quantitative and qualitative deficiency of the subset of T lymphocytes referred to as helper or inducer T cells. This subset of T cells is defined phenotypically by the presence on its surface of the CD4 molecule, which serves as the primary cellular receptor for HIV. When the number of CD4+ T cells declines below a certain level, the patient is at high risk of developing a variety of opportunistic diseases, particularly the infections and neoplasms that are AIDS-defining illnesses.

Primary HIV infection, initial viremia, and dissemination of virus Virus that enters directly into the bloodstream via infected blood or blood products (i.e., transfusions, use of contaminated needles for injecting drugs, sharp-object injuries, maternal-to-fetal transmission either intrapartum or perinatally, or, in certain cases, sexual intercourse where there is enough trauma to cause bleeding) is likely cleared from the circulation to the spleen and other lymphoid organs, where it replicates to a critical level and then leads to a burst of viremia that disseminates virus throughout the body. The likely scenario in infection contracted via blood exposure is that free virus or virus-infected cells are cleared by the reticuloendothelial system and come into contact with susceptible target cells in these tissues, or that blood dendritic cells carry virus to tissues, particularly lymph nodes, where they put the virus in contact with susceptible CD4+ T cells.

Mucosal dendritic cells, known as Langerhans cells, become infected following mucosal exposure to the virus, as might occur when infected seminal fluid comes into contact with mucosal surfaces of the urogenital tract, the upper gastrointestinal tract, or the rectum. The common denominator of local infection is the drainage of Langerhans cells to the regional lymph nodes; these cells either are themselves infected or carry virus to the lymphoid tissue. CD4+ T cells in the regional lymph nodes become infected after contact with the Langerhans cells, and virus replication intensifies prior to the initiation of an HIV-specific immune response, leading to a burst of viremia, which then leads to rapid dissemination of virus to other lymphoid organs, the brain, and other tissues.

Establishment of chronic and persistent infection The HIV is, with very few exceptions, not cleared completely from the body. Rather, a chronic infection develops that persists with varying degrees of virus replication for a median of approximately 10 years before the patient becomes clinically ill.

Viral dynamics HIV replication occurs throughout the course of HIV infection, even during clinical latency. Plasma viremia is present at all stages of HIV disease (Figure 1).

Immunopathogenic events during clinical latency The level of CD4+ T cells in blood decreases gradually and progressively in HIV-infected individuals. The slope of this decline, together with the level of plasma viremia, predicts well the pattern of the clinical course and the development of advanced disease.

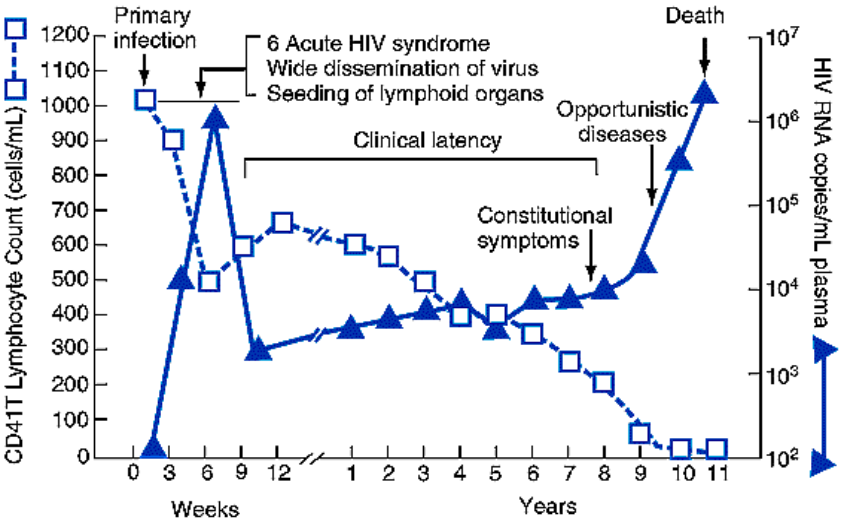

Figure 1. Typical course of an HIV-infected individual

Advanced HIV disease After a variable period, usually measured in years, the CD4+ T cell count falls below a critical level (less than 200 cells per microliter), and the patient becomes highly susceptible to opportunistic disease. The depletion of CD4+ T cells continues to be progressive and unrelenting in this phase.

Long-term survivors and long-term nonprogressors The median time from primary HIV infection to the development of AIDS is approximately 10 years. Less than 5% of HIV-infected individuals are characterized as long-term nonprogressors. Individuals who have been infected with HIV for a long period (approximately 10 or more years), whose CD4+ T cell counts are in the normal range and have remained stable over years, and who have not received antiretroviral therapy are considered to be long-term nonprogressors.

Diagnosis of HIV infection The diagnosis of HIV infection depends on the demonstration of antibodies to HIV and/or the direct detection of HIV or one of its components. Antibodies to HIV generally appear in the circulation 4 to 8 weeks after infection.

