MINISTRY OF HEALTH OF THE REPUBLIC OF BELARUS
EDUCATIONAL INSTITUTION "VITEBSK STATE ORDER OF PEOPLES' FRIENDSHIP MEDICAL UNIVERSITY"

AUTOIMMUNE RHEUMATIC DISEASES: PRINCIPLES OF DIAGNOSIS AND TREATMENT

АУТОИММУННЫЕ РЕВМАТИЧЕСКИЕ ЗАБОЛЕВАНИЯ: ПРИНЦИПЫ ДИАГНОСТИКИ И ЛЕЧЕНИЯ

Рекомендовано учебно-методическим объединением по высшему медицинскому, фармацевтическому образованию Республики Беларусь в качестве учебно-методического пособия для студентов учреждений высшего образования обучающихся по специальностям:
1-79 01 01 «Лечебное дело», 1-79 01 07 «Стоматология»

Vitebsk, 2020

УДК 616.72-002.77-08:57.083.3=111(07)
ВВК 55.5я73+53.17я73
А 94

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А 94 Аутоиммунные ревматические заболевания: принципы диагностики и лечения = Autoimmune rheumatic diseases: principles of diagnosis and treatment : пособие. / Л. Р. Выхристенко, Н. А. Подолинская, Е. А. Дикарева, Е. В. Сидоренко Витебск, ВГМУ, 2020. – 130 с.

ISBN 978-985-580-010-2

The manual presents the modern classification criteria of autoimmune rheumatic diseases, examines the issues of diagnosis and differential diagnosis based on the analysis of clinical data, the results of laboratory and instrumental studies, provides modern generally accepted treatment regimens for autoimmune rheumatic diseases. The manual is intended for medical students, undergraduates, graduate students, clinical residents, interns, as well as rheumatologists, general practitioners, general practitioners, doctors of other specialties.

УДК 616.72-002.77-08:57.083.3=111(07)
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ISBN 978-985-580-010-2

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List of main abbreviations

ACL	- antibodies to cardiolipin
ALT	- alanine aminotransferase
AMCV	- antibodies to modified citrulline vimentin
ANA	- antinuclear antibodies
ANF	- antinuclear factor
ANCA	- antineutrophilic cytoplasmic antibodies
ANCA-SV	- systemic vasculitis associated with antineutrophilic cytoplasmic antibodies
ACE	- angiotensin-converting enzyme
ARD	- autoimmune rheumatic diseases
AST	- aspartic aminotransferase
APLA	- antiphospholipid antibodies
APS	- atiphospholipid syndrome
ACA	- anticentromeric antibodies
ACP	- antibodies to citrulline proteins
ACCP	- antibodies to cyclic citrulline peptide
DMARDs	- basic anti-inflammatory drugs
LA	- lupus anticoagulant
GEBD	-genetic engineering biological drugs
GCS	- glucocorticosteroids
GPA	- granulomatous polyangiitis
DM	- dermatomyositis
DNA	- Deoxyribonucleic acid
DS	- diagnostic specificity
DS	- diagnostic sensitivity
GIT	- gastrointestinal tract
IL	- interleukin
ELISA	- enzyme-linked immunosorbent assay
CPK	- creatine phosphokinase
IIF	- indirect immunofluorescence
NSAIDs	- non-steroidal anti-inflammatory drugs
MPO	- myeloperoxidase
MP	- microscopic polyangiitis
MRI	- Magnetic resonance imaging
PR-3	- proteinase 3
PM	- polymyositis
RA	- rheumatoid arthritis
RF	- rheumatoid factor

MCTD	- mixed connective tissue disease
SLE	- systemic lupus erythematosus
SS/SSD	- systemic sclerosis / systemic scleroderma
ESR	- sedimentation rate of erythrocytes
RP	- C-reactive protein
SS	- Sjogren's syndrome
TGF-β	- transforming growth factor beta
FER	- function of external respiration
FC	- functional class
TNF-α	- tumor necrosis factor alpha
CNS	- central nervous system
COX-1	- cyclooxygenase type 1
COX-2	- cyclooxygenase type 2
EGPA	- eosinophilic granulomatosis with polyangiitis
aβ2-GP 1	- antibodies to β2-glycoprotein 1
aSS-A/Ro	- antibodies to antigenic determinants on two nuclear proteins (61 and 52 kDa) (Sjogren syndrome A / Robert)
aSS-B/La	- antibodies to the antigenic determinant associated with the protein (43 kDa), forming a complex with RNA (Sjogren syndrome B / Lane)
aSm	- antibodies to the nuclear protein Sm
aScl-70	- antibodies to topoisomerase I (Scl-70)
aRNA polymerase III	- antibodies to RNA polymerase III
aCENP-A, CENP-B, CENP-C	- anti-acetromeric antibodies, antibodies to centromere antigens - Centromere protein-A (CENP-A), -B, -C
anRNP (U1-RNP)	- antibodies to small nuclear ribonucleoprotein
aRib- P	- antibodies to ribosomal protein P
aPM-Scl, aU3-RNP, aRNA polymerase I-III	- antinucleolar autoantibodies
aPCNA	- antibodies to the nuclear antigen of proliferating cells (proliferating cell nuclear antigen 1)
aJo-1, aPL-7, aPL-12, aEJ, aOJ	- antibodies to tRNA synthetases of cytoplasm
ACR	- American College of Rheumatology (American College of Rheumatologists)
CD	- cluster of differentiation
CD20	- CD20 antigen - protein, coreceptor located on the

	surface of B-lymphocytes
DAS28	- Disease Activity Score 28– disease activity index
dsDNA	- double-stranded deoxyribonucleic acid
EULAR	- European League Against Rheumatism (European League Against Rheumatism)
IgM, IgG, IgA, IgE, IgD	- immunoglobulin (s) class A, G, E, D
HLA	- human leucocyte antigens
SLICC	- Systemic Lupus International Collaboratoring Clinics (criteria for systemic international joint clinics for systemic lupus erythematosus)
SICCA	- Sjogren's International Collaborative Clinical Alliance (Sjogren's International Clinical Clinical Alliance criteria)
Th1Th2	- T-helper of the first type and second type
Treg	- T-regulatory cells

1. CLASSIFICATION AND IMMUNOPATHOGENESIS OF AUTOIMMUNE RHEUMATIC DISEASES

Autoimmune diseases are characterized by a high prevalence in the population, the difficulty of early diagnosis, and often cause the rapid disability of patients, reduce their life expectancy. Treatment of autoimmune diseases requires large financial costs and is characterized by low efficiency in some patients.

Autoimmune diseases occur as a result of increased immune responses to the molecular components of their own cells, tissues, and organs that act as antigens. The recognition of "their own" molecules by cells of the immune system is disrupted, so autoantibodies and sensitized T-lymphocytes with specific T-cell receptors are formed.

According to modern concepts, in the pathogenesis of autoimmune diseases, along with the activation of acquired immunity (hyperproduction of autoantibodies), a large role belongs to the innate link of immunity responsible for the formation of autoimmune inflammation. A key role in the activation of innate immunity is played by Toll-(Toll-like receptor, TLR) and NOD-like (Nod-like-receptor, NLR) receptors that recognize certain sequences (patterns) of microorganisms, core components released from cells subjected to apoptosis, uric acid crystals, cholesterol, etc.

In 2006, a classification - a *continuum of immuno-inflammatory diseases* [28] - was proposed, which combines a group of clinically heterogeneous diseases with common pathogenesis mechanisms characterized by a combination of autoinflammation and autoimmunity processes, which are associated with genetically determined and induced by environmental factors defects in the activation of the innate and acquired immune response. The frequency of immuno-inflammatory diseases in the population is 8% and has 100 nosological forms.

The continuum of immuno-inflammatory diseases includes:

1. *Rare monogenic auto-inflammatory diseases*: systemic Mediterranean fever, pyogenic sterile arthritis, etc.
2. *Polygenic auto-inflammatory diseases*: Crohn's disease, ulcerative colitis, osteoarthritis, gout, etc. crystalline arthritis, giant cell arteritis, Takayasu disease, etc.
3. *Auto-inflammatory autoimmune diseases associated with HLA* (human leucocyte antigens – human leukocyte antigens) class I: ankylosing spondylitis, psoriatic arthritis, Behcet's disease, uveitis, still's disease, multiple sclerosis.
4. *Classic polygenic autoimmune diseases (*organ-specific and organ-specific):

▪ *organ-specific*: celiac disease, primary biliary cirrhosis, type 1 diabetes, autoimmune diseases of the thyroid gland, myasthenia gravis, pemphigus, etc.

▪ *organ-specific (systemic) autoimmune rheumatoid diseases*: rheumatoid arthritis (RA), systemic lupus erythematosus (SLE); Sjogren's syndrome (SS); systemic sclerosis/systemic scleroderma (SS/SSD); dermatomyositis/polymyositis (DM/PM); systemic vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCA-SV), antiphospholipid syndrome (APS).

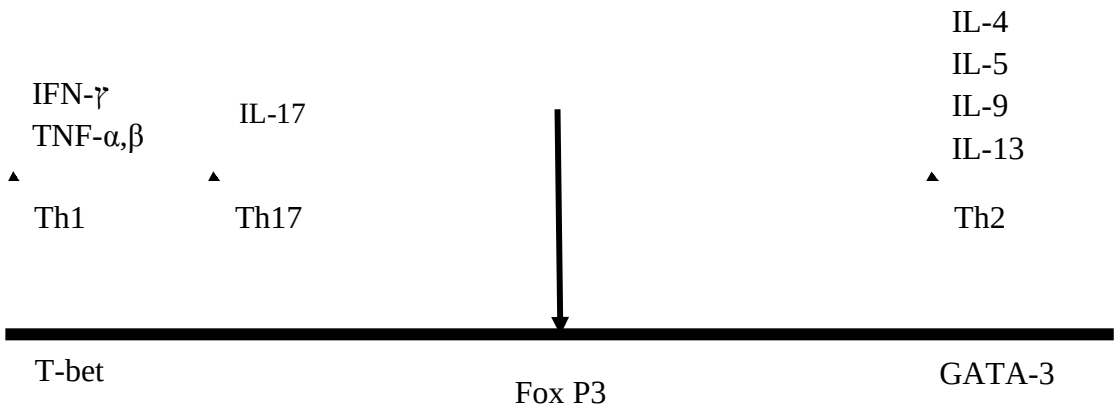
5. *Rare monogenic autoimmune diseases:* autoimmune lymphoproliferative syndrome, autoimmune syndrome of polyendocrinopathy-candidiasis-ectodermal dystrophy.

A heterogeneous group of *autoimmune rheumatic diseases (ARD)* is united by common genetic predisposition factors, immunopathogenesis, and similarity of clinical symptoms that reflect systemic inflammation [6, 19].

Combinations of factors that ensure the ARD development:

- genetic predisposition associated with HLA-system genes, which is realized through the interaction of immune system cells, target cells and pathogenic antigens that share epitopes with autologous organ-specific molecules-hormones, enzymes, and cytokines;
- genetically determined presence of affine variants of variable chains and active receptor centers on T-and B-lymphocytes to organ-specific molecules, which increases the potential ability of lymphocytes to form clones of autoreactive cells;
- presence of adverse factors-chemical, physical and biological (infections, Smoking, obesity, violation of the intestinal microbiota, etc.) that stimulate autoallergia.

The immunopathogenesis of ARD is based on the concept of disruption of t-cell tolerance, which leads to an imbalance between Th (t-helpers) type 1, Th17 and Th2, resulting in the predominant synthesis of proinflammatory cytokines - TNF-α (tumor necrosis factor alpha), interleukin (IL)-1, IL-6, IL-8, IL-12, IL-17, IL-23, etc.over anti - inflammatory cytokines-IL-10, TFR-β (transforming growth factor beta) and Others. Defects of t-regulatory (tged) cells play a fundamental role in the violation of immune tolerance to their own proteins in ARD (figure 1). Th1 and TH17 are involved in the anti-infectious immune response and the development of autoimmune reactions, Th2-in the development of allergic reactions. Cytokines secreted by Th1 and Th2 have an opposite effect, and an imbalance between cells leads to the development of pathology. Thed cells play an important role in maintaining immune tolerance, influencing the functions of Th1 and Th2, participating in the pathogenesis of infectious, allergic, autoimmune, cancer, and transplant immunity.



T-bet, FoxP3, GATA-3 - transcription factors of Th1, T-regulatory and Th2 cells.
(adapted from [19])

2. IMMUNODIAGNOSIS OF AUTOIMMUNE RHEUMATIC DISEASES

Early diagnosis of ARD using only clinical and instrumental research methods is often difficult. Progress in the diagnosis of ARD is closely related to the determination of the spectrum of *molecular and cellular biomarkers*, including: autoantibodies, acute-phase inflammatory proteins, cytokines, chemokines, markers of vascular endothelial activation, components of the complement system, lymphocyte subpopulations, products of bone and cartilage metabolism, genetic, epigenetic, transcriptomic markers in blood, synovial fluid, urine, synovial membrane biopsies, kidneys, and others affected tissue. The study of molecular and cellular biomarkers makes it possible to assess the activity of the pathological process, determine the prognosis of the disease, and also predict the effectiveness of treatment, which is especially important in the case of pharmacotherapy using immunobiological drugs.

Autoantibodies are the main diagnostic laboratory markers of ARD, allowing to evaluate the activity and prognosis of ARD.

The group of autoantibodies detected in ARD includes:

* Antinuclear antibodies (ANA).
* Rheumatoid factor (RF).
* Antibodies to citrullinated proteins (ACP).
* Antineutrophilic cytoplasmic antibodies (ANCA).
* Antiphospholipid antibodies (APLA).

It is important to remember that the detection of autoantibodies in the absence of clinical signs is not sufficient for diagnosis.

Autoantibodies are often detected out of association with ARD:

- in the elderly and senile;
- on the background of taking medicines;
- for viral and bacterial infections;
- for malignant neoplasms;
- in healthy relatives of patients with autoimmune diseases.

ARD is characterized by persistent and pronounced hyperproduction of autoantibodies, while in other cases - moderate transient formation of them.

Immunological diagnostics of ARD is carried out in 2 stages: 1-performing screening tests; 2 - performing tests for differential diagnosis.

Indications for the appointment of immunological studies and interpretation of their results in the manual are presented from the position of ACR/EULAR (American College of Rheumatology/European League Against Rheumatism-American College of rheumatology/European League against rheumatism),

according to the recommendations for laboratory diagnostics proposed by the Association of rheumatologists in Russia (ARR) [1, 4], the clinical Protocol for the diagnosis and treatment of patients with rheumatic diseases in the Republic of Belarus [5].

Screening tests for the diagnosis of autoimmune rheumatic diseases

Determination of antibodies to the nuclear structures of the cell-antinuclear autoantibodies

ANA is a heterogeneous group of antibodies that react with various components of the cell nucleus and cytoplasm.

Indications for use: SLE, SS, localized scleroderma, DM, PM, SS, mixed connective tissue disease (MCTD, Sharpe syndrome), juvenile chronic arthritis, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, exclusion of ARD with an unclear clinical picture.