The enzyme-linked immunosorbent assay (ELISA) This is a screening test, with a sensitivity of 99.5 . Laboratories use ELISA kit that contains antigens from HIV-1 and -2. ELISA tests are scored as positive (highly reactive), negative (nonreactive), or indeterminate (partially reactive). While the ELISA is sensitive, it is not optimal with regard to specificity. The factors associated with false-positive ELISA tests: antibodies to class II MHC antigens, autoantibodies, hepatic disease, and recent influenza vaccination. Anyone suspected of having HIV infection on the basis of an inconclusive or positive ELISA result must have the result confirmed with a more specific assay.

The western blot It takes advantage of the fact that multiple HIV antigens having different, well-characterized molecular weights elicit the production of specific antibodies. These antigens can be separated on the basis of molecular weight, and antibodies to each component can be detected as discrete bands on the WB. A negative WB is one in which no bands are present at molecular weights corresponding to HIV gene products. In a patient with a positive or indeterminate ELISA and a negative WB, one can conclude with certainty that the ELISA reactivity was a false positive. A WB demonstrating antibodies to products of all three of the genes of HIV (gag, pol, and env) is conclusive evidence of infection with HIV. A WB can be considered positive for HIV-1 if it contains bands to at least two of the following gene products p24, gp41, and gp120/160. The WB should be repeated in 1 month to confirm whether or not the indeterminate pattern is a pattern in evolution.

The sera from the patient immunized to the HIV-1 envelope only contains antibodies to the HIV-1 envelope proteins. The sera from the patient with HIV-2 infection cross-reacts with both reverse transcriptase and gag gene products of HIV-1.

One may attempt to confirm a diagnosis of HIV infection with the p24 antigen capture assay or one of the tests for HIV RNA. A variety of laboratory tests are available for the direct detection of HIV or its components (Table 1).

Table 1

Characteristics of tests for direct detection of HIV

Test	Technique	Sensitivity
Immune complex-dissociated p24 antigen capture assay	Measurement of levels of HIV-1 core protein in an ELISA-based format following dissociation of antigen-antibody complexes by weak acid treatment	Positive in 50% of patients Detects down to 15 pg/mL of p24 protein
HIV RNA by PCR	PCR amplification of cDNA generated from viral RNA (target amplification)	Positive in >98% of patients. Detects down to 40 copies/ml of HIV RNA
HIV RNA by bDNA	Measurement of levels of particle-associated HIV RNA in a nucleic acid capture assay employing signal amplification	Positive in 90% of patients. Detects down to 500 copies/ml of HIV RNA

The close relationship between clinical manifestations of HIV infection and *CD4+ T cell count* has made measurement of the latter quantity a routine part of the evaluation of HIV-infected individuals. Patients with CD4+ T cell counts below 200/μL are at high risk of infection with Pneumocystis carinii, while patients with CD4+ T cell counts below 100/uL are at high risk of infection with cytomegalovirus and the Mycobacterium avium-intraceltulare complex. Patients with an initial diagnosis of HIV infection should have CD4+ T cell measurements performed approximately every 6 months, and more frequently if a declining trend is noted. Antiretroviral therapy is generally indicated when the CD4+ T cell count falls below 500/μL, and a declining CD4+ T cell count may provide an indication for changing therapy. Once the CD4+ T cell count is below 200/μL, patients should be placed on a regimen for P. carinii pneumonia (PCP) prophylaxis.

Direct measurements of HIV RNA Measurements of levels of HIV RNA over time have been of great value in delineating the relationship between levels of virus and rates of disease progression, the rates of viral turnover, the relationship between immune system activation and viral replication, and the time to development of antiviral drug resistance. Measurements of HIV RNA levels should be made approximately every 6 months and more frequently in the setting of changes in antiretroviral therapy. While precise guidelines have yet to be established, a level of HIV RNA of >20,000 copies per milliliter is felt by many experts to be an indication for antiretroviral therapy, regardless of the CD4+ T cell count.

Clinical manifestations

The clinical consequences of HIV infection encompass a spectrum ranging from an acute syndrome associated with primary infection to a prolonged asymptomatic state to advanced disease. The clinical syndromes seen in patients with HIV disease: the acute syndrome, the asymptomatic stage, early symptomatic disease, neurologic disease, secondary infections, neoplasms, and organ-specific syndromes.

HIV disease can be divided empirically on the basis of the degree of immunodeficiency into an early stage (CD4+ T cell count >500/μL), an intermediate stage (CD4+ T cell count 200 to 500/μL), and an advanced stage (CD4+ T cell count <200/μL).

The acute HIV syndrome It is estimated that 50 to 70 % of individuals with HIV infection experience an acute clinical syndrome approximately 3 to 6 weeks after primary infection. They occur along with a burst of plasma viremia and p24 antigenemia.

Symptoms usually persist for 1 to several weeks and gradually subside as an immune response to HIV develops and the levels of plasma viremia decrease. Total lymphocyte and T cell subsets (CD4+ and CD8+) are initially reduced. Opportunistic infections have been reported during this stage of infection, reflecting the immunodeficiency that results from reduced numbers of CD4+ T cells and likely also from functional suppression of CD4+ T cells.

Most patients recover spontaneously from this syndrome and have a mildly depressed CD4+ T cell count that remains stable for a variable period before beginning its progressive decline; in some individuals, the CD4+ T cell count returns to the normal range. Approximately 10 percent of patients manifest a fulminant course of immunologic and clinical deterioration after primary infection, even after the disappearance of symptoms. In most patients, primary infection with or without the acute syndrome is followed by a prolonged period of clinical latency.

The asymptomatic stage–clinical latency Although the length of time from initial infection to the development of clinical disease varies greatly, the median time is approximately 10 years. HIV disease with active virus replication usually progresses during this asymptomatic period. The rate of disease progression is directly correlated with HIV RNA levels. Patients with high levels of HIV RNA progress to symptomatic disease faster than do patients with low levels of HIV RNA. Some patients, called long-term nonprogressors, show little if any decline in CD4+ T cell counts over an extended period. These patients generally have extremely low levels of HIV RNA. Certain other patients remain entirely asymptomatic despite the fact that their CD4+ T cell counts fall extremely low. Some patients, otherwise asymptomatic, develop persistent generalized lymphadenopathy during this time. With few exceptions, CD4+ T cell counts fall progressively during this asymptomatic period at an average rate of approximately 50 cells/μL per year. When the CD4+ cell count falls below about 200/μL, the resulting state of immunodeficiency is severe enough to place the patient at high risk for opportunistic infections and neoplasms, and hence for clinically apparent disease.

Early symptomatic disease After the CD4+ T cell count has fallen below 500/μL, patients begin to develop signs and symptoms of clinical illness: Generalized lymphadenopathy, Thrush, Oral hairy leukoplakia, Shingles, Thrombocytopenia, Molluscum contagiosum, Recurrent herpes simplex, Condyloma acuminata, Aphthous ulcers.

Generalized lymphadenopathy defined as the presence of enlarged lymph nodes (>1 cm) in two or more sites for more than 3 months without an obvious cause is often *the earliest symptom of HIV infection* and may be seen at any point in the spectrum of immune dysfunction. A loss in lymphadenopathy or a decrease in lymph node size may be a prognostic marker of disease progression. In the early and intermediate stages of HIV infection (CD4+ T cell counts >200/μL), the main differential diagnosis is an adenopathic form of Kaposi's sarcoma. Late in the course of disease, differential diagnosis expands to include lymphoma, mycobacterial infection, toxoplasmosis, systemic fungal infection, and bacillary angiomatosis.

Oral lesions: thrush, hairy leukoplakia, and aphthous ulcers. Thrush, due to Candida infection, and oral hairy leukoplakia, presumed due to Epstein-Barr virus, are usually indicative of fairly advanced immunologic decline, generally occurring in patients with fewer than 300 CD4+ T cells per microliter. Thrush appears as a white, cheesy exudate, often on an erythematous mucosa. While most commonly seen on the soft palate, early lesions are often found along the gingival border. Oral hairy leukoplakia presents as a filamentous white lesion, generally along the lateral borders of the tongue. Aphthous ulcers of the posterior oropharynx are also seen with regularity in patients with HIV infection. These lesions are of unknown etiology and can be quite painful and interfere with swallowing. The fact that thalidomide is an effective treatment for this condition suggests that the pathogenesis may involve the action of tissue-destructive cytokines.

Reactivation Herpes Zoster *(Shingles)* This condition (see Plate ID-37) is seen in 10 to 20 percent of patients with HIV infection. This reactivation syndrome of varicella-zoster virus indicates a modest decline in immune function and is often the first clinical indication of immunodeficiency. Patients with HIV infection tend to have recurrences of zoster, with a relapse rate of approximately 20%.

Thrombocytopenia may be an early consequence of HIV infection. 3% of patients with HIV infection and CD4+ T cell counts above 400/μL have platelet counts under 150,000/μL. For patients with CD4+ T cell counts below 400/μL, this incidence increases to 10 %. Most patients retain platelet counts above 50,000/μL, and the condition can be managed conservatively. Bone marrow examination should be done to rule out other causes of thrombocytopenia.

High-dose intravenous immunoglobulin (IVIG) and glucocorticoids can induce a transient increase in platelet count. The most effective medical approach to this problem has been the use of antiretroviral agents. Splenectomy is an option in patients refractory to management. Because of the risk of serious infections all patients with HIV infection, especially those about to undergo splenectomy, are immunized with pneumococcal polysaccharide.

Miscellaneous Clinical Conditions include molluscum contagiosum, basal cell carcinomas of the skin, headache, condyloma acuminata, and recurrent bouts of oral or genital herpes simplex.