To detect ANA, a combination of 2 tests is recommended:

- Determination of antibodies that react with the components of the nucleus of epithelial cells of human laryngeal adenocarcinoma of the ner-2 line by indirect immunofluorescence (IIF). The antibodies detected by the IIF method were called *antinuclear factor (ANF).*
- Determination of antibodies to extractable nuclear antigen - *ANA-screening* (or ENA- / ENA-screen, ENA - extractable nuclear antigen / ENA - extractible nuclear antigen) by enzyme-linked immunosorbent assay (ELISA). Antinuclear antibodies include ribonucleoprotein antigens SS-A, SS-B, Sm, U1-RNP, antibodies to topoisomerase I (Scl-70), Jo-1.

This set of tests is used to reduce the frequency of false-negative results. Simultaneous detection of ANA-screen and ANF provides recognition of antibodies to soluble antigens (SS-A, Jo-1, RibP), which can be lost from the cell nuclei or diffuse into the cell cytoplasm. 1-10% of patients who do not have ANF are diagnosed with *"ANF-negative SLE"* based on IIF results.

Interpretation of results

ANA is missing. Negative result - no ANA. In 95% of cases, it allows you to exclude ARD. A negative test result in a patient with signs of an autoimmune process does not exclude the presence of an autoimmune disease.

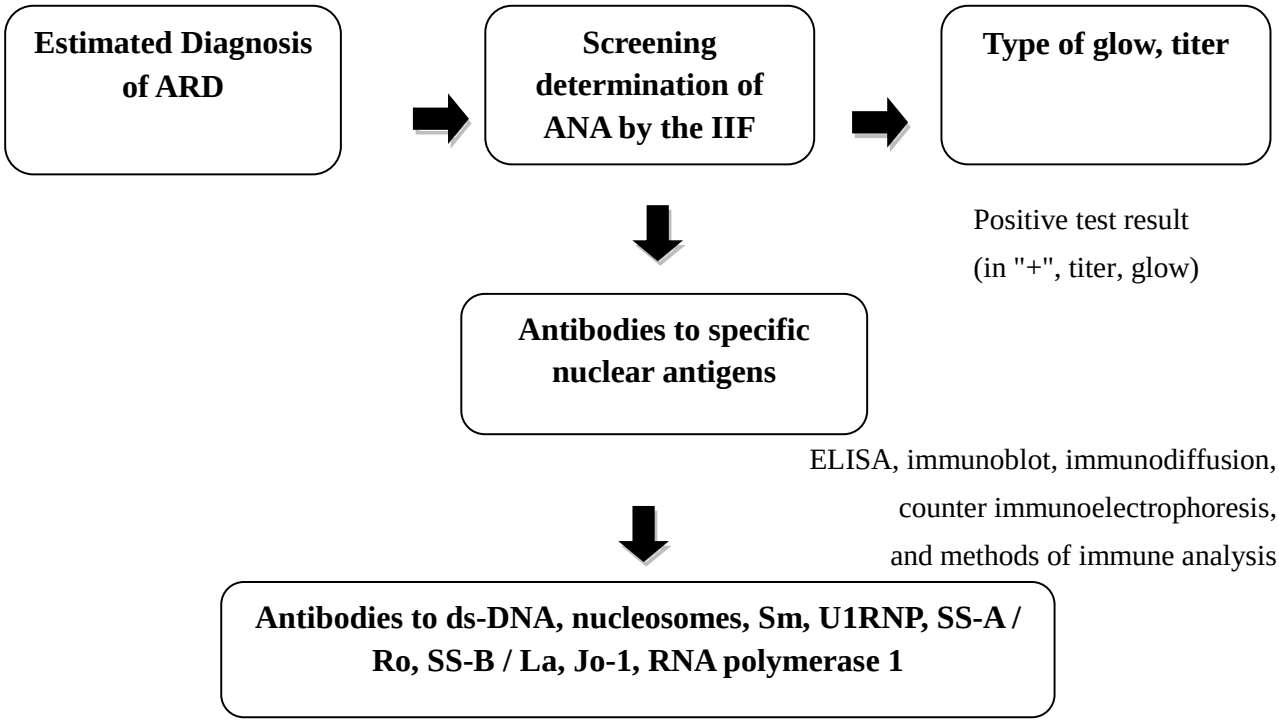
ANA are present. Positive result - ANA present. Most often, ANA is found in MCTD (in 99% of cases), SLE (93% -95%),SS (60% -95%), SS (95%), DM / PM (30-50%), RA (30 -40%). The content of antinuclear antibodies is quantified in + (from 1+ to 4+), and as a serum titer. A higher titer of ANA indicates a high probability of ARD, especially SLE.

Normal ANF titers in blood serum are < 1: 40 when using cryostat sections of the liver or kidneys of laboratory animals and <1:160 when using Hep-2 cells. There are levels of anf-HEp-2 positivity: low-positive titles-1: 160, moderately positive titles-1:320-1:640, high-positive titles-1:1280 or more.
When performing the IIF, the type of core glow is described and the associated antigens are specified (table 1).

Table 1 - Characterization of antinuclear factor

Type of glow	Type of autoantibodies	Association with diseases
Homogeneous	Antibodies to deoxyribonucleic acid of DNA (two and one-chiral), histones (H1, H2A, H2B, H3, H4)	SLE, medicinal lupus, any ARD and non-rheumatic diseases
Peripheral	Antibodies to double-stranded, native DNA	SLE
(boundary)	Antibodies Sm, RNP, SS-A/Ro, SS-B/La, Jo-1	SLE, MCTD, Sjogren's syndrome, PM/DM
Mottled	Antibodies to Scl-70	S / SSD
Netted speckled	Anti-centromeric antibodies (ACA)	CREST syndrome, Raynaud's syndrome
Discrete speckled	Antibodies to RNA polymerase 1, PM/Scl, U3-RNP	S / SSD

The standardization and reproducibility of IIF results is significantly enhanced when using automated systems for interpreting research results.



With a "+" result of tests revealing ANF or ANA, it is required to find the specificity of autoantibodies to individual nuclear antigens. The most informative method for identifying the specificity of ANA is an immunoblot, additionally, the ELISA methods, double immunodiffusion method, counter immunoelectrophoresis, etc. This sequence of immunological tests for suspected ARD is shown in Figure 2.

Figure 2 - Algorithm of immunodiagnosis of ARD

Some types of ANA (anticentromeric, PCNA-proliferating cell nuclear antigen 1, antibodies to the mitotic apparatus of the cell-NUMA, Golgi apparatus) are detected only by the NIF method on HEp-2 cells, which eliminates the need for further research.

A positive ANF/ANA result in a patient without symptoms of an autoimmune process must be interpreted taking into account additional anamnestic, clinical and laboratory data, since ANA is detected in 3-5% of healthy people (10-37% aged over 65 years), as well as in infectious, inflammatory, oncological diseases, and in 25-30% of relatives of patients with ARD.

Immunological tests for differential diagnosis of autoimmune rheumatic diseases

Immunoblot of antinuclear antibodies

The method allows us to evaluate the specificity of antinuclear antibodies. Antibodies to autoantigens are detected: Sm, RNP/Sm, SS-A, SS-B, Scl-70, PM-Scl, PCNA, CENT-B, dsDNA/Histone/Nucleosome, RibP, AMA-M2, Jo-1.

Interpretation of results

The result is presented as follows:

"+" - low content of antibodies to autoantigen;

"++"- the average content of antibodies to the autoantigen,

"+++" - high content of antibodies to autoantigen;

"–"- antibodies to the autoantigen were not detected.

A positive test result that detects the presence of specific antibodies does not allow diagnosing ARD in the absence of a clinical picture.

A negative result of the immunoblot does not exclude ARD in the presence of a characteristic clinical picture. In this case, it is recommended to conduct additional studies using a complex of highly sensitive immunological methods in dynamics.

In ARD, a different combination of autoantibodies is most often found.
Based on international recommendations, standard autoantibody profiles have been developed for the diagnosis of ARD (table 2).
The list of screening tests with high diagnostic sensitivity (DS) and confirming immunological tests with high diagnostic specificity (DS), as well as additional serological tests for the diagnosis of ARD, presented in table 3, is convenient for the clinician.
Immunological studies contribute to the early diagnosis of ARD, allow assessing the activity and severity of the disease, and predict the effectiveness of therapy. However, the frequency of detection of autoantibodies differs significantly in ARD, many of them are not highly specific (table 4).
The development of ARD immunodiagnostics is aimed at using *multiplex analysis of biomarkers* based on genetic, epigenomic, transcriptomic and proteomic technologies using DNA and protein microchips, polymerase chain reaction, and flow cytometry.

Table 2-Autoantibodies included in the diagnostic and/or classification criteria of ARD

Disease	*Autoantibodies*	*Diagnostic and / or classificatory ARD criteria*
RA	Rheumatoid factor (RF)	Classification criteria ACR/EULAR (2010)
SLE	Antibodies to citrulline proteins (ACP)	Classification criteria SLICC (2012)
SS	Antinuclear Antibodies (ANA)	Classification criteria ACR/EULAR (2013)
Sjogren's syndrome	Antibodies to double-stranded (ds) DNA (anti-dsDNA)	Classification criteria ACR (2012), SICCA (2012)
MCTD	Anti Sm	Diagnostic criteria (1996)
Undifferentiated connective tissue disease	Anti-SSA / Ro	Preliminary classification criteria (1997)
APS	Anti-SSB / La	Classification criteria (consensus; 2006)
ANCA-SV	Antiphospholipid antibodies: antibodies to cardiolipin (AKL), antibodies to β2-	Classification criteria (consensus; 2007)

	glycoprotein 1 (aβ2-GP 1), lupus anticoagulant (LA), false positive Wasserman reaction	
PM / DM	Antibodies to tRNA aminoacyl synthetases - Jo-1, PL-7, PL-12, EJ, OJ, KS; antibodies to SRP, Mi-2, PM-Scl, KJ	Diagnostic criteria (1995)
Notes: 1. ACR/EULAR - American College of Rheumatology/ European League Against Rheumatism-American College of rheumatology/ European League against rheumatism. 2. SLICK-systematic Lupus International Collaborator and Clinics-criteria for systemic international joint clinics for systemic lupus. 3. SICCA - Sjogren's International Collaborative Clinical Alliance-criteria for the Sjogren international collaborative clinical Alliance.		

Table 3-List of primary (screening) and secondary (confirming) immunological tests for the diagnosis of autoimmune rheumatic diseases [24, 26]

Diagnosis	ANA-IIF	aDNA	aSm	aU1RNP	aSSA/SSB	aScl-70	aJo-1	ariboRNP	ANCA- IIF	MPO-ANCA	PR3-ANCA	ACL	aβ2-GP1	IgMRF	ACCP
Systemic lupus erythematosus	1	2	2	3	2			2				2	3	3	
Sjogren's syndrome	1	3	3		2			3				3		3	
Systemic sclerosis / systemic scleroderma	1			2		2						3			
Mixed connective tissue diseases	1	2	2	2				2				3		3	
Polymyositis / Dermatomyositis	1			2			2								
Antiphospholipid Syndrome	1											1	2		
Rheumatoid arthritis														1	1
Vasculitis with predominant lesion of small-caliber vessels										1	2	2			
Connective tissue diseases	1	3	3	3	2		2			1	3		1	2	1

Notes:
1 - primary tests;
2 - confirmatory tests;
3 - additional tests.
• ANA-IIF - antinuclear antibodies determined by indirect immunofluorescence test;
• aDNA - antibodies to native DNA;
• aSm - antibodies to the Sm nuclear protein;
• aU1RNP - antibodies to aU1RNP;
• aSSA / SSB - antibodies to SSA / SSB;
• aScl-70 - antibodies to topoisomerase I;
• aJo-1 - antibodies to histidyl tRNA synthetase;
• ariboRNP - antibodies to riboRNP;
• ANCA - antineutrophilic cytoplasmic antibodies (IIF method);
• MPO-ANCA - antibodies to myeloperoxidase;
• PR3-ANCA - antibodies to proteinase 3;
• ACL - antibodies to cardiolipin;
• aβ2-GP 1 - antibodies to β2-glycoprotein 1;
• IgM RF - autoantibodies of the IgM class rheumatoid factor;
• ACCP - antibodies to a cyclic citrulline peptide.

Table 4 - Frequency of antibodies in autoimmune rheumatic diseases (%)

Antibodies	Diseases						
	SLE	Medicinal lupus	MCTD	PA	Sjogren's syndrome	SS	DM
Anti-dsDNA	>90	-	10-30	-	10-30	10-30	10-30
Antihistone	30-50	50-90	-	30-50	-	-	-
Anti-SS-A (Ro)	10-30	-	-	10-30	>90	10-30	-
Anti-SS-B (LA)	30-50	-	-	-	>90	-	-
Anti Sm	10-30	-	-	-	-	-	-
Anti-RNP / Sm	10-30	-	>90	-	-	-	-
Anti-scl-70	-	-	-	-	-	>90	-
Anti-Jo-1	-	-	-	-	-	-	50-90

It should be remembered that the interpretation of these immunological tests should always be carried out in accordance with the clinical symptoms of the suspected disease.

3. RHEUMATOID ARTHRITIS

RA is a chronic autoimmune systemic connective tissue disease characterized by persistent progressive inflammation of mainly peripheral joints in the form of symmetrical erosive-destructive polyarthritis, often with extra-articular lesions of internal organs.

- RA affects approximately 1% of the population (0.2% to 5.3%).
- It affects people of all ages, but is most common in 40-60 years. There are three age peaks in the development of RA (the last one is 60-80 years old).
- Women get sick 3 times more often than men.
- Disability develops in 10 years in 30%, in 20 years-in 60-90% of patients.
- Life expectancy is reduced by 3-7 years.
- Increased mortality due to the rapid development of atherosclerosis against the background of immune inflammation.

ICD-10 codes

M05. Seropositive RA

- M05. 0. Felty Syndrome
- M05. 1. Rheumatoid lung disease
- M05. 2. Rheumatoid vasculitis
- M05. 3. RA with the participation of other bodies and systems
- M05. 8. Other seropositive RA
- M05. 9. Unspecified seropositive RA

M06. Other RA

- M06. 0. Seronegative RA
- M06. 1. Still's disease in adults
- M06. 2. Rheumatoid Bursitis
- M06. 3. Rheumatoid node
- M06. 4. Inflammatory polyarthropathy
- M06. 8. Other specified RA
- M06. 9. Unspecified RA

Etiology of RA. There is a genetic predisposition to the disease, mediated by HLA-DR4 or HLA-DR1 antigens, polymorphism of the T-cell receptor, IgG, receptors for cytokines TNF-α, IL-10, and others. Carrier of HLA-DR4 in seropositive RA reaches 70% (in the population - 25%). The relationship between the HLA-DR4 locus and the severity of RA, hyperproduction of rheumatoid factor, and rapid development of erosive changes in the joints was revealed.

The role of viruses (Epstein-Barr virus, lymphotropic T-cell virus, human B19 parvovirus, retroviruses, rubella virus, herpes, cytomegalovirus), bacterial

infections (Mycoplasma, chlamydia, etc.), and microbiocinosis disorders are considered.
Hormonal background and its disorders (sex hormones, prolactin) have a certain value.