Neurologic disease in patients with HIV infection

Opportunistic infections*:* Toxoplasmosis, Cryptococcosis, Progressive multifocal Leukoencephalopathy, Cytomegalovirus, Syphilis, Mycobacterium tuberculosis HTLV-I infection;

Neoplasms: CNS lymphoma, Kaposi's sarcoma;

Result of HIV*-1 infection:* Aseptic meningitis, AIDS dementia (HIV encephalopathy), *Myelopathy* (Vacuolar myelopathy, Pure sensory ataxia, Paresthesia/dysesthesia)

Peripheral neuropathy: Acute demyelinating polyneuropathy, Mononeuritis multiplex, *Distal symmetric polyneuropathy*

Myopathy

Seizures Seizures are a relatively frequent complication of HIV infection and may be a consequence of opportunistic infections, neoplasms, or HIV encephalopathy.

Opportunistic infections are late complications of HIV infection, for the most part occurring in patients with less than 200 CD4+ T cells per microliter. While the causative agents characteristically are opportunistic organisms, such as Pneumocystis carinii, Mycobacterium avium complex, CMV and other organisms that do not ordinarily cause disease in the absence of a compromised immune system, they also include common bacterial and mycobacterial pathogens. Opportunistic infections are the leading cause of morbidity and mortality in patients with HIV infection. Approximately 80% of AIDS patients die as a direct result of an infection other than HIV, with bacterial infections heading the list.

Protozoal infections

Pneumocystis Carinii **P**. carinii pneumonia (PCP) is the initial AlPS-defining illness in close to 20% of patients. It is recommended that all patients with HIV infection who have either experienced a previous bout of PCP or have a CD4+ T cell count of <200/μL (or a CD4 percentage of less than 15), receive PCP prophylaxis. A diagnosis of PCP requires demonstration of the trophozoite or cyst form of the organisms in samples obtained from induced sputum, bronchoalveofar lavage, transbronchial biopsy, or open lung biopsy. PCR has been used in to identify specific DNA sequences for P. carinii in clinical specimens.

Extrapulmonary manifestations of pneumocystis carinii: Acute otitis, Retinitis, Visceral cystic calcifications, Necrotizing vasculitis, Intestinal obstruction, Lymphadenopathy, Bone marrow involvement, Ascites, Thyroiditis.

Toxoplasmosis. Toxoplasma gondii, the etiologic agent of toxoplasmosis, is the most common cause of secondary CNS infection in patients with AIDS. It accounts for 50 to 60% of all mass lesions in the CNS of patients with HIV infection and is responsible for 28% of first seizures. Patients should be screened for IgG antibody to Toxoplasma. Those who are seronegative should be counseled about ways to avoid infection, including avoiding the consumption of undercooked meat and careful hand washing after contact with soil or changing the cat litter box.

The most common clinical presentation in patients with HIV infection is one of fever, headache, and focal neurologic deficits. Patients may present with seizure, hemiparesis, or aphasia as a manifestation of focal neurologic defects or with a picture more related to accompanying cerebral edema and consisting of confusion, dementia, lethargy, and progression to coma. In this clinical setting, the diagnosis is suspected on the basis of radiologic findings, MRI or double-dose contrast CT are the preferred techniques.

Protozoal diarrhea Cryptosporidia, microsporidia, and Isospora belli are the most common opportunistic protozoa that infect the gastrointestinal tract and cause diarrhea in HIV-infected patients. It is spread through fecal-oral contact, and nosocomial outbreaks have been reported. Patients give a history of several months of intermittent diarrhea evolving to a several-month history of persistent diarrhea with copious watery stools, often up to several liters per day. Cryptosporidia may cause cholecystitis with or without accompanying cholangitis. The diagnosis of cryptosporidial diarrhea is made by stool examination.

Bacterial infections

Bacterial infections are the leading cause of death in patients with HIV infection. Infections with Atypical Mycobacteria (Mycobacterium avium complex, MAC), MAC infection probably represents an acute infection with organisms that are ubiquitous in the environment in both soil and water. The most common presentation of MAC infection is fever, weight loss, and night sweats, presumably due to disseminated disease. At least 85% of HIV-infected patients with MAC infection are mycobacteremic. Other clinical findings include lymphadenopathy, abdominal pain, and diarrhea. The diagnosis is suggested by the demonstration of long, slender acid-fast bacilli in biopsy specimens of bone marrow, lymph node, or liver or in stool specimens and is confirmed by culture of blood or involved tissue. Approximately 5% of AIDS patients have active tuberculosis. For the patient with HIV infection and a positive PPD skin test, the rate of reactivation is 7 to 10% per year. Infections with enteric pathogens such as Salmonella, Shigelta, and Campylobacter are more common in homosexual men and are often more severe and more apt to relapse in patients with HIV infection.

Fungal infections

Candidiasis Candida infections are the most common fungal infections in patients with HIV infection; virtually all patients experience some type of Candida infection over the course of their illness. Candida infections of the esophagus, trachea, bronchi, or lungs may occur. Esophagitis generally presents as odynophagia and retrosternal pain or burning.

Cryptococcosis Cryptococcus neoformans is the leading cause of meningitis in patients with AIDS. A presumptive diagnosis of cryptococcal infection can be made by the identification of organisms in spinal fluid with India ink examination, by the detection of cryptococcal antigen in blood or spinal fluid, or by histologic evidence of cryptococcal infection in a biopsy specimen.

Viral infections

Cytomegalovirus Infection (CMV) generally occur late in the course of HIV infection. Retinitis, esophagitis, and colitis are the most common manifestations of CMV infection. The characteristic retinal appearance is that of perivascular hemorrhage and exudate. CMV infection of the retina results in a necrotic inflammatory process, and the visual loss that develops is irreversible.

Infection with *herpes simplex virus* (HSV) in HIV-infected individuals is associated with recurrent orolabial, genital, and perianal lesions. Lesions often appear beefy red, are exquisitely painful, and have a tendency to occur high in the gluteal cleft. Perirectal HSV may be associated with proctitis and anal fissures. May cause esophagitis. HSV esophagitis often occurs together with active orolabial lesions.

Varicella-Zoster Virus Infections Varicella-zoster virus (VZV), the etiologic agent of chickenpox, assumes a latent form in dorsal root ganglia following primary infection. Later in life, reactivation ; the appearance of shingles in any patient under 50 years of age should be an indication for workup of an underlying immunodeficiency, particularly HIV. VZV infection in a patient with HIV infection is almost exclusively confined to the skin, is associated with shingles, although the skin eruptions may be extensive, over several dermatomes, and extremely painful.

Epstein-Barr Virus Infections EBV, one of the causative agents of infectious mononucleosis, is also a very common infection in patients with HIV infection. Aside from the association with lymphoma, EBV is thought to play a causative role in oral hairy leukoplakia. This condition presents as white, frondlike lesions on the lateral aspect of the tongue and sometimes on the adjacent buccal mucosa.

Neoplastic diseases

Kaposi's sarcoma is a multicentric neoplasm consisting of multiple vascular nodules appearing in the skin, mucous membranes, and viscera. Kaposi's sarcoma may be seen at any stage of HIV infection. The initial lesion may be a small, raised reddish-purple nodule on the skin, a discoloration on the oral mucosa, or a swollen lymph node. Lesions often appear in sun-exposed areas, particularly the tip of the nose, and have a propensity to occur in areas of trauma (Koebner phenomenon).

Because of the vascular nature of the tumors and the presence of extravasated red blood cells in the lesions, their color ranges from reddish to purple to brown and often take the appearance of a bruise, with yellowish discoloration. Lesions range in size from a few millimeters to several centimeters in diameter and may be either discrete or confluent. Kaposi's sarcoma lesions most commonly appear as raised macules. A diagnosis of Kaposi's sarcoma is based on biopsy of a suspicious lesion. Histologically one sees a proliferation of spindle cells and endothelial cells, extravasation of red blood cells and hemosiderin-laden macrophages.

Lymphomas occur with an increased frequency in patients with congenital or acquired T cell immunodeficiencies.

Intraepithelial dysplasia of the cervix or anus This condition has been recognized increasingly as a complication of long-standing HIV infection. This human papillomavirus-associated condition correlates with the subsequent development of intraepithelial neoplasia and eventually invasive cancer.

Cervical ectopy (ectropion). A. When viewed with the naked eye, the endocervical mucosa of the cervical ectopy appears as a red, velvety zone, sharply contrasting with the neighboring pink and shiny squamous portio epithelium. This is a large cervical ectopy in a young female. B. With time, the cervical ectopy becomes reduced, as a pink, metaplastic squamous epithelium replaces the red columnar epithelium. Tongues of metaplastic epithelium are seen growing into the cervical ectopy. C. Mature cervix. In older women, the process of squamous metaplasia totally replaces the cervical ectopy, and the external surface of the portio cervix becomes covered by a stratified squamous epithelium.

Management of AlDS-Associated Kaposi's Sarcoma

Observation

Single or limited number of lesions: Radiation, Intralesional vinblastine, Cryotherapy.

Extensive, non-life-threatening disease: Single-agent chemotherapy (etoposide, vinblastine, adriamycin, or bleomycin), Interferon-alfa (if CD4+ T cell >150/μL)

Life-threatening disease: Combination chemotherapy with low-dose doxorubicin, bleomycin, and vinblastine (ABV).

Radiation treatment

Antiretroviral therapy

Nucleoside Analogues (reverse transcriptase)

Zidovudine **(Retrovir)** act as DNA chain terminators owing to their inability to form a 3'-5'-phosphodiester linkage with another nucleoside. They bind to the active site of the RNA-dependent DNA polymerase of HIV. Zidovudine has avidity for the DNA polymerase of human mitochondria, which may contribute to the development of the myopathy sometimes in patients receiving zidovudine.

Nonnucleoside Reverse Transcriptase Inhibitors interfere with the function of the viral enzyme reverse transcriptase by binding to regions outside the active site and causing conformational changes in the enzyme that render it inactive. Although these agents are potent in the nanomolar range, they are selective for the reverse transcriptase of HIV-1, have no activity against HIV-2, and, when used as monotherapy, are associated with the rapid emergence of drug-resistant mutants.

Protease Inhibitors are selective for the protease enzyme of HIV-1. This potency is accompanied by the emergence of resistant isolates when these drugs are used alone.