Immunopathogenesis of RA. T and B lymphocytes stimulated by an unknown antigen migrate from the postcapillary venules of the synovial membrane to the tissues. Then, synovial cells carrying abnormal class II HLA antigens and costimulatory molecules present an unknown arthritogenic peptide to T cells. After this, cytokines stimulate the activation of various cellular systems. B cells are activated by the mechanism of polyclonal stimulation, synthesize immunoglobulins (rheumatoid factors - immunoglobulins directed against IgG Fc fragments), which activate the complement system through immune complexes, which contributes to the development of vasculitis. Pro-inflammatory cytokines, especially TNF-a and IL-1, lead to increased proliferation and activation of fibroblasts. Chondrocytes activated by cytokines produce a large number of fibroblast growth factor and granulocyte-monocyte colony stimulating factor. All this causes the development of synovitis and the formation of a pannus, and, as a result, the destruction of the bone and joint.
Along with T-lymphocytes, macrophages secreting TNF-α and IL-1 play an important role in the destruction of the joint. Macrophages are characterized by enhanced phagocytosis and chemotaxis. These cells make up about 30% of the cells in the inflamed synovial membrane. The regulatory (anti-inflammatory) cytokines of macrophages and T-regulatory cells (IL-10, TGF-β) cannot withstand pro-inflammatory cytokines.

Rheumatoid arthritis has a staged development:
• *Preclinical stage* (genetic risk, asymptomatic autoimmunity disorder, subclinical symptoms of joint damage detected by special studies).
• *Very early stage* (disease duration <6 months).
• *Early stage* (duration is from 6 months to 1 year). The treatment prescribed in the early period of RA is most effective, which is why this period is called the “window of opportunity”.
• *Advanced stage* (disease duration> 1 year in the presence of a clinical picture of RA). After 2 years of illness, the presence of erosion in the joints is observed in 90% of patients.
• *Late stage*. The presence of proliferative changes in the joints, characteristic deformations due to subluxations, dislocations in the joints is characteristic.

Clinical Symptoms of RA

General clinical manifestations in RA can occur even before joint damage. These include weight loss, fever, generalized weakness, morning stiffness.

Joint damage. In 70-80% of cases, the disease begins with polyarthritis, less often with monoarthritis and oligoarthritis. Joint syndrome is characterized by bilateral symmetrical damage to the joints. Small joints of the hands are usually involved in the pathological process: metacarpophalangeal, proximal interphalangeal ("exception" joints - distal interphalangeal joints of the fingers, 1st metacarpophalangeal joint, 5th proximal interphalangeal joint), foot joints (metatarsophalangeal), wrist joints, less commonly affected are the hip, knee, shoulder and spinal joints. A gradual increase in joint pain and morning stiffness lasting 1 hour or more is characteristic. Affected joints are hyperemic, swollen, painful on palpation, local hyperthermia is determined above the joints. Active and passive movements in the joints are limited.

Joint lesions in RA can be reversible and irreversible. Reversible changes are associated with the development of synovitis, irreversible changes are caused by structural changes in the joints in the later stages. With a long course of the disease, ankylosis of the joints develops and their complete immobilization.

"Rheumatoid hand" is a typical lesion of the joints of the hand that occurs with RA. Signs of a "rheumatoid wrist" are: symmetric swelling of the metacarpophalangeal, proximal interphalangeal joints of the hand (usually 2-4 fingers are involved), in the wrist, deformation of the wrist like "boutonniere", "swan's neck", development of amyotrafia and ulnar deviation (table 5).

Table 5 - Picture of rheumatoid lesions of the hand

Symptom	**Characteristic**
Symptom of the "buttonhole" or deformation of the fingers of the hand according to the type of "buttonhole"	Re-extension of the distal interphalangeal joints in combination with flexion of the proximal interphalangeal joints of the hand
Deformation of the fingers of the hand according to the type of "swan neck"	Flexion of the distal interphalangeal joints, overextension in the proximal interphalangeal joints in combination with flexion contracture in the metacarpophalangeal joints
Z-shaped deformation of the first finger of the brush	Subluxation of the metacarpophalangeal joint with hyperextension of the interphalangeal joint of the first finger
Symptom of "lorgnet"	Due to the formation of flexion contracture of the fingers and limitation of extension in the distal

	and proximal interphalangeal joints, the patient cannot fully extend his palm and touch it on a flat surface. This deformation is accompanied by almost complete inoperability of the brush
Amyotrophy symptom	Atrophy of the interosseous muscles of the rear of the hand
Ulnar deviation	Subluxations in the metacarpophalangeal joints with deviation of the fingers to the elbow side. This shape of the brush is called "walrus fin"

Foot joints damage is accompanied by lateral deviation and deformation of the first toe (hallus valgus - valgus deformity), as well as the formation of subluxations in the metatarsophalangeal joints and hammer-like deformation of the toes of the foot.

Damage to the elbow joint leads to the formation of a “symptom of a key,” which is characterized by a subluxation of the head of the ulnar bone due to damage to the ulnar collateral ligament and instability in the radiolar joint. This symptom is characterized by pathological mobility of the ulnar head.

Damage to the shoulder joint is associated with synovitis and involvement in the pathological process of the distal third of the clavicle, muscles of the shoulder girdle, neck and chest. Pain syndrome is accompanied by restriction of movements in the shoulder joint and the development of muscle atrophy. Weakness of the articular bag leads to anterior subluxation of the humeral head.

Arthritis of the knee joints is characterized by flexion and hallux valgus, as well as the formation of a Baker cyst (protrusion of the posterior inversion of the joint bag into the popliteal fossa). The development of synovitis of the joints leads to a configuration of the knee joints, palpation determines the ballot of the patella. Hallux valgus is characterized by strong lateral curvature. With this deformation, an open outward angle is formed between the lower leg and thigh.

Damage to the ankle joint is rare and is accompanied by swelling in the ankle. With the involvement of the ligamentous apparatus, instability of the ankle joint with frequent subluxations develops.

The involvement of the hip joint is observed with a prolonged course of the disease. The pain may radiate to the inguinal region or lower part of the gluteal region. The fixation of the thigh in the position of slight flexion is characteristic. With the development of aseptic necrosis of the head of the hip and protrusion of the acetabulum, there is a sharp restriction of active and passive movements in the joint.

Damage to the joints of the spine can be observed in the late stage of RA. The cervical spine is most often involved in the pathological process. Subluxation of

the atlantoaxial joint (in 10% of cases) is accompanied by severe pain, neck stiffness, can be complicated by compression of the vertebral artery and spinal cord, leading to the development of neurological dysfunction.
Involvement of the temporomandibular joint is accompanied by a restriction on the opening of the mouth and makes eating difficult.

Extraarticular manifestations of RA. They are developed in the debut of RA, sometimes even prevail in the clinical picture of the disease (table 6).
By the nature of the progression of destructive processes in the joints and extra-articular manifestations, the following variants of the course of RA are distinguished:
• prolonged spontaneous clinical remission (less than 10%);
• intermittent course (15-30%);
• progressive course (60-75%);
• fast progressing course (10-20%).
In 2007, the Association of Rheumatologists of Russia proposed the classification of RA, which consists of 8 headings (table 7)

Table 6 - Extraarticular manifestations in rheumatoid arthritis

Extraarticular manifestations	**Clinical picture**
Constitutional symptoms	Fever, weight loss, general well-being, sweating, asthenia, generalized weakness, myalgia. Symptoms are associated with a high degree of inflammation activity, may develop before the onset of articular syndrome.
Damage to the skin	Rheumatoid nodules are found in 30-40% of patients with RA, more often with high disease activity. They are dense formations from 1-2 mm to 1.5-2 cm in diameter, painless on palpation, mobile, can be soldered with aponeurosis or underlying bone. They develop in places of increased traumatization (over small joints of the hands, in the region of the bag of the ulnar process, extensor surface of the forearm), can be single or multiple, located symmetrically or asymmetrically. Usually appear during an exacerbation of the disease and may disappear after the onset of remission. Thinning and dryness of the skin, especially at the fingertips. Hyperpigmentation of the skin develops on the lower extremities. Violation of trophic nails leads to their thinning, brittleness, longitudinal striation. Due to the development of cutaneous vasculitis, subcutaneous hemorrhages may occur,

	accompanied by small focal necrosis of the soft tissues under the nail plates or in the area of the nail bed (digital arteritis)
Muscle damage	Muscle weakness amid the development of atrophy. Active RA can lead to the development of myositis, necrosis of muscle fibers, an increase in the level of creatine phosphokinase, transaminases, aldolases
Lymphadenopathy	In 20% of cases with high activity. During remission, a decrease in the size and number of lymph nodes
Eye damage	Scleritis, episiscleritis, dry keratoconjunctivitis, scleromalacia, peripheral ulcerative keratopathy are rare
Secondary Sjogren's Syndrome	10% of patients with RA develop keratoconjunctivitis (discomfort, itching, burning eyes, a feeling of “sand in the eyes”), xerostomia (dry mouth, associated with a decrease or complete cessation of salivation)
Lung damage	Dry and effusion pleurisy, interstitial pulmonary fibrosis, bronchiolitis, pulmonary vasculitis, rheumatoid nodules in the lungs
Damage to the cardiovascular system	With pronounced activity of RA - pericarditis, myocarditis, endocarditis, cardiomyopathy, damage to the conduction pathways of the heart, coronary arteritis, granulomatous damage to the heart valves, vasculitis
Kidney damage	Glomerulonephritis, with prolonged course and high activity of RA - amyloidosis (proteinuria, cylindruria, peripheral edema, arterial hypertension, decreased glomerular filtration rate, impaired renal excretory function of the kidneys)
Damage to the nervous system	Compression neuropathy, symmetric sensory-motor neuropathy, multiple mononeuritis, cervical myelopathy
Systemic rheumatoid vasculitis	Less than 1%, prevails in men with highly active seropositive RA. Characterized by the development of palmar, plantar capillaritis, digital arteritis, obliterating endarteritis of large arteries

Table 7 - Classification of RA (APP, 2007), [8]

1. The main diagnosis
Seropositive RA
Seronegative RA
Special clinical forms of RA: Felty's syndrome, Still's disease in adults
Probable RA
2. Clinical stage

Very early stage: disease duration <6 months Early stage: disease duration 6 months - 1 year Advanced stage: disease duration> 1 year in the presence of typical symptoms of RA Late stage: the duration of the disease is 2 years or more + pronounced destruction of small (III-IV radiological stage) and large joints, the presence of complications
3. Disease activity score (DAS - Disease Activity Score - disease activity index) 0 - remission (DAS28 <2.6), 1 - low (DAS28 = 2.6–3.2), 2 - medium (DAS28 = 3.3–5.1), 3 - high (DAS28> 5.1)
4. Extraarticular (systemic) manifestations Rheumatoid nodules Cutaneous vasculitis (ulcerative necrotic vasculitis, nail bed heart attacks, digital arteritis, live-angiitis) Vasculitis of other organs Neuropathy (mononeuritis, polyneuropathy) Pleurisy (dry, effusion), pericarditis (dry, effusion) Sjogren's syndrome Eye damage (scleritis, episiscleritis, retinal vasculitis)
5. Instrumental characteristic The presence of erosion (according to x-ray, possibly magnetic resonance imaging, ultrasound): non-erosive, erosive X-ray stage (according to Steinbroker with modification): I - periarticular osteoporosis II - periarticular osteoporosis + narrowing of the joint space, there may be a single erosion III - signs of the previous stage + multiple erosion + subluxation in the joints IV - signs of a previous stage + bone ankylosis
6. Additional immunological characteristic - anti-citrulline antibodies (ACCP) ACCP - positive, ACCP - negative
7. Functional class (FC) I - self-service, unprofessional and professional activities are fully preserved II - self-service and professional activity are preserved, unprofessional activity is limited III - self-service is maintained, unprofessional and professional activity is limited IV - limited self-care, unprofessional and professional activities
8. Complications Secondary systemic amyloidosis Secondary arthrosis Osteoporosis (systemic) Osteonecrosis

Tunnel syndromes (carpal tunnel syndrome, compression syndromes of the ulnar, tibial nerves)
Subluxation in the atlanto-axial joint, including with myelopathy, instability of the cervical spine
Atherosclerosis

Comments on Rheumatoid arthritis classification (Association of Rheumatologists of Russia, 2007)

Heading "The main diagnosis." Seropositivity and seronegativity are diagnosed on the basis of a determination in the blood serum of the Russian Federation. Its identification must be performed using a reliable quantitative or semi-quantitative test (latex test, enzyme immunoassay, immunonefelometric method).

The heading "Activity of the disease." To determine the activity of RA, it is recommended to use the DAS28 index. The following parameters must be considered:

- the number of painful joints (CPJ);
- the number of swollen joints (NSJ);
- erythrocyte sedimentation rate (ESR);
- the general state of health of the patient (GSHP).

Formula for calculating DAS 28:

$DAS28 = 0.56 \times \sqrt{CPJ} + 0.28 \times \sqrt{NSJ} + 0.7 \times \lg ESR + 0.014 \times GSHP$

CPJ and NSJ are diagnosed in evaluating 28 joints (shoulder, elbow, wrist, metacarpophalangeal, proximal interphalangeal, knee). GSHP is evaluated on a 100 mm visual analogue pain scale. ESR is determined by the method of Westergren. It is possible to use other methods of counting activity, for which good compatibility with DAS28 is proved.

Heading "Instrumental characteristic".

Detailed description of the radiological stages:

Stage I:

- small periarticular osteoporosis;
- single cystic enlightenment of bone tissue;
- slight narrowing of the joint spaces in individual joints.

II stage:

- moderate (severe) periarticular osteoporosis;
- multiple cystic enlightenment of bone tissue;
- narrowing of the joint spaces;
- single erosion of articular surfaces (1-4);

- slight bone deformities.

Stage III:

- moderate (severe) periarticular osteoporosis;
- multiple cystic enlightenment of bone tissue;
- narrowing of the joint spaces;
- multiple erosion of articular surfaces (5 or more);
- multiple pronounced bone deformities;
- subluxations and dislocations of the joints.

IV stage:

- moderate / severe periarticular or common osteoporosis;
- multiple cystic enlightenment of bone tissue;
- narrowing of the joint spaces;
- multiple erosion of bones and articular surfaces;
- multiple pronounced bone deformities;
- subluxations and dislocations of the joints;
- single (multiple) bone ankyloses;
- subchondral osteosclerosis;
- osteophytes at the edges of the articular surfaces.

Category "Functional class"

- self-care: dressing, eating, personal care, etc.
- unprofessional activity: elements of recreation, leisure, sports, etc., taking into account gender and age
- professional activity: work, study, housekeeping (for patients working at home) taking into account gender and age.

Determining the degree of activity of RA can also be carried out using the recommendations of the Association of Rheumatologists of Russia (ARP, 2003). To do this, it is necessary to assess the pain on a visual analogue scale (VAS), CRP, ESR, and also to clarify the duration of morning stiffness. Assessment of the degree of activity of RA in accordance with the recommendations of the Association of Rheumatologists of Russia (2003) is presented in table 8.

Table 8 - Assessment of the degree of activity of rheumatoid arthritis (APP, 2003), [8]

Indicator	Degree of activity			
	0	1	2	3
Pain on a visual analogue scale (10 cm)	0	≤3	4-6	>6
Morning stiffness	is absent	30-60 minutes	till 12 o'clock	during the day
ESR (mm / h)	≤15	16-30	31-45	>45

CRP	Норма (N)	≤2N	≤3N	>3N

Diagnosis of RA

For the diagnosis of RA, the diagnostic criteria proposed by the American College of Rheumatology in 1987 are used (Table 9).