Prophylaxis against secondary infections

P. carini pneumonie (PCP) rarely occurs before the CD4+ T cell count drops below 200/μL or the CD4 percentage declines below 15 percent. At that point, patients should be started on a regimen of PCP prophylaxis. The preferred regimen, for patients who can tolerate it, is trimethoprim/sulfamethoxazole at a dose of one double-strength tablet daily. A benefit of this regimen is that it also provides protection against toxoplasmosis as well as certain bacterial infections. Alternative strategies for PCP prophylaxis include dapsone/pyrimethamine and clindamycin/primaquine. These are currently being evaluated for patients who are sulfa intolerant. Aerosolized pentamidine remains an option for individuals unable to tolerate any systemic therapy.

Another opportunistic infection for which primary prophylaxis is clearly indicated is Mycobacterium avium complex (MAC). This infection is rarely seen with CD4+ T cell counts above 100/μL. Rifabutin, 100 mg/d, was effective in a clinical trial in delaying the onset of MAC bacteremia by an average of 6 months. Based on these data, rifabutin has been licensed for use as primary prophylaxis for MAC infection in patients with HIV infection and less than 100 CD4+ T cells per microliter. Even better results have been seen with the macrolides clarithyomycin and azithromycin.

Given the resurgence of tuberculosis in the HIV-infected population, any patient with HIV infection and at least 5 mm of induration upon PPD skin testing should receive a 1-year course of isoniazid. In addition, any patient with HIV infection who is anergic and at high risk of tuberculosis should be given 1 year of isoniazid therapy.

Patients with HIV infection are at increased risk for infection with encapsulated bacteria, particularly H. influenzae and S, pneumoniae. For this reason, these patients, and especially those in whom splenectomy is being considered, should be given the pneumococcal polysaccharide vaccine and possibly also the H. influenzae type b vaccine.

Patients who are seronegative for Toxoplasma gondii should be encouraged to avoid ingestion of partially cooked meat and to use care when handling cat litter.

HIV and the health care worker

Health care workers, especially those who deal with large numbers of HIV-infected patients, have a small but definite risk of becoming infected with HIV as a result of professional activities. By 1997, there were a total of 52 well-documented seroconversions in health care workers that occurred as a direct result of exposure to contaminated blood or bloody body fluids. Forty-five of these infections were due to percutaneous exposures, five were associated with mucous membrane exposures, one involved both percutaneous and mucous membrane exposures, and in one the route of exposure was unknown. Forty-seven of these accidents involved blood, one involved bloody pleural fluid, one involved an unspecified fluid, and three involved concentrated virus stocks. Taken together, the data from several large studies suggest that the risk of HIV infection following a percutaneous injury with an HIV-contaminated hollow-

bore needle (in contrast to a solid-bore needle, i.e., a suture needle) is approximately 0.3 percent.

There is debate concerning the best management for a percutaneous injury with a needle contaminated with blood from an HIV-infected patient. The wound should be cleansed immediately and antiseptic applied. While the precise regimen remains a topic of debate and will undoubtedly evolve, the authors currently recommend a combination of zidovudine, lamivudine, and indinavir.

Since antiretroviral prophylaxis, if it is going to be given, should probably be started as soon as possible after the injury, health care workers at potential risk should think beforehand about what they want to do. Given the prevalence of zidovudine resistance in the community, many experts advocate the use of combination therapy under such circumstances.

Health care workers can minimize their risk of occupational HIV infection by following the CDC guidelines of July 1991, which include adherence to universal precautions; refraining from direct patient care if one has exudative lesions or weeping dermatitis; and disinfecting and sterilizing reusable devices employed in invasive procedures. The premise of universal precautions is that every specimen should be handled as if it came from someone infected with a bloodborne pathogen. All samples should be double-bagged, gloves should be worn when drawing blood, and spills should be immediately disinfected with bleach.

Prevention

Widespread voluntary testing of individuals who have practiced or are practicing high-risk behavior, together with counseling of infected individuals, is recommended. Information gathered from such an approach should serve as the basis for behavior-modification programs, both for infected individuals who may be unaware of their HIV status and who could infect others and for uninfected individuals practicing high-risk behavior. The practice of safe sex is the most effective way for sexually active uninfected individuals to avoid contracting HIV infection and for infected individuals to avoid spreading infection. Abstinence from sexual relations is the only absolute way to prevent sexual transmission of HIV infection. However, this may not be feasible, and there are a number of relatively safe practices that can markedly decrease the chances of transmission of HIV infection. Partners engaged in monogamous sexual relationships who wish to be assured of safety should both be tested for HIV antibody. If both are negative, it must be understood that any divergence from monogamy puts both partners at risk; open discussion of the importance of honesty in such relationships should be encouraged.

When the HIV status of either partner is not known, or when one partner is positive, there are a number of options. Use of condoms, preferably together with the HIV-inhibiting spermicide nonoxynol-9, can markedly decrease the chance of HIV transmission. It should be remembered that condoms are not 100 percent effective in preventing transmission of HIV infection, and there is an

approximately 10 percent failure rate of condoms used for contraceptive purposes. Most condom failures result from breakage or improper usage, such as not wearing the condom for the entire period of intercourse. Latex condoms are preferable, since virus has been shown to leak through natural skin condoms. Petroleum-based gels should never be used for lubrication of the condom, since they increase the likelihood of condom rupture. Mutual masturbation is considered safe provided there is no oral or open-cut exposure to or ingestion of semen, vaginal secretions, or other potentially infected body fluids.

Topical microbicides for vaginal use are being pursued actively as a means by which women could avoid infection when the male partner cannot be relied on to use a condom. Kissing is considered safe, although there is a theoretical possibility of transmission via virus in saliva.

The most effective way to prevent transmission of HIV infection among IDUs is to stop the use of injecting drugs. Unfortunately, that is extremely difficult to accomplish unless the addict enters a treatment program. For those who will not or cannot participate in a drug treatment program and who will continue to inject drugs, the avoidance of sharing of needles and other paraphernalia ("works") is the next best way to avoid transmission of infection.

Transmission of HIV via transfused blood or blood products has been decreased dramatically by a combination of screening of all blood donors for HIV infection by assays for both HIV antibody and p24 antigen and self-deferral of individuals at risk for HIV infection. In addition, clotting factor concentrates are heat-treated, essentially eliminating the risk to hemophiliacs who require these products. Autologous transfusions are preferable to transfusions from another individual.

HIV can be transmitted via breast milk and colostrum. Breast feeding from an infected mother should be avoided if at all possible.

The HIV-infected traveler

The traveler infected with human immunodeficiency virus (H1V) is at special risk of serious infections due to a number of pathogens that may be more prevalent at travel destinations than at home. However, the degree of risk depends primarily on the state of the immune system at the time of travel. For persons whose CD4+ cell counts are normal or above 500/μL, no data suggest a greater risk during travel than for persons without HIV infection. Individuals with AIDS (CD4+ counts of <200/μL) and others who are symptomatic need special counseling and should visit their primary care physician before traveling, especially to the developing world.

Immunizations. All of the HIV-infected traveler's routine immunizations should be up to date. The response to immunization may be impaired at CD4+ cell counts of <200/μL (and in some cases at even higher counts). However, when the risk of illness is high or the sequelae of illness are serious, immunization is recommended. In certain circumstances, it may be prudent to

check the adequacy of the serum antibody response before departure (e.g., yellow fever neutralization if exposure is unavoidable).

Because of the increased risk of infections due to Streptococcus pneumoniae and other bacterial pathogens that cause pneumonia following influenza, pneumococcal polysaccharide and influenza vaccines should be administered. The estimated rates of response to influenza vaccine are more than 80 percent among persons with asymptomatic HIV infection and less than 50 percent among those with AIDS.

In general, live attenuated vaccines are contraindicated for persons with immune dysfunction. Live oral polio vaccine should not be given to HIV-infected patients or to members of their households. Instead, inactivated polio vaccine (elPV) should be used; most HIV-infected individuals without AIDS will develop protective antibody levels in response to this vaccine.

Because measles (rubeola) can be a severe and lethal infection in HlV-positive patients, the measles vaccine (or the combination measles-mumps-rubella vaccine) should be given to these individuals. Although this is a live vaccine, there have been no reports of serious complications in this population.

The decision of whether or not to administer any of the special vaccines to an HIV-infected traveler should be based on the individual's risk. Inactivated vaccines can be administered without concern for safety but with concern about adequate protection. For example, data suggest that HIV-infected persons do not have as strong an antibody response to the meningococcal meningitis vaccine as do uninfected persons. Moreover, few data are available on the efficacy of many of the other vaccines (e.g., those for hepatitis A, typhoid, and cholera).

It is recommended that live yellow-fever vaccine not be given to HIV-infected travelers. Nevertheless, when inadvertently administered to HIV-positive military personnel, this vaccine elicited no adverse reactions. Therefore, if the traveler's CD4+ count is >200/μL and travel in an endemic area is absolutely necessary, the vaccine can probably be administered safely. HIV-infected persons whose CD4+ count is <200/μL should be discouraged from traveling to these regions. If the traveler is passing through or traveling to an area where the vaccine is required but the disease risk is low, a physician's waiver should be issued. Bacille Calmette-Guerin vaccine should not be given because of reports of disseminated infection in HIV-infected persons.

Principles of treatment of secondary immunodeficiency's

Stages of treatment and immunorehabilitation patients with secondary immunodeficiency.

1. Removing etiological factor.
2. Antimicrobial therapy.
3. Replacement immunotherapy.
4. Preventing infection.
5. Immunocorective therapy.
6. Preventive immunotherapy and immunorehabilitation.

Tests for the final control of knowledge

1. What is the mode of transmission is the most dangerous in the secondary immunodeficiency?

A. Airborne.
B. Alimentary.
C. Contact
D. Sexual.
E. No significantly difference.

2. What factors protect violated in immunodeficiency's?

A. Mechanical protection of penetration into infectious pathogen organism.
B. Humoral factors which destroy the agent that he was in the organism.
C. Factors phagocytosis.
D. None of these variants.