Table 9 - Diagnostic criteria for RA (ACR, 1987), [15]

Criterion	**Characteristic**
Morning stiffness	Stiffness in the morning in the area of joints or periarticular tissues, which lasts at least 1 hour
Arthritis of three joints and more	Swelling of the periarticular soft tissues or the presence of effusion in the articular cavity in at least three joints. Possible damage to 14 joints on the right and left extremities (proximal interphalangeal, metacarpophalangeal, carpal, ulnar, knee and ankle)
Arthritis of the joints of the hands	Swelling of at least one group of joints of the following localization: proximal interphalangeal, metacarpophalangeal, wrist
Symmetric Arthritis	Simultaneous bilateral joint damage (absolute symmetry is not required)
Rheumatoid nodules	Subcutaneous nodules, localized mainly on protruding parts of the body, extensor surfaces or in the periarticular regions
Rheumatoid factor	Detection of an increase in the concentration of rheumatoid factor in serum by any standard method that gives positive results in no more than 5% of healthy people
X-ray changes	Diagnosis of radiological changes typical of RA in the hands and feet (erosion or periarticular osteoporosis, most pronounced in clinically affected joints)

The diagnosis of RA is established in the presence of at least 4 of the 7 criteria presented above. The first four criteria should be maintained for at least six weeks.
Certain difficulties in the early diagnosis of RA are associated with the fact that rheumatoid nodules and radiological changes usually appear in the late stages of the disease, and the RF in some patients may be negative. With this in mind, in 2010 the American College of Rheumatologists, together with the European League against Rheumatism, proposed new diagnostic criteria (table 10).
In order to diagnose RA according to new criteria, the following conditions must be fulfilled*: to determine if the patient has at least one joint with swelling*

(synovitis) according to physical examination; exclude other diseases that may be associated with the development of synovitis; score ≥6 points out of 10 in four positions (A-D).

Patients who scored less than six points at the time of examination are considered to have no RA. It is recommended that their condition be reevaluated, since diagnostic criteria can cumulatively cumulate over time.

Table 10 - Diagnostic criteria for RA (ACR / EULAR, 2010), [10]

Diagnostic criteria	**Points**
A. Joint damage	
• 1 large joint	0
• 2-10 large joints	1
• 1-3 small joints (large joints are not counted)	2
• 4-10 small joints (large joints are not counted)	3
•> 10 joints (at least 1 small joint)	5
B. Serological data (at least one test is required for diagnosis)	
• Negative RF and ACCP	0
• Weakly positive RF and slightly positive ACCP s (exceed the upper limit of the norm by three or less times)	2
• Sharp-positive RF and sharply positive ACCP s (exceed the upper limit of the norm by three or more times)	3
C. Acute phase reagents (at least one test is required for diagnosis)	
• Normal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)	0
• Increased ESR or CRP	1
D. Duration of symptoms	
• <6 weeks	0
• ≥6 weeks	1

Laboratory examinations

• *General blood test*: increased ESR; hypochromic anemia; leukocyte shift to the left; leukocytosis, thrombocytosis, eosinophilia can be observed in severe RA; neutropenia is diagnosed with Felty's syndrome.

• *Biochemical blood test*: increased CRP; an increase in the level of liver enzymes may be associated with therapy with basic anti-inflammatory drugs (DMARDs) and genetically engineered biological drugs (GEBD); hyperglycemia is diagnosed in the treatment of glucocorticosteroids (GCS); an increase in creatinine and uric acid is determined by the nephrotoxic effect of DMARDs and GEBD or the development of renal amyloidosis.

• *Diagnostic immunological biomarkers*: simultaneous assessment of concentrations of RF IgM / IgA, levels of antibodies to cyclic citrulline peptide and antibodies to modified citrulinated vimentin increase diagnostic sensitivity to 90% in the early stage of RA, to 92% in the late stage.

Rheumatoid factor

• RF - IgM, IgG and IgA autoantibodies that react with the IgG Fc fragment. Of greatest importance is the definition of IgM RF.

• The normal level of RF IgM when testing sera with latex agglutination is ≤1: 40, nephelometry ≤ 15 IU / ml, ELISA ≤20 IU / ml. Allocate negative (less than or equal to the upper limit of the norm); low positive (≤3 upper normal) and highly positive (> 3 upper normal) IgM RF levels.

• A positive result of detection of RF IgM in serum confirms RA in case of symptoms of RA. A negative analysis result does not exclude RA.

• In the early stages of RA, only high IgM RF titers are of diagnostic value.

• RF IgM - sensitive (PM: 50-90%), but not specific enough (DS: 80-93%), a marker of RA. *High titers of RF are determined* for Sjögren's disease, sarcoidosis, low titers for hepatitis, autoimmune thyroiditis, psoriatic arthritis, mononucleosis, Epstein-Barr infection and other IgM RF are determined in approximately 5% of healthy people, 5-25% of elderly people (table eleven).

Table 11 - Frequency of occurrence of Rheumatoid factor in various diseases and in healthy people

Groups surveyed	**RF detection frequency**
Rheumatoid arthritis	80%
Sjogren's syndrome	70%
SLE	30%
Polymyositis	20%
Systemic sclerosis	20%
Cirrhosis of the liver	25%
Infectious hepatitis	25%
Tuberculosis	15%
Syphilis	10%
Healthy	Less than 5%

• RF has prognostic value in relation to clinical manifestations of RA severity. High concentration IgM RF is a predictor of rapidly progressive destructive joint damage and systemic manifestations in RA. An increase in the concentration of

IgM RF correlates with indicators of the acute phase of inflammation - ESR, CRP. Seroconversion in RF may be observed during RA treatment.

Antibodies to citrulline proteins (ACPs) are a heterogeneous group of autoantibodies that recognize the antigenic determinants of phyllagrin and other proteins containing the atypical amino acid citrulline, resulting from post-translational modification of arginine residues under the action of the peptidylarginin deiminase enzyme. The ACP family includes: antibodies to a cyclic citrulline peptide, antibodies to a modified citrulinated vimentin, antiperinuclear factor, antikeratin antibodies, antifillagrine antibodies, antibodies to citrulinated fibrinogen, antibodies to citrulliniron histrionins, citruliniron histrionins antibodies. Among ACPs, the most standardized marker for early diagnosis and assessment of prognosis of RA is the definition of ACCP.

Antibodies to cyclic citrulline-containing peptide

• Negative (≤ the upper limit of the norm, that is, from 5 to 25 U / ml, depending on the manufacturer of the reagents); low positive (≤3 upper limit of normal) and highly positive (> 3 upper limit of normal) ACCP level are distinguished.

• The positive results of detecting ACCP in serum serve as a diagnostic criterion for RA. Only in 2% of cases, the level of ACCP is increased in SLE, SS, Sjögren's syndrome, systemic vasculitis (Wegener's granulomatosis), autoimmune thyroiditis.

• ACCP is a marker of RA at a very early stage (disease duration <6 months) and at an early stage (disease duration 6 months - 1 year), can be determined 1.5 years or more before the onset of symptoms of RA.

• ACCP C is a highly specific diagnostic marker for RA (AF: 49-91%, DS: 73-99%), especially at an early stage of the disease (AF: 39-71%, DS: 93-99%) compared with the RA IgM. The detection rate of ADC in IgM RF-negative patients with RA is 20–40%.

• The detection of ACCP is predictive in relation to the development of joint destruction in patients with early RA.

Antibodies to Modified Citrulline Vimentin (AMCV)

• The upper limit of the norm in determining AMCV using ELISA is 20 IU / ml. It is recommended to highlight the negative (≤ the upper limit of the norm); low positive (≤3 upper bounds of the norm) and highly positive (> 3 upper bounds of the norm) levels of AMCV.

• Positive results of determination of AMCV in blood serum serve as an additional diagnostic marker of RA with negative results of determination of RF IgM and

ACCP in blood serum. In patients with RA, negative in Rheumatoid factor, AMCV is detected in 50%.
• AMCVs have a higher or similar sensitivity (PM: 77%), but less specificity (DS: 89%) compared to ACCP.
• Identification of AMCV predicts the development of severe erosive joint damage in patients with RA. AMCV is more associated with clinical and laboratory indicators of RA activity than ACCP.
• The multiplicity of determining the level of AMCV in RA is similar to that for ACCP.

At present, *multiparametric research methods* have been developed for diagnosing RA, evaluating activity, predicting the course of the disease and the effectiveness of therapy. *The complex of defined immunological biomarkers includes*: autoantibodies, acute phase inflammatory proteins, cytokines, chemokines, vascular endothelial activation markers, complement system components, lymphocyte subpopulations, markers of bone and cartilage tissue metabolism, etc.
Promising diagnostic biomarkers of RA include: antibodies to carbamylated proteins (anti-CarrP); protein 14-3-3η, belonging to the family of regulatory molecules that affect the cell cycle, metabolic control, apoptosis, gene transcription control, adhesion. Both markers play an important role in the immunopathogenesis of RA, reflect the degree of joint damage and disease activity.
Immunogenetic study: determination of HLA-DR4 (allele DRB 1 * 0401), which is a marker of severe RA and poor prognosis.
Synovial fluid analysis: in patients with RA there is a decrease in synovial fluid viscosity, leukocytosis (> 6 × 109 / L), an increase in the number of neutrophils (25-90%), a loose mucinous clot).

Instrumental research methods

Radiography of the joints is carried out to confirm the diagnosis of RA, to determine the radiological stage, to assess the progression of destructive lesions of the joints.
First of all, X-rays of the hands and feet are performed, since in RA small joints are initially affected. In patients with RA, periarticular osteoporosis, erosion (usury) of articular surfaces, narrowing of the joint spaces up to their complete disappearance and formation of joint ankylosis, dislocation and subluxation in the joints are revealed. There are 4 radiological stages of RA (table 7, p. 5).
For the early diagnosis of RA, it is necessary to use ultrasonography (ultrasound) and magnetic resonance imaging (MRI). These methods have great diagnostic

capabilities in detecting joint pathology at the onset of the disease compared with radiographic examination.
Joint MRI is most sensitive in detecting synovitis of joints and early changes in the articular surface of bones in comparison with radiography.
Ultrasonography (ultrasound) of the joints allows us to assess the state of the articular surface of the joints, synovial membrane, joint capsule, cartilage and periarticular tissues. Using this method, it is possible at an early stage of RA to visualize inflammation of the synovial membrane, characterized by an accumulation of effusion in the cavity lined by it.

Clinical and laboratory monitoring in RA.

The definition of prognostic and pharmacotherapeutic biomarkers of disease activity and the rate of progression of RA is shown: DAS28 index, functional ability of the patient, radiological changes in the joints.
Studies are being carried out on a general blood test, ESR, CRP, a biochemical blood test (liver enzymes, total protein and protein fractions, glucose, creatinine, urea), in the treatment with TNF-α inhibitors, the determination of antinuclear antibodies, antibodies to double-stranded DNA (development of other autoimmune diseases).

Recommended multiplicity to determine RF IgM:
• in seronegative patients at an early stage of RA, once every 3 to 6 months, at a developed stage - once a year, at a late stage, re-analysis is not carried out;
• in low / highly seropositive patients at an early stage 1 time in 3 months, at a developed stage - 1 time in 3-6 months, at a late stage - 1 time per year.
Recommended multiplicity to determine ACCP and AMCV:
• to monitor the effectiveness of therapy with basic and symptomatic drugs, the definition of ACCP / AMCV is uninformative;
• in patients who are seronegative for ACCP / AMCV, the recommended rate of determining indicators at an early stage of RA is 1 time in 6 months, at a developed stage - once. ACCP / AMCV are not exposed to seroconversion;
• with a low level of ACCP / AMCV in the early stage of RA, their repeated determination should be carried out once every 3-6 months, at the expanded stage - once a year.
• in case of revealing a high positivity on ACCP / AMCV at the early and developed stages of RA, repeated studies are not carried out;
• at a late stage of RA, the study of ACCP / AMCV is impractical.

Diagnosis Examples

1. Rheumatoid arthritis, late stage, seropositive, ACCP-negative, activity 2 degrees, stage IV, functional class III.
2. Rheumatoid arthritis, early stage, seronegative, ACCP -positive, activity 3 degrees (DAS28-5,4 points), stage I, functional class I.
3. Rheumatoid arthritis, advanced stage, seronegative, ACCP -negative, activity 2 degrees, stage II with systemic manifestations (rheumatoid nodules, digital arteritis), functional class I.

Treatment of rheumatoid arthritis [5, 9, 7, 22]

Tactics for treating patients with RA are presented in the international program "Treat to target" ("T2T, targeted therapy"), 2013 [22] - the concept of "Treatment to achieve the goal", where the main goal is to achieve remission of RA, the alternative is to achieve low activity of RA.

Tactics of *early aggressive therapy* are adhered to, since the highest degree of joint destruction, which determines the unfavorable prognosis of the disease, is observed precisely in the debut of RA.

The principle of a *personalized approach* is used – choosing the therapy taking into account the individual characteristics of the patient. This takes into account:

• The prevailing immunopathogenesis of RA. At present, RF IgM and antibodies to citrulline proteins are considered as different systems of autoantibodies, which allows us to distinguish two main clinical and laboratory subtypes of RA - ACP-positive and ACP-negative. These RA subtypes have differences in pathogenesis, severity, and treatment approaches.
• Stage (early, full, late).
• The nature of the course of RA (rapidly or slowly progressing), etc.
• Comorbid pathology.
• Polymorphism of genes responsible for drug metabolism.
• The nature of the metabolism.

From the perspective of evidence-based medicine, pharmacotherapy of RA includes:

• Pain Relief Medicines – Non-steroidal anti-inflammatory drugs (NSAIDs).
• Glucocorticosteroids.
• Basic synthetic anti-inflammatory drugs (or disease-modifying drugs).
• Biological genetic engineering disease-modifying drugs (original, biosimilars).

NSAIDs are prescribed for the relief of joint pain for a short time. As the pain in the joints decreases with the use of synthetic immunosuppressants, NSAIDs are canceled. Aceclofenac 200 mg / day by mouth, or diclofenac 100-150 mg / day, by

mouth or IM, or ibuprofen 1200-2400 mg / day by mouth, or meloxicam 15 mg / day, by mouth or IM, or nimesulide 200-400 mg are prescribed. / day inside, or celecoxib 400 mg / day inside or etodolac 600-1200 mg / day inside.
More often than other side effects with NSAIDs, gastropathy and enteropathy develop. In order to prevent them, it is advisable to use selective type 2 cyclooxygenase inhibitors (COX-2) (nimesulide, meloxicam).
It should be remembered that highly selective COX-2 inhibitors (coxibs) increase platelet aggregation and increase the risk of cardiovascular complications. With a combination of risk factors from the gastrointestinal tract (GIT) and the cardiovascular system, it is advisable to use combinations: naproxen + proton pump inhibitors, or celecoxib + low doses of aspirin + proton pump inhibitors.

Basic synthetic anti-inflammatory drugs (DMARDs): methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, tofacitinib, azathioprine, cyclosporine, cyclophosphamide, D-penicillamine, gold salts.
The principles of therapy:
- Appointed from the moment of diagnosis of RA to each patient, regardless of age.
- Reduce pain, swelling and joint destruction.
- It takes 6 months to achieve the effect. Slow increase in the effect of DMARDs is compensated by small doses of corticosteroids.
- When long-term remission is achieved, prolonged dose titration.
- Monitoring of side effects is required.
- Women of reproductive age with the use of DMARDs need reliable contraception.
Methotrexate is a first-line drug in the treatment of RA. 2.5 mg tablet, 2.0 ml vials (5 and 50 mg) for intramuscular and intravenous administration. An early appointment in the form of monotherapy or in combination with immunobiological drugs is recommended, which allows achieving remission in more than half of patients. Treatment with methotrexate begins with a dose of 10-15 mg / week. Then the dose can be increased to 20-30 mg / week, 5 mg every 2-4 weeks, monitoring the effectiveness and tolerability of drugs. The effect is evaluated after 3-6 months of therapy. If the patient notes poor tolerance to the oral form of methotrexate or the desired effect cannot be achieved, then it is administered subcutaneously.
You should remember that you need to take folic acid at least 5 mg / week (on those days when the patient does not take methotrexate).
It is necessary to monitor side effects (liver damage, pulmonary fibrosis, stomatitis, cytopenia), which are monitored once every 1-3 months, monitoring the level of hemoglobin, the number of leukocytes, platelets, creatinine level, activity of

aspartate aminotransferase (AST), alanine aminotransferase (ALT). In the case of an increase in the level of liver enzymes up to 3 times, methotrexate is not canceled, but the dose is reduced. Methotrexate is not canceled during surgical treatment.

It is undesirable to combine methotrexate with DMARDs, aspirin. Methotrexate can be combined with leflunomide, sulfasalazine, hydroxychloroquine (but the risk of side effects increases).

In the presence of factors of an *unfavorable prognosis of RA*, which include: identification of the RF and ACCP in the onset of the disease, high activity of the disease, early appearance and rapid progression of erosion in the joints, early impairment of joint functions, the presence of extra-articular manifestations, methotrexate are combined with GEBD.

With contraindications to methotrexate, leflunomide, or sulfasalazine, is prescribed. With intolerance to methotrexate, it is possible to prescribe GEBD monotherapy or combination therapy of GEBD with other DMARDs. When planning pregnancy, methotrexate is canceled after 6 months.

Leflunomide. Tablets, 10 and 20 mg. The initial dose of LF is 100 mg, taken daily for 3 days, then they switch to a maintenance dose of 10-20 mg / day. It is indicated for intolerance to methotrexate, high activity of RA, the presence of foci of chronic infection, with a seropositive variant of RA. It is necessary to monitor liver enzymes, a general blood test (cytopenia). It has a long elimination period. Women of reproductive age are not recommended to plan a pregnancy earlier than 2 years after the withdrawal of leflunomide.

Sulfasalazine. Tablets, 500 mg. The drug of choice with moderate activity, a seronegative variant of RA, with a combination of RA with chronic hepatitis, when planning pregnancy. Start therapy with 500 mg / day. The dosage is increased by 500 mg once a week so that after four weeks the dose is 2-3 g / day in two divided doses. Contraindication for the appointment is a lupus erythematosus and a positive reaction to ANA.

Hydroxychloroquine. Tablets, 200 mg. It is used to treat early lung RA, or as an adjunctive therapy with other DMARDs, or for differential diagnosis between undifferentiated arthritis and systemic connective tissue disease. It is prescribed in minimally effective doses - 200 or 400 mg / day.

Azathioprine, cyclophosphamide, D-penicillamine, cyclosporine do not have proven effectiveness in preventing the development of destructive changes in the joints, but can be used for intolerance to methotrexate, sulfasalazine, leflunomide.

An inhibitor of the Janus kinase family is a synthetic low molecular weight drug *tofacitinib*. Registered in Russia under the brand name Yakvinus for the treatment of RA, psoriatic arthritis, ulcerative colitis. Janus kinases are signaling membrane proteins that affect the activity of the predominantly T-cell component of the

immune system. Tofacitinib acts on intracellular signaling pathways, blocking IL-6. Efficiency is comparable with biological drugs, but it is deprived of immunogenicity. Tofacitinib is used to treat patients with moderate to high activity RA with an inadequate response to one or more of the DMARDs. Tofacitinib can be used as monotherapy or in combination treatment with methotrexate or other DMARDs. The recommended dose of tofacitinib is 5 mg twice a day, it is possible to increase the dose to 10 mg twice a day.
Baritinib is an inhibitor of Janus kinases (phase 3 clinical trials are conducted).

Glucocorticosteroids

- Do not prevent the development of joint destruction and are prescribed in the acute period of the disease to reduce the activity of RA before the development of the effect of taking DMARDs. Combined therapy of corticosteroids with DMARDs is also used to relieve exacerbation of RA.
- Duration of taking GCS no more than 6 months. It is necessary to properly reduce the dose of corticosteroids as soon as it becomes clinically possible.
- GCS can be prescribed in the form of monotherapy in case of inefficiency or inability to prescribe DMARDs and GEBD.
- For elderly patients, corticosteroids (5-10 mg per prednisolone) may be prescribed with reduced sensitivity to NSAIDs.
- To take per os (methylprednisolone, prednisone, dexamethasone) small (<7.5 mg) or medium doses are used ("bridge therapy") until the development of the effect of DMARDs. With high RA activity, medium or high doses are prescribed short-term (15 mg / day or more, usually 30-40 mg).
- For intravenous administration (methylprednisolone) in the form of pulse therapy (1000; 500; 250 mg). GCS is administered 1 time per day for 3 days. The recommended dose is 15-20 mg / kg of the patient’s body weight or 1000 mg / m2 of body surface per day; lower doses are administered to elderly patients. Methylprednisolone is diluted in 250 ml of isotonic sodium chloride solution or 5% glucose solution and injected over 35-45 minutes. In severe RA with extra-articular manifestations, combined pulse therapy of GCS with cyclophosphamide is recommended. Cyclophosphamide is added on the 2nd day of metipred administration (diluted in the same vial with metipred) at the rate of 15-20 mg / kg or 1000 mg / m2, administered once.
- GCS are used for intraarticular injection (diprospan, Kenalog). Perform no more than two intraarticular injections of corticosteroids in one joint during the year.
- GCS is associated with the development of many side effects that require careful monitoring and compliance with recommendations that minimize the risk of their development.

Biological therapy is carried out by drugs that affect the cellular-molecular mechanisms of the disease. Biological drugs block specific pathways and signals of the inflammatory process, have a selective damaging effect on specific target cells, minimally negatively affecting normal tissues and organs of the host.
According to the definition of the European Medicines Agency (EMA), *biotechnological drugs* are immunobiological drugs produced using genetic engineering methods of recombinant DNA technology, or the method of controlled expression of genes encoding the production of biologically active proteins, or the method of hybridization of monoclonal antibodies.

Groups of immunobiological drugs for the treatment of RA

TNF-α Inhibitors:
• infliximab (Remicade) - chimeric monoclonal antibody to TNF- *α*;
• adalimumab (Humira) - a humanized monoclonal antibody to TNF- *α*
• golimumab (Simponi) - a fully human monoclonal antibody to TNF- *α*;
• certolizumab pegol (Symzia) - pegylated Fab fragment for TNF- *α*;
• etanercept (Enbrel) - a humanized soluble receptor for TNF- *α*.
Anticytokines:
• Anakinra (Kineret) - an antagonist of IL-1 receptor;
• tocilizumab (Actemra) - humanized monoclonal antibody IgG1 to the soluble / fixed receptor IL-6;
• sarilumab (Kevzara) - a human monoclonal antibody to the IL-6 receptor.

Anti-B-cell therapy (anti-CD20) - rituximab (MabThera) - a chimeric monoclonal antibody.

Anti-T cell blocker of co-stimulation molecules CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4) - abatacept (Orencia) - monoclonal antibody to CD80 / CD86.

Indications for the appointment of the GEBD *in RA*
GEBD are prescribed for the insufficient effect of monotherapy with methotrexate or combination therapy of methotrexate with other DMARDs, which must be used in adequate doses for ≥ 3 months.

The effectiveness of immunobiological drugs. In 70-80% of patients, good disease control is achieved, in 50% of cases - clinical remission, reverse development of pathological changes in the joints.

Safety of immunobiological drugs. The purpose of the GEBD may be accompanied by:

• inhibition of anti-infection immunity (development of bacterial and fungal infections, reactivation of latent tuberculosis);

• inhibition of antitumor immunity;

• the development of allergic reactions;

• an increase in the risk of developing autoimmune syndromes and autoimmune diseases (about 50 nosological forms of autoimmune diseases have been described with the use of GEBD).

To enhance the effect of drug therapy and reduce the immunogenicity of GEBD, it is advisable to combine with methotrexate.

Inhibitors of TNF-□α

• They are the main GEBD used in the treatment of RA. TNF-□α is a pro-inflammatory cytokine produced by monocytes, macrophages, mast cells activated by T-lymphocytes. TNF-□α has the following biological effects in patients with RA: it stimulates the synthesis of IL-1, IL-6, IL-8; induces angiogenesis; promotes intensive proliferation and pannus growth; triggers an immune response that induces the transformation of b-lymphocytes into plasma cells producing immunoglobulins; induces the formation of granulocyte macrophage colony stimulating factor; promotes mast cell degranulation; stimulates the synthesis of metalloproteinases, which have a destructive effect on the intraarticular cartilage and articular surfaces of bones; activates osteoclasts that damage bone tissue.

• Used either as monotherapy or in combination with methotrexate.

• Have a fast onset of action, which is already observed within the first 2-4 weeks. The full effect of the use of TNF-□α inhibitors develops within 3-6 months.

• Contraindicated in patients with active infection, hypersensitivity to these drugs, in the presence of chronic hepatitis B.

Infliximab is a chimeric monoclonal antibody against TNF-□α, 25% consists of mouse and 75% of human IgG1. Infliximab has a high affinity for TNF-□α and forms a stable complex with both soluble and membrane-associated forms of human TNF-□α, which is accompanied by inhibition of its functional activity. Also, the effect of infliximab is associated with the activation of apoptosis of activated T-lymphocytes. Infliximab is administered intravenously once for two hours at a dosage of 3 mg / kg body weight. Then infliximab is prescribed after 2, 6 and 8 weeks, then every 8 weeks. Duration of use is set individually, depending on the indications and regimen of the therapy.

Adalimumab is a fully humanized monoclonal antibody to TNF-□α. Adalimumab can be prescribed as monotherapy, and it is also possible to prescribe a combination of adalimumab with DMARDs. Adalimumab is administered

subcutaneously in the abdomen or anterolateral thigh at a dosage of 40 mg once every 1-2 weeks.

Certolizumab pegol is a pegylated Fab fragment of a fully humanized monoclonal antibody against TNF-□α. Tsertolizumab pegol is prescribed at the beginning of therapy at a dose of 400 mg (two subcutaneous injections of 200 mg per day on the 1st, 2nd and 4th week of treatment). Then 200 mg every two weeks or 400 mg every four weeks.

*Golimuma*b is a fully human monoclonal antibody of class IgG1 to TNF-□ α. Golimumab has a high affinity for the soluble form of TNF-□α, which is 2.4 and 7.1 times higher in comparison with infliximab and adalimumab, respectively. It is used in a dosage of 50 mg once a month on the same day. In patients weighing more than 100 kg, if there is no adequate therapeutic effect after performing 3-4 injections, it is possible to increase the dosage to 100 mg per month. If the effect is also absent at a dosage of 100 mg for 12-14 weeks, then it is necessary to consider the feasibility of further use of golimumab.

Etanercept is a soluble p75 receptor for TNF-□ α, which is coupled to the Fc fragment of human IgG1 immunoglobulin. Unlike other inhibitors, TNF- α can block not only TNF-□α, but also TNF-β (lymphotoxin). Etanercept does not form strong complexes with membrane molecules and does not cause apoptosis of the corresponding cells (T-lymphocytes, macrophages) on which these molecules are located. In this regard, when using etanercept, the risk of developing pulmonary tuberculosis is significantly reduced. Etanercept in RA is administered subcutaneously at 25 mg twice a week (twice a week with an interval of 3-4 days) or 50 mg once a week. The administration of etanercept twice a week is associated with the achievement of two times higher equilibrium concentrations.

Anticytokines

Anakinra is an artificially synthesized selective IL-1 receptor antagonist. Blockade of the IL-1 receptor is accompanied by a decrease in inflammation and destruction of cartilage in rheumatoid arthritis. Anakinra is administered subcutaneously at 100 mg once a day. The duration of therapy is currently not known.

Tocilizumab is a recombinant humanized monoclonal antibody to the human IL-6 receptor. Tocilizumab is administered intravenously at a dose of 8 mg / kg 1 time per month. Each patient's dose is calculated individually depending on body weight. It is not recommended to exceed the dose of tocilizumab more than 800 mg per infusion in patients whose body weight is more than 100 kg. before administration, the drug is diluted in a solution of 0.9% sodium chloride, administered within one hour. Tocilizumab is used when there is an inadequate therapeutic effect on DMARDs, TNF - α inhibitors, or when they are intolerant.

Anti-B-cell therapy

Rituximab is a chimeric monoclonal antibody that is specific for CD20 transmembrane receptors. Rituximab refers to IgG1. Its molecule contains murine variable fragments of light and heavy chains and a human constant segment. The CD20 receptor is involved in the regulation of all stages of B-lymphocyte maturation. The mechanism of action of rituximab unfolds due to the interaction of the Fab fragment with the CD20 antigen on lymphocytes, then immunological reactions are induced with the participation of the Fc domain, which are accompanied by lysis of B cells. The administration of rituximab leads to the rapid depletion of CD20-positive B cells in peripheral blood. After 6–9 months, the number of B-lymphocytes begins to recover, returning to normal by 12 months after completion of rituximab treatment. The use of rituximab is associated with the development of persistent hypogammammaglobulinemia after repeated courses, but this does not lead to a sharp increase in the frequency of infectious complications. Rituximab is administered intravenously in a dosage of 1000 mg on days 1 and 15. Further, the infusion is repeated once every six months.

The administration of rituximab is carried out after premedication with methylprednisolone (100-250 mg methylprednisolone intravenously 30-60 minutes before the rituximab infusion) and antihistamines (chloropyramine hydrochloride 20 mg intramuscularly) to reduce the risk of developing a “cytokine release syndrome”.

Contraindication for the appointment of rituximab is the presence of a positive intradermal tuberculin test, infection with hepatitis B virus, a decrease in serum IgG, neutropenia.

Anti-T Cell Therapy

Abatacept is a protein molecule consisting of the outer domain of a cytotoxic antigen – 4 T-lymphocytes (cytotoxic T-lymphocyte-associated antigen 4 — CTLA-4) bound to an Fc-modified fragment of human IgG. Abatacept is a modulator of costimulation of the interaction of CD80 and CD86 on antigen-presenting cells with CD28 on T-lymphocytes. The binding of CTLA4-Ig to CD80 / 86 provides a negative feedback mechanism that leads to T cell deactivation. Abatacept is used to treat RA in the event of an inadequate response to therapy with TNF- α inhibitors. Abatacept is prescribed 500-1000 mg (depending on body weight) intravenously in the form of infusion for 30 minutes at the 1^{st}, 2^{nd} and 4^{th} week, and then – monthly.

Principles of GEBD treatment

- If the first TNF- α inhibitor is not effective enough, then another TNF - α inhibitor, or methotrexate, is prescribed (in patients who have not previously taken methotrexate).
- If two drugs from the group of TNF- α inhibitors were not effective enough, then they are prescribed GEBD with a different mechanism of action (abatacept, rituximab, tocilizumab).
- Abatacept, or rituximab, or tocilizumab, for patients who are resistant to standard DMARDs, can be prescribed as the first GEBD.
- In the case of resistance to abatacept, rituximab, or tocilizumab, it is possible to prescribe any GEBD or DMARDs that has not been previously used.
- Patients with RA who have rheumatoid factor and/or ACCP, extra-articular manifestations of RA, or contraindications to the appointment of TNF-□ α inhibitors the rituximab is to be prescribed better. To maintain the effect, repeated courses of rituximab should be carried out 6 better months after the previous course.
- With the development of multidrug resistance, simultaneous therapy with low doses of rituximab and TNF-α inhibitors (etanercept and adalimumab) can be used.

Prognostic markers for assessing the effectiveness of biological drugs

Currently, the concentration of a number of biomarkers is being actively studied to predict the response to GEBD therapy in RA, which contributes to its personalized choice. Thus, a high basal level of RF IgM is associated with a good response to rituximab, tocilizumab. With ACCP-positive RA, the best effects of methotrexate, abatacept, infliximab, tocilizumab, rituximab were obtained compared with ACCP-negative RA. A profile of 24 autoantibodies and cytokines was identified to predict the response to etanercept therapy in patients with RA. The efficacy of etanercept and golimumab therapy is higher in patients with high basal serum CRP; basal serum levels of C3, hyaluronic acid, IL-6, IL-8, myeloperoxidase are associated with the effectiveness of *golimumab.*

Duration of RA Therapy

• It is necessary to regularly evaluate data on disease activity:
- In patients with moderate / high degree of activity - monthly,
- In patients with persistent low activity or in remission once every 3-6 months.

• RA treatment aims to achieve remission or low disease activity. Revision of therapy should be carried out at least 1 time in 3 months.

• When RA remission is achieved, GCS is first canceled, then the dose of biological drugs is reduced with their complete cancellation, then the volume of basic therapy is reduced by titrating a dose of or DMARDs.

Prospects for the treatment of autoimmune rheumatic diseases

For the treatment of RA, *biosimilars (bio analogs, similar biological medicinal product)* are used - these are biotechnological drugs that are similar, but not identical in molecular structure to the original GEBD. They are registered after the expiration of the patent of the original drug. Biosimilars are not copies of the original biological drugs, since GEBDs contain a large molecule with a complex composition that cannot be exactly repeated. According to the definition of the World Health Organization, “a bioanalogue is a biotherapeutic product similar in quality, safety and effectiveness to a licensed “reference” biotherapeutic product.” The cost of treating 1 patient per year of GEBD is from 10 to 30 thousand dollars, while biosimilars are approximately 30% cheaper. At different stages of clinical trials, bioanalogs of infliximab, etanercept, adalimumab, rituximab are currently located. In 2013, the first bioanalog of infliximab, Flammagis, was registered in the Republic of Belarus.

New biological drugs are being developed for the treatment of autoimmune and autoinflammatory diseases. Some of new biological drugs are already used to treat psoriasis, psoric arthropathy (ustekinumab (Stelara) - an anti-IL-12 / IL-23 monoclonal antibody; secukinumab (Cosentix) - an anti-IL-17A monoclonal antibody), ankylosing spondylitis (secukinumab), youth (juvenile) arthritis, gout (kanakinumab (Ilaris) - a fully human monoclonal antibody against IL-1beta).

The development of parenteral and oral immunotherapy with antigens with the aim of inducing Foxp3 + T-regulatory cells in RA, systemic sclerosis, ulcerative colitis, type 1diabetes.

4. SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus is a chronic systemic autoimmune connective tissue disease of unknown etiology with a genetic predisposition, characterized by the hyperproduction of numerous autoantibodies to various structures of the cell nucleus and immune complexes, and the development of an immuno-inflammatory process in various organs and tissues.

* The prevalence of SLE is 4-250 cases per 100,000 population.
* Ratio of women with SLE to men: 8:1-10: 1.
* Onset of the disease at the age of 14-40 years.
* Peak incidence occurs at the age of 15-25 years.

Code according to ICD-10

* M. 32 Systemic lupus erythematosus
- M32. 0 Medicinal systemic lupus erythematosus
- M32. 1 Systemic lupus erythematosus with lesions of other organs or systems
- M32. 8 Other forms of systemic lupus erythematosus
- M32. 9 Systemic lupus erythematosus, unspecified

Etiology and immunopathogenesis of SLE

- HLA-A1, B8, HLA-DR2, HLA-DR3, etc., IG and T-cell receptor genes.
- immunological factors-violation of the regulatory mechanism and disruption of peripheral tolerance:
- genetically determined polymorphism of T-cell receptors and IgG Fc receptors (FcyRIIA);
- violation of the function of T-regulatory cells;
- violation of lymphocyte apoptosis;
- accumulation of antibodies against cell antigens, leading to the development of antibody-dependent cytotoxic reactions;
- formation of immune complexes and, as a result, the development of vasculitis;
- deficiency of early complement components-C2, C4.• Hormonal factor.
- environmental factors (UV exposure).
- microbial factors (viruses, vaccination).
- medications (hydralazine, isoniazide, procainamide).

SLE clinic

Systemic lupus erythematosus is a disease that affects many organs and systems (table 12).

Table 12-Clinical characteristics of systemic lupus erythematosus

Localization of lesions	**Symptoms**
Common manifestations of SLE	Weakness, fever, weight loss (80% of cases)
Skin and mucous membranes	Often (20-50% of cases): butterfly rash, photosensitization, chronic discoid lesions, alopecia, petechiae, finger vasculitis; less common (5-20%): ulcers on the mucous membranes and extremities, urticaria, hyperpigmentation, rarely (less than 5%) - panniculitis, itching, jaundice, periorbital edema, bullae, etc.
Musculoskeletal symptoms	Arthralgia, arthritis (90-100%), morning stiffness (50%), tendinitis, synovitis (10%), myalgia (60%), myositis (5%)
Lesion of lungs	Pleurisy (60%), intrestitial fibrosis (30%), pneumonitis, pulmonary hypertension
Cardiovascular system	Adhesive pericarditis (20%), exudative pericarditis (50%), myocarditis (15%), Libman-Sachs endocarditis (abacal), coronariitis, myocardial infarction
Gastrointestinal signs	Hepatomegelia (25%), splenomegaly (10%), gastropathies (10-20%), peritonitis (rarely), pancreatitis (rarely), mesenteric vascular thrombosis
Kidney damage	Jade (50%)
Damage to the nervous system	Migraine (40%), psychosis, convulsions (5-10%), Cerebro-vascular lesions, sensory peripheral neuropathy, cranial nerve damage, organic brain syndrome
Defeat of the hematopoietic system	Hemolytic anemia (10-20%), leukopenia and lymphopenia (50%), thrombocytopenia
Other symptoms	Sjogren's syndrome, Raynaud's phenomenon, lymphadenopathy

There are variants of the course of SLE: acute, subacute, chronic.

Acute flow is characterized by rapid onset, marked fever, polyarthritis, massive skin lesions and internal organs with the development of renal, cardiac and pulmonary insufficiency, damage to the nervous system, the development of

polyserositis, a sharp decline in body weight, the presence of polycythemia and high ESR, high immunological activity with the formation of large amounts of antibodies characteristic of SLE. With a high degree of SLE activity, *lupus crisis* can develop, which is characterized by the occurrence of functional insufficiency of organs and systems.

In the *subacute course*, there is a gradual development of SLE over several years. Initially, constitutional symptoms develop - weight loss, general weakness, a slight increase in temperature. Multiple organ failure develops 2-3 years after the onset of the disease.

Chronic course of the disease development for 5-10 years. There are one or more symptoms-mono / oligoarthritis, Raynaud's syndrome, Sjogren's syndrome, hematological changes, damage to the kidneys, nervous system, cardiovascular, respiratory system.

Diagnosis of SLE

Table 13 presents the diagnostic criteria for SLE of the American College of rheumatologists (1997), [25].

Immunological tests for the diagnosis of SLE

Determination of antinuclear antibodies. ANA are detected in SLE in the indirect immunofluorescence response to human laryngeal epithelial cell culture (IIF-HEp-2) in 95% of patients with a high titer of 1:1280 or more (in a low positive titer of 1:160 or higher in 3-5% of healthy people, and in 10-37% of those over 65 years of age).

Antibodies to double-chiral deoxyribonucleic acid (dsDNA)

- DsDNA antibodies are a highly specific marker of SLE. In other cases, ARD are detected very rarely (≤5% of cases) and in low titers.
- The detection rate of dsDNA antibodies in SLE is 70-90%, and a positive result is associated with a high risk of kidney damage. High titers of the antibody to dsDNA can be detected before the development of a detailed picture of SLE.
- Characterized by a homogeneous type of glow of the nucleus of Hep-2 cells in the detection of antinuclear factor. The norm for detecting antibodies by the IIF method (the simplest microorganism Crithidia lucilliae is used as a substrate) is < 1: 10, by the ELISA method < 10-20 IU / ml; DH-57.3%, DS-97.4%.
- Often is correlated with disease activity. Monitoring the concentration of dsDNA antibodies is important for monitoring the effectiveness of therapy for SLE (1 time every 3 months).

Table 13-Criteria of the American College of rheumatologists for the diagnosis of systemic lupus erythematosus, 1997 (abbreviated version)

Criterion	**Brief description**
Rashes in the zygomatic area	Spotty or papular rash on both cheeks and the bridge of the nose
Discoid rash	Erythematous convex spots with areas of keratosis and atrophic scars that occur primarily in open areas of the skin
Increased sensitivity to light	A rash that appears quickly when exposed to sunlight
(photosensitization)	Painless ulcers of the mouth or nasopharynx
Ulceration of the oral cavity	Arthritis (without erosions) in at least 2 peripheral joints (stiffness, swelling, effusion)
Arthritis	One of the following changes is detected: - pleurisy (pleural pain and / or pleural friction noise, and / or pleural effusion, and/or thickening of the pleural leaflets) - pericarditis (noise of pericardial friction during auscultation and / or signs of pericarditis during echocardiography).
The effusions	Stable proteinuria (>0.5 g / day) and / or cylindruria (hyaline cylinders, granular and erythrocyte conglomerates)
Impaired kidney function	Convulsions or psychoses that are not related to metabolic causes or the effects of medications
Neurological disorders	Hemolytic anemia (reticulocytosis, positive Coombs test) and / or leukopenia <4×109/l, and / or lymphopenia <1.5×109/l, and / or thrombocytopenia 100×109/l)
Hematological disorders	A positive test result for LE cells or the presence of anti-dsDNA antibodies, or anti-Sm antibodies, or a false positive reaction to syphilis
Immunological disorders	Abnormally high titer of antinuclear antibodies (ANA) in a patient who has not taken medications that can cause lupus-like syndrome
The presence of 4 of the 11 criteria simultaneously or their occurrence sequentially during observation is the basis for diagnosing SLE. *The identification of a smaller number of criteria does not exclude the diagnosis of SLE.* *To make a diagnosis, it is mandatory to identify one of the characteristic immunological markers (usually antibodies to dsDNA or anti-Sm antibodies), but it*	

is necessary to combine it with some clinical symptom of SLE.

Antibodies to the Sm (Smith) antigen

- Antibodies to Sm (Smith)-nuclear antigen - a highly specific marker of SLE, the norm for ELISA <25 U / ml; DH-8-20%; DS-99%.
- Occur in approximately 20-30% of patients with SLE. The presence of antibodies is associated with the aggressive course of SLE, Central nervous system (CNS) damage, and the development of pulmonary fibrosis of kidney damage.
- A single detection of sm-antigen antibodies is recommended, since they do not reflect the dynamics of SLE activity.

Antibodies to SS-A / Ro (Sjogren syndrome A / Robert)

- SS-A/Ro antibodies are found in the sera of 30-50% of SLE patients, 40-80% of SS patients, and 30-40% of RA patients.
- In SLE, positive test results are found in patients with photosensitization, SH, RF hyperproduction, lung damage, and lymphopenia.
- Antibodies to the SS-A/Ro antigen are found in 98% of mothers whose children suffer from congenital SLE (discoid lupus, transverse atrioventricular block, hepatitis, hemolytic anemia, thrombocytopenia). All pregnant women with suspected ARD should be tested for the presence of antibodies to SS-A / Ro-52 kDa and SS-B/La-48 kDa.

Antibodies to SS-B/La (Sjogren syndrome B/Lane)

- SS-B/La antibodies are found in 20% of SLE patients and 40-50% of SS patients. Most often observed in combination with antibodies to SS-A/Ro. The combination of antibodies occurs in 60% of patients with cross syndrome (SH+SLE).
- In SLE, SS-B/La antibodies are associated with a low incidence of kidney damage.
- During pregnancy, an increase in the level of SS-B/La antibodies serves as a prognostic marker for the development of complete transverse heart block in the fetus.

Antibodies to small nuclear ribonucleoprotein (RNP/U1-RNP)

- Occur in 30% of patients with SLE (often together with Sm antigen), in 5% of cases of SS, in 10% - with polymyositis.
- Isolated detectionof antibodies to U1-RNP in high titers is typical for MCTD (DH 95-100%, DS 98%), (see the section "Antiphospholipid syndrome").
- U1-RNP antibody detection is used to predict the adverse course of SLE with the development of severe internal organ damage.

- U1-RNP-positive mothers have a high risk of having a child with congenital lupus erythematosus syndrome.

Antibodies to phospholipids (cardiolipin, β2-glycoprotein 1, lupus anticoagulant, false positive Wasserman reaction within 6 months in the absence of syphilis) - in 1/3 of patients with SLE, markers of antiphospholipid syndrome are detected (see the section "Antiphospholipid syndrome").

Antibodies to nucleosomes are highly specific markers of SLE, drug lupus.

- The cumulative detection rate of antibodies to nucleosomes in SLE is 60-90%.
- High antibody titers to nucleosomes are characteristic only for patients with active SLE accompanied by nephritis, their level is positively correlated with indicators of disease activity.

Antibodies to histones

- In 80% of patients with SLE antibodies to histones are detected.
- These antibodies are often detected in patients with drug-induced lupus in the absence of anti-dsDNA or Sm antibodies. Simultaneous detection of anti-dsDNA, Sm-antibodies, and histone antibodies allows for differential diagnosis of SLE and drug lupus. Drug lupus syndrome is often developed when treated with phenytoin, quinidine, hydralazine, methyldopa, procainamide, isoniazide. Cancellation of the drug leads to a gradual decrease and disappearance of antibodies within 6 months.
- High-titer histone antibodies can be found in patients with systemic scleroderma and autoimmune hepatitis.

Antibodies to PCNA (proliferating cell nuclear antigen 1)

-PCNA antibodies are found in 2-5% of patients with SLE, rarely in RA. Detection in SLE is associated with kidney damage, central nervous system, and thrombocytopenia.
- In SLE with the nervous system damage, PCNA antibodies are found in isolation without dsDNA antibodies.
- Antibody content correlates with SLE activity.

Antibodies to Ribo P

- Antibodies to ribosomal protein P are highly specific for SLE, found in 10-20% of patients, often together with antibodies to Sm-antigen.
- Typical (50-80% of cases) for SLE with CNS damage (depression, lupus psychosis).

There was a correlation with skin and mucous membrane lesions in SLE (discoid rashes, photosensitization, aphthous stomatitis), and liver damage.

Antibodies to the C1q complement system protein-increased levels are associated with lupus nephritis. A decrease in C3, C4, and total complement hemolytic activity indicates SLE activity.
LE cells (lupus cells, lupus erythematodes cells – are neutrophilic white blood cells containing phagocytic homogeneous nuclear material.) and antibodies to single-chiral DNA-non-specific markers for SLE, often found in other ARD, infections, tumors, etc.

Immunological tests to assess prognosis and monitor SLE activity:

- DsDNA antibodies-often correlate with disease activity.
- Antibodies to C1q-increased levels are associated with lupus nephritis.
- The total hemolytic activity of complement may be reduced during the active period of SLE.

Diagnosis of organ pathology in SLE includes the following studies:

- General blood test.
- General urine analysis, Zimnitsky test, Rehberg test, determination of daily proteinuria.
- Biochemical blood analysis: CRP, fibrinogen, total protein and protein fractions, bilirubin, cholesterol, urea, creatinine, electrolytes.
- Coagulogram.
- Chest x-ray.
- Radiography of affected joints.
- Electrocardiography (ECG), echocardiography.
- Spirometry.
- Ultrasound of the pleural, abdominal cavities, liver, spleen, and kidneys.
- MRI or other types of brain tomography.
- Skin and muscle flap biopsy, kidney biopsy.

In 2012, SLICC (systematic Lupus International Collaborating Clinics) diagnostic criteria were proposed, consisting of 11 clinical and 6 immunological criteria (table 14).

Table 14 - Diagnostic criteria for SLE (SLICC, 2012), [14, 20]

Clinical criteria
1.Acute, active lesions of the skin
• Lupus rash on the cheekbones (discoid rashes are not taken into account)
• Bullous rashes
• Toxic epidermal necrolysis
• Maculopapular lupus rash
• Photodermatitis (in the absence of dermatomyositis)

- Subacute cutaneous lupus (non-indurative psoriaform and / or ring-shaped polycyclic lesions that resolve without scarring, sometimes post-inflammatory depigmentation or telangiectasia may remain)

2. Chronic lesions of the skin

- Classic discoid rash: localized (above the neck), generalized (above and below the neck)
- Hypertrophic (warty) skin lesions
- Panniculitis
- Mucosal lesions
- Edematous erythematous plaques on the torso
- Capillaritis (lupus erythematosus of frostbite, Gatchinson, manifested by lesions of the fingertips, ears, heel and calf areas)
- Discoid lupus erythematosus by type of lichen planus or overlap syndrome (cross syndrome)

3. Ulcers of the oral mucosa (palate, cheeks, tongue), nasal cavity (in the absence of other causes, such as vasculitis, Behcet's disease, herpes virus, inflammatory bowel diseases, spicy food, reactive arthritis)

4. Alopecia that does not lead to scar formation (diffuse hair loss or short-lived hair with visible damage), with the exception of side effects of drugs, intoxication, androgen alopecia

5. Arthritis: synovitis of two or more joints characterized by effusion and swelling or morning stiffness for more than 30 minutes

6. Serositis: pleurisy (pleural effusion or pleural friction noise) for more than 1 day; pericarditis (pericardial pain-lying down, increased when the body is lifted, pericardial effusion or pericardial friction noise, or ECG-signs of pericarditis) for more than 1 day

7. Kidney damage: persistent proteinuria more than 0.5 g / day or cylindruria (erythrocyte, tubular, granular, mixed), hematuria>5 red blood cells in p/HR

8. Central nervous system damage: convulsions, psychosis, mononeuritis/polyneuritis, myelitis, peripheral or Central neuropathy, acute impairment of consciousness

9. Hemolytic anemia

10. Leukopenia: less than 4, 0x109/l in the absence of other causes-Felty syndrome, medications, portal hypertension, lymphopenia less than 1, 0x109/l in the absence of GCS, medications, infection

11. Thrombocytopenia: less than 100 x109/l once in the absence of other known causes-medications, portal hypertension, thrombocytopenic purpura

Immunological criteria

- ANA-level above the reference values of the laboratory
- Anti-dsDNA is a level above the reference values of the laboratory

- Anti-Sm –antibodies against nuclear antigen Smith
- Positive antiphospholipid antibodies identified in any of the following cases:
- positive lupus anticoagulant test
- false positive ELISA for syphilis
- medium or high titer of lupus antibodies (IgA, IgG, or IgM)
- positive test to anti-β2-glycoprotein 1 (IgA, IgG, or IgM)
- Low complement fractions: low C 3, low C 4, low CH 50
- Positive direct Coombs reaction in the absence of hemolytic anemia

To establish a SLE diagnosis, there must be 4 criteria:

- 1st option: one clinical and one immunological (any of: antibodies to dsDNA, ANF, Sm, ACL, C3, C4);
- 2 option: nephritis, confirmed by biopsy, with the presence of ANF or dsDNA antibodies.

Determining the activity of the disease is a mandatory component when prescribing treatment. When calculating the SLE activity index, the degree of organ damage and patient's quality of life are evaluated, and the presence of concomitant diseases and side effects of immunosuppressive therapy are taken into account.

According to EULAR recommendations of (2010), validated questionnaires are used to standardize the activity of SLE:

- Systematic Lupus Erythematosus Disease Activity Index (SLEDAI), 1992;
- Systemic Lupus Activity Measure (SLAM), 1989;
- European Consensus Lupus Activity Measurement (ECLAM), 1992;
- Lupus Activity Index, (LAI) 1992;
- Classic British Isles Lupus Assessment Group Index (BILAG Classic), 1993.

The SLEDAI activity index is most often used, which includes 24 indicators (16 clinical and 8 laboratory parameters). Each attribute is assigned from 1 to 8 points, depending on its significance. The maximum number of points is 105. When evaluating activity on this index, it is necessary to note the signs of SLE that the patient had during the previous 10 days before the examination.

The following degrees of SLE activity are distinguished according to the SLEDAI activity index:

- no activity – SLEDAI score of 0;
- low level of activity-SLEDAI 1-5 points;
- the average level of activity – SLEDAI 6-10 points;
- high degree of activity-SLEDAI 11-19 points;

- very high level of activity-SLEDAI >20 points.

If the patient on the next visit on the SLEDAI activity index scores 3-12 points more than on the previous one, this indicates the presence of a moderate exacerbation, and if more than 12 points, this is regarded as a severe exacerbation.
Table 15 shows the clinical and laboratory characteristics of the degrees of SLE activity proposed by V. A. Nasonova.

Examples of diagnosis formulation

1. Systemic lupus erythematosus, acute course, grade III activity (SLEDAI 16), with skin lesions (butterfly, capillaritis, discoid lupus), joints (polyarthritis), serous membranes (bilateral pleurisy, pericarditis), heart (diffuse myocarditis, Libman-Sachs endocarditis, chronic heart failure IIA, functional class II), kidneys (diffuse glomerulonephritis, nephrotic syndrome, chronic kidney disease, C3A), the nervous system (cerebral vasculitis with epileptiform syndrome).
2. Systemic lupus erythematosus, subacute course, grade II activity (SLEDAI 8), with skin lesions ("butterfly", capillaritis), joints (arthralgia), heart (mitral valve insufficiency of grade I, chronic heart failure I, functional class I), kidneys (glomerulonephritis with minimal urinary syndrome (subclinical proteinuria), chronic kidney disease, stage C1).
3. Systemic lupus erythematosus, chronic course, activity of Ist degree, with skin lesions (discoid lupus), joints (arthralgia), Sjogren's syndrome, Raynaud's syndrome.

Table 15-Clinical and laboratory characteristics of the degrees of activity of systemic lupus erythematosus (Nasonova V. A., 1972-1986)

Indicator	**Degree of activity**		
	III	**II**	**I**
Body temperature	38°C and above	Below 38°	Normal
Losing weight	Expressed	Moderate	Minor
Skin lesion	"Butterfly" and lupus erythema, capillaries	Exudative erythema	Discoid
Polyarthritis	Acute	Subacute	Deforming, arthralgia
Pericarditis	Exudate	Dry	Adhesive
Myocarditis	Diffuse	Focal	Cardiosclerosis, myocardial dystrophy
Endocarditis	Damage to many valves	Defeat of one (usually	Mitral valve insufficiency

		mitral) valve	
Pleurisy	Exudate	Dry	Adhesive
Pneumonitis	Acute (vasculitis)	Chronic (inter-daily)	Pneumofibrosis
Jade	Nephrotic syndrome	Nephrotic syndrome or the urinary	Chronic glomerulonephritis
Nervous system	Acute encephalo-radiculoneuritis	Encephalopat	Polyneuritis
Crises (hemolytic, nephrotic, adrenal)	+	-	-
Hemoglobin, g / l	Less than 100	100-110	120 or more
ESR, mm / h	45 or more	30-40	16-20
Fibrinogen, g / l	6 or more	5	5
Albumins, %	30-35	40-45	48-60
α2-globulins, % *γ-globulins, %*	13-17 30-40	11-12 24-25	10-11 20-23
LE cells	5: 1000 white blood cells or more	(1-2): 1000 leukocytes'	Single or absent
Antinuclear antibodies, titers	1:128 and higher	1:64	1:32
Type of glow	Peripheral	Homogeneous and peripheral	Homogeneous
Antibodies to dsDNA, titers	High	Medium	Low

Treatment of SLE [5, 7, 9, 23, 25]

General recommendation

- Photoprotection: use of creams with sun protection factor SPF15 (Sun Protection Factor) or more.
- Foods high in polyunsaturated fatty acids, calcium, and vitamin D.
- Treatment of concomitant infections, vaccination.
- Refusal of smoking.
- Oral contraceptives and hormone replacement therapy are not recommended.
- Avoid stressful situations.

- Maintain a normal body weight.

Drug therapy

Therapy of SLE is performed with the use of corticosteroids, cytostatics, and biological drugs aminohinolinovogo.

There are two types of induction and maintenance therapy.

Glucocorticosteroids

- GCS prescription is mandatory in SLE.

-*Induction therapy of GCS* is carried out in different doses, the choice of which is determined by the degree of activity of SLE:

- < 10 mg / day of prednisone at low activity;
- 10-40 mg/day - with moderate activity for at least 3-4 weeks;
- 1 mg / kg / day or more-with high activity for 4-12 weeks.

- If the activity decreases, they switch to maintenance therapy of GCS, gradually reducing their dose after improving the patient's well-being and normalizing laboratory parameters. Reduce the dose by 1 mg in 7-10 days, aiming to receive 5-7, 5-10 mg/day. Treatment is long-term (many years).

- *GCS pulse therapy* is indicated for high SLE activity, severe visceral lesions, and catastrophic antiphospholipid syndrome:

- MET methylprednisolone 15-20 mg / kg (usually 500-1000 mg of methylprednisolone) is diluted in 100-250 ml of 0.9% sodium chloride solution or 5% glucose, injected intravenously for 30 minutes 3 days in a row;
- on day 2: cyclophosphamide 0.5-1.0 g / m2 intravenous drip 1 time per month for 6 months, then 1 time every 3 months for 18-24 months.

- Combination pulse therapy of corticosteroids and cytotoxic agents is the lack of effectiveness of monotherapy with high doses of corticosteroids:

- on the 2nd day of GCS pulse therapy: cyclophosphamide 0.5-1.0 g / m2 intravenously for 35-45 minutes;
- program combined pulse therapy is performed 1 time per month for 6 months according to the pulse therapy method, then 1 time every 3 months for 2 years.

Aminoquinoline drugs

Aminoquinoline drugs are prescribed to all patients with SLE, if they do not have contraindications for this therapy.

They are used for long-term use with low activity of the inflammatory process, chronic SLE, with predominant skin and joint damage. Reduce the activity of the disease, the risk of developing cardiovascular lesions, kidney lesions. They are prescribed to prevent relapses when reducing the dose of GCS or canceling

cyclosporine. In combination with antiplatelet agents, they are prescribed for the prevention of thrombotic complications.

- Hydroxychloroquine (immard) 200-400 mg/day. Hydroxychloroquine can be used for probable SLE.
- Chloroquine (delagil) 250-500 mg per day for 6-12 months.

Cytostatics

Cytostatics are prescribed in addition to GCS for progressive course, high activity of the disease (nephritis, CNS lesion, polyserositis, pneumonitis, alveolitis). Induction therapy is carried out for 3-6 months, after achieving the effect, they proceed to taking maintenance doses. One of the following drugs or a combination of them is assigned:

- Cyclophosphamide 1-2 mg /kg/day orally or intravenously at a dose of 0.5-0.75 mg/m2 for administration once every 2 weeks, or 500-1000 mg/m2 for administration once/month., or at a dose of 15 mg/kg for administration once every 2 weeks, a maintenance dose of 50-100 mg per day for a long time. It is necessary to monitor General clinical laboratory parameters 7-9 days after each intravenous injection, and 1 time every 7 days when taken orally. If the number of leukocytes in the peripheral blood is less than 2,5x109/l, platelets less than 100x109/l, increasing the concentration of ALT/AST more than 3 times from the upper limit of the norm, treatment is stopped. The appearance of signs of hemorrhagic cystitis is an absolute contraindication for continuing treatment with cyclophosphamide.
- Azathioprine 2-4 mg/kg/day, a maintenance dose of 2 mg/kg/day.
- Mycophenalate mofetil 2-3 g/day, supporting dose 1-2 g/day. It is used for moderate or high SLE activity.
- Methotrexate-7.5-15 mg / week.
- Less frequently, cyclosporine < 5mg/kg of body weight per day.

Cytostatics are used as maintenance therapy in combination with oral administration of GCS. It is prescribed for non-severe, non-renal variants of SLE with resistant skin and muscle-joint syndromes to achieve remission more quickly. The use of cytostatics allows the use of low doses of GCS.

Non-steroidal anti-inflammatory drugs with a short course are indicated for arthralgia, myalgia, and serositis. Choose NSAIDs with a low risk of complications, take into account the comorbid pathology of the patient, the presence of APS.

Anticoagulants, antiaggregants are prescribed for secondary antiphospholipid syndrome (see the section "Antiphospholipid syndrome").

Immunoglobulins for intravenous administration

Indications for use: CNS lesions, thrombocytopenia, bacterial infections, APS, decreased Ig levels in the treatment of rituximab, resistance to GCS therapy in combination with immunosuppressants with high SLE activity.

Dose: 1-2 g/kg of body weight per course, for the treatment of infectious complications-in a dose of 0.4–0.5 g/kg per course.

Biological Medicines

- Indications: uncontrolled activity of SLE (inefficiency of GCS in combination with immunosuppressants in hemorrhagic alveolitis, rapidly progressive kidney damage, Central nervous system, thrombocytopenia, and other life-threatening conditions);
- Rituximab (Mabtera) – antibodies to the CD20 receptor of B lymphocytes. Dose: 375 mg/m2 intravenous drip 1 time per week for 4 weeks, or 750mg / m2 at 2-week intervals.
- Belimumab (Benlista) - human monoclonal antibodies to BLyS (B-lymphocytic stimulator or B-cell activation factor), block the activation of B cells. The first 3 infusions (0-14-28 days) of 10 mg/kg of weight, then 10 mg/kg monthly for at least 6 months.
- Anakinra-Il-1 receptor antagonist is used for symptoms of arthritis.

Extracorporeal therapies (plasmapheresis, rarely hemosorption) are indicated for rapidly progressive glomerulonephritis, APS, generalized vasculitis with skin and internal organ damage, thrombotic thrombocytopenic purpura, and severe CNS lesions.

Synchronous intensive care: plasmapheresis + combined pulse therapy (GCS in combination with cytostatics). Plasmapheresis (3-6 procedures) is performed daily or every other day, with exfusion of 20-30 ml/kg of plasma weight. After the end of plasmapheresis, it is recommended to administer intravenous immunoglobulin in doses of 0.5-1.0 g/kg.

If there is no effect during the first 3-4 days from the beginning of synchronous intensive therapy for life-threatening CNS lesions, Rituximab is additionally prescribed 500-1000 mg weekly (the maximum total dose is 2000 mg).

Additionally, when SLE is used according to the indications:

- broad-spectrum antibiotics,
- antiviral drugs,
- anabolic hormone,
- diuretic drugs,
- antiotensin converting enzyme (ACE) inhibitors),
- peripheral vasodilators, etc.

Pregnancy in patients with SLE. You can use hydroxychloroquine, low-dose aspirin, prednisone. Methotrexate, cyclophosphamide, cyclosporine, mycophenolate mofetil have a teratogenic effect. The teratogenic effect of azathioprine in doses of no more than 2 mg/ kg is considered minimal.

Evaluation of the effectiveness of therapy in SLE. It is performed in 1 week, 1 and 3 months, then every 6 months. At any stage of treatment, the therapy should be corrected if it is ineffective and/or intolerant.

5. ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (APS) is an autoimmune disease caused by an increase in the formation of autoantibodies to phospholipid-binding proteins, which is characterized by recurrent arterial and / or venous thrombosis, and / or pregnancy pathology (habitual miscarriage, fetal death, intrauterine development delay, preeclampsia, etc.), thrombocytopenia, stroke, and other clinical symptoms.
In 1-5% of healthy people, antiphospholipid antibodies (APLA) are detected, in high titer – less than 0.2%.
The prevalence of APS is 40-50 cases per 100,000 population. APS is more common in women than in men (5:1), usually at the age of about 35 years.
During pregnancy, antiphospholipid antibodies are detected in 2-11% (on average, 5%) of healthy women. Habitual miscarriage is associated with APS in 27-42% of cases.

Classification of APS
The following forms of APS *are distinguished:*

- primary APS
- secondary APS
- catastrophic APS
- seronegative APS
- probable or prefix

Primary APS is an independent nosological form.
Secondary APS occurs in diseases accompanied by hyperproduction of autoantibodies-SLE, SS/SSD, RA, etc., malignant neoplasms, lymphoproliferative diseases, on the background of acute and chronic infections, when taking certain drugs (oral contraceptives, psychotropic drugs, etc.). Most often, APS is associated with SLE – about 30% of patients have antibodies to cardiolipin, and 25% have a lupus anticoagulant. APS in SLE may be the first manifestation of the disease in approximately 8% of patients.
The catastrophic version of APS is characterized by widespread thrombosis with damage to many internal organs, with a mortality rate of about 50%.
Seronegative APS is established in the presence of clinical manifestations associated with APS, but not included so far in the diagnostic criteria (reticular livedo, skin ulcers, thrombocytopenia, hemolytic anemia, heart valve lesions, nephropathy, cognitive disorders, etc.). Seronegativity can be explained by imperfect laboratory diagnostics, or disappearance of antibodies to phospholipids over time, or the presence of other coagulopathies.

Probable APS (or preAPS), described in 2005, is characterized by asymptomatic carriers of antiphospholipid antibodies. APS is excluded if only antiphospholipid antibodies without clinical manifestations are detected for less than 12 weeks or more than 5 years, or there are clinical manifestations of APS without antibodies to phospholipids.

ICD code 10: D68. Other blood clotting disorders.
D68. 6. Other thrombophilia. Antiphospholipid syndrome.

Etiology and pathogenesis of APS
The role of various bacterial and viral infections as the cause of APS is considered. There is a genetic predisposition to hyperproduction of antibodies to phospholipids, associated with the carrier of HLA antigens DR7, DR6, DR4, and genetic polymorphism of β2-glycoprotein I.
In APS, antibodies appear to phospholipids, which are components of the cell membranes of platelets, endothelial cells, and nervous tissue, as well as to phospholipid-binding proteins, which normally prevent excessive activation of blood clotting.

***Antiphospholipid antibodies include**:*

- *Lupus anticoagulant-antibodies* of the IgG or IgM class that can in vitro suppress phospholipid-dependent coagulation reactions by interacting with the phospholipid component of the prothrombinase activator complex. In SLE, the production of lupus anticoagulant is associated, unlike in vitro results, not with bleeding, but with a paradoxical increase in the frequency of thrombosis.

- *Antibodies to cardiolipin* – a heterogeneous population of antibodies (IgG, IgM, IgA) that react with a negatively charged phospholipid-cardiolipin, which is the main antigen of the Wasserman reaction.

- *Antibodies to β2-glycoprotein* 1-inhibit the natural anticoagulant and antiaggregant activity of β2-GP 1. β2-glycoprotein 1 acts as a cofactor (autoantigen) necessary for binding APLA to phospholipids.

- *Antibodies that react with various phospholipids, antithrombin antibodies, antiplatelet antibodies, antiendothelial antibodies, etc.*
Antiphospholipid antibodies affect the vascular, cellular and humoral components of the coagulation system, which leads to a violation of the balance between prothrombotic and antithrombotic processes and the development of

hypercoagulation. When antiphospholipid antibodies interact with phospholipids on cell membranes, systemic endothelial dysfunction and dysregulation in the hemostatic system develop, manifested by adhesion and platelet aggregation, a violation of the balance between the synthesis of the antiplatelet prostacyclin and the synthesis of thromboxane, which increases platelet aggregation. APLA reduces the activity of natural anticoagulants (protein C, S, and antithrombin III) and contributes to the development of thrombotic and immune thrombocytopenia. The basis of pathology of pregnancy in APS is thrombosis of the vessels of the placenta and trophoblast.

In the development of thrombosis in APS, additional risk factors are important: the patient has arterial hypertension, diabetes, obesity, as well as smoking, pregnancy, and surgical interventions.

The clinical picture of APS is presented in table 16.

Catastrophic antiphospholipid syndrome (CAPS) is a rare complication of APS that developed in a relatively short period of time (less than one week) due to diffuse thrombosis of small and medium vessels, and leads to acute multi – organ failure.

Infections, injuries, surgical interventions, autoimmune diseases (SLE, SSD, RA), cancer, pregnancy, the withdrawal of warfarin in APS, the use of certain drugs (vaccines, oral contraceptives, thiazide diuretics, danazol, etc.) are considered to be the provoking factors of APS. KAPS can develop in the absence of a history of antiphospholipid antibodies and clinical symptoms of APS.

Table 16-Clinical picture of antiphospholipid syndrome

Venous thrombosis	Recurrent deep vein thrombosis of the lower extremities, pulmonary embolism, small vascular thromboembolism of the lungs with the development of pulmonary hypertension; hepatic, splenic, renal, mesenteric vein thrombosis, Central adrenal vein, subclavian vein, retinal vein
Arterial thrombosis	Recurrent strokes, transient ischemic attacks, aortic arch syndrome, lesion of mesenteric arteries (intestinal ischemia), peripheral arteries (ischemia and gangrene of the lower extremities), ocular artery occlusion
Hematological manifestations	Thrombocytopenia, hemolytic anemia (positive Coombs test), Evans syndrome (combination of thrombocytopenia and hemolytic anemia), microangiopathy
Obstetric	Habitual miscarriage, recurrent spontaneous abortions,

pathology	intrauterine fetal death, late pregnancy toxicosis, preeclampsia, eclampsia, delayed fetal development, premature birth, HELLP syndrome: H-hemolysis (hemolysis), EL – elevated liver enzymes (increased activity of liver enzymes in the blood serum), LP – low level platelet (thrombocytopenia), usually occurs in the 3rd trimester of pregnancy at 33-35 weeks, in 30% of cases, develops on 1-3 days after delivery
Skin lesion	Reticulated livedo, hemorrhagic rash, hemorrhages in the subarachnoid bed, skin necrosis, chronic leg ulcers
Lesion of lungs	Pulmonary embolism, pulmonary hypertension
Heart failure	Heart valve damage, formation of intracardiac blood clots, myocardial infarction, arterial hypertension
Liver damage	Hepatic vein thrombosis (Budd-Chiari syndrome), arterial damage with the development of a liver infarction
Kidney damage	Thrombosis (stenosis) of renal arteries, infarction of kidney, vnutrikletochnyi the mikrotromboza
CNS defeat	Transient ischemic attacks, strokes, convulsive syndrome, dementia, mental disorders, less often-migraine, chorea, transverse myelitis

Clinical manifestations of CAPS:

- impaired kidney function (80%),
- acute respiratory distress syndrome and respiratory failure (25%),
- pulmonary embolism,
- acute cerebral distress syndrome (60%),
- heart lesions (50%) - reduced myocardial contractile activity (aortic and mitral insufficiency, cardiogenic shock, myocardial infarction), development of catecholamine-refractory hypotension,
- gastrointestinal thrombosis,
- DIC-syndrome (bleeding, thrombocytopenia, microthrombosis); atypical thrombosis (pancreatic, prostate, bone marrow, adrenal, spleen, etc.).

Classification criteria of KAPS (2002), [30, 34]

- Clinical manifestations of vascular occlusion of 3 or more organs and systems.
- Development of clinical manifestations simultaneously or with an interval of no more than a week.

- Histological confirmation of vascular occlusion in at least one organ.
- Serological confirmation of the presence of APA: lupus anticoagulant, and / or antibodies to cardiolipin, and / or antibodies to beta-2-glycoprotein 1.
- The diagnosis of CAPS corresponds to the presence of all four specified criteria. If the patient has only 3 of the 4 criteria, a diagnosis of probable CAPS is made.

Diagnosis of antiphospholipid syndrome

International criteria for APS have been developed, including clinical and serological features (table 17).

Antiphospholipid antibodies are a heterogeneous group of autoantibodies that recognize antigenic determinants of phospholipids, and epitopes formed during the interaction of phospholipids and phospholipid-binding proteins in blood plasma.

APLA includes: *lupus anticoagulant, antibodies to cardiolipin of IgG/IgM classes, and antibodies to β2-glycoprotein 1 of IgG/IgM classes.*

-ACLs occur in 30-40% of patients with SLE, in patients with systemic vasculitis, appear against the background of infections (HIV infection, hepatitis B and C, malaria, herpes zoster, syphilis), cancer, chronic intoxication, myocardial infarction, deep vein thrombosis, taking drugs (penicillin, procainamide, phenytoin, chlorpromazine, minocycline) , etc.

Table 17 - Diagnostic criteria for APs (2006), [29]

1. Vascular thrombosis One or more clinical episodes of arterial, venous, or small vessel thrombosis in any tissue or organ. Thrombosis must be confirmed by image reproduction or Doppler examination, or morphologically, with the exception of superficial venous thrombosis. Morphological confirmation should be provided without significant inflammation of the vascular wall. **2. Pathology of pregnancy** a) one or more cases of intrauterine death of a morphologically normal fetus after 10 weeks of gestation (normal morphological signs of the fetus are documented on ultrasound or by direct examination of the fetus) or b) one or more cases of premature birth of a morphologically normal fetus before 34 weeks of gestation due to severe preeclampsia or eclampsia, or severe placental insufficiency, or C) three or more consecutive cases of spontaneous abortions before 10 weeks of gestation (exceptions are anatomical defects of the uterus, hormonal disorders, maternal or paternal chromosomal disorders).
Laboratory criteria

- Antibodies to cardiolipin IgG or IgM detected in serum in medium or high titers at least 2 times during 12 weeks with the help of the ELISA.
- Antibodies to β2-glycoprotein 1 IgG and / or IgM isotype detected in serum in medium or high titers at least 2 times during 12 weeks with the help of the ELISA.
- Lupus anticoagulant in plasma in two or more studies with an interval of at least 12 weeks, determined according to the recommendations of the International society of thrombosis and hemostasis:

a) prolongation of plasma clotting time in phospholipid-dependent coagulological tests: activated partial thromboplastin time, kaolin test, Russell Viper venom test;
b) prolongation of blood clotting time (in screening tests) is preserved when mixed with donor plasma without platelets;
c) normalization of blood clotting time when adding phospholipids;
d) exclusion of other coagulopathies (presence of a blood coagulation factor VIII inhibitor or heparin).

Notes:
1. APS is diagnosed when there is one clinical and one serological criterion.
2. APS is excluded if antibodies to phospholipids without clinical manifestations or clinical manifestations without antibodies to phospholipids are detected for less than 12 weeks or more than 5 years.
3. The presence of congenital or acquired risk factors for thrombosis does not exclude APS. Patients should be stratified for: a) the presence of risk factors for thrombosis;
b) with no risk factors for thrombosis.

- For differential diagnosis of transient and persistent ACL products, the test (ELISA) is repeated after 6-12 weeks. In APS, IgG / IgM antibodies to cardiolipin should be detected in serum in 2 or more studies at intervals of at least 12 weeks. The result of the analysis should be evaluated together with additional laboratory data (antibodies to β2-glycoprotein 1 of IgG/IgM classes, lupus anticoagulant) and instrumental studies.
- Antibodies to β2-glycoprotein 1 are detected in primary or secondary APS (ELISA).
- Lupus anticoagulant is detected in SLE, APS, RA, multiple myeloma, ulcerative colitis, malignant tumors, after taking some drugs.

To make a diagnosis of APS, it is sufficient to have one of 3 laboratory criteria: ACL, or antibodies to β2-GP 1 of IgG/IgM classes, or VA of IgG/IgM classes.

- LA and antibodies to β2-GP 1 are more specific but less sensitive diagnostic markers of APS compared to ACL.

- For predicting the risk of thrombotic complications or obstetric pathology in APS, the most useful markers are LA, IgG ACL, and IgG to β2-GP 1.
- Recommended multiplicity of determination of LA, IgG / IgM ACL, IgG / IgM to β2-GP 1 in APS is 1 every 3-6 months.

Depending on positivity for antibodies to phospholipids, it is recommended to divide patients with APS into the following categories:

- I-detection of more than one laboratory marker (in any combination);
- IIa – only LA;
- IIb-ACL only;
- IIc-only antibodies to β2-glycoprotein 1.

There is a high and low risk of subsequent thrombosis (table 18).

Table 18-High and low risk of various antiphospholipid antibodies for subsequent thrombosis [21]

High risk Positivity for lupus anticoagulant Positivity of three types of antiphospholipid