3. The examination of patients to assess the immune status must:

A. The study of cellular immunity
B. The study of humoral immunity
C. The study of the complement system
D. All study parameters.

4. Immunological examination of patients is as

A. one-time examination of the patient at the time of admission to hospital
B. double examination of the patient
C. immunological monitoring the progress of the disease
D. immunological study the dynamics using immunocorective therapy.

5. Task immunological examination of patients in the clinic:

A. Immunodiagnostics
B. Prognosis of the disease
C. Control the quality of treatment
D. Immunocorrective therapy appointment.

6. What environmental factors contribute to the development of secondary immunodeficiency states:

A. long-term stress
B. adverse climatic factors
C. bacteria
D. viruses.

7. Infections in secondary Immunodeficiency B -cells type:

A. virus
B. fungal
C. bacterial
D. parasitic.

8. Time of onset of clinical signs of secondary immunodeficiency:

A. the first month of life
B. with 4–6 months of life
C. in adolescence.
D. in any age

9. Clinical markers of T- cells secondary immunodeficiency are:
A. reccurent pyogenic infection
B. recurrent viral infections
C. thymic hypoplasia
D. pathology of the parathyroid glands.
10. Infections often occur when phagocytosis defects in patients with secondary immunodeficiency:
A. bacterial
B. virus
C. parasitic
D. yeast.
11. The causes of secondary immunodeficiency states:
A. chromosomal abnormalities
B. immunosuppressive therapy
C. cancer
D. chronic infection.
12. Secondary immune deficiency can be investigated:
A. malnutrition
B. radiation therapy
C. many transfusions
D. burn disease
13. On the importance of participation in the destruction of virus-infected cells are immune factors in the following order:
A. NK-nonspecific destruction of T-cells cytotoxicity, cytolysis compliment dependent
B. effect of interferon, NK- nonspecific destruction of T-cells cytotoxicity, the effect of macrophages, antibodies and cytolysis compliment dependent
C. antibodies dependent cytotoxicity, NK-nonspecific destruction effect of interferon.
14. Circulating immune complexes are:
A. + complex antigen antibodies
B. myeloma proteins
C. complex antigen antibodies + complement
D. IgE + Allergen
E. aggregated IgG.
15. Immunodeficiency state characterized by increased sensitivity of the patient to viral and fungal infections. The main defect of the immune system dysfunction is defined:
A. macrophages
B. T lymphocytes
C. B lymphocytes
D. the complement system
E. neutrophils.

16. Immunodeficiency state developed on the background of burn disease. The main defect of the immune system characterized by impaired:

A. T lymphocytes
B. B lymphocytes
C. of the complement system
D. phagocytosis.

17. Direction for determining the content of immunoglobulin's in the serum is often:

A. Suspected primary immunodeficiency
B. Suspected secondary immunodeficiency
C. To confirm the diagnosis of any infectious disease
D. If necessary, the study of specific immune responses by ELISA and RIA.

18. Evidence for a / in the introduction of immunoglobulin's:

A. Primary immunodeficiency
B. Secondary immunodeficiency
C. Bacterial infection
D. Virus infection
E. Allergy
F. Endotoxin shock.

19. Which neutrophil antimicrobial systems include:

A. cationic proteins
B. proteinase
C. acid hydrolase
D. lactoferrin
E. reactive oxygen species
F. myeloperoxidase
G. hydrogen peroxide.

20. What are the most effective immunomodulators in secondary Immunodeficiency caused by persistent viruses

A. Timalin
B. Polyoxidonium
C. Miyelopid
D. Halavit
E. Nuklyeyinat sodium

Correct answers to the question: 1 – E. **2** – A, B, C. **3** – D. **4** – C, D. **5** – A, B, C, D. **6** – A, B, C, D. **7** – C, D. **8** – D. **9** – B. **10** – A, D. **11** – B, C, D. **12** – A, B, C, D. **13** – B. **14** – A, C. **15** – B. **16** – C, D. **17** – A, B. **18** – A, B, C, D. **19** – A, B/C, D. **20** – A, B, D.

Навчальне видання

Модуль 1.
Клінічна імунологія та алергологія.
Тема 5.
НАБУТІ ІМУНОДЕФІЦИТНІ ЗАХВОРЮВАННЯ

Методичні вказівки до практичних занять студентів медичних вузів з англійською мовою навчання

Упорядники Кравчун Павло Григорович
Бабаджан Володимир Данилович
Кадикова Ольга Ігорівна

Відповідальний за випуск: П.Г. Кравчун

Комп'ютерний набор О. І. Кадикова
Комп'ютерна верстка О. Ю. Лавриненко

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Редакційно-видавничий відділ
ХНМУ, пр. Леніна, 4, м. Харків, 61022
izdatknmu@mail.ru, izdat@knmu.kharkov.ua

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Module 1.
Clinical immunology and allergology.
Theme 5.
ACQUIRED IMMUNODEFICIENTES

Manual for practical lessons students having higher Medical education in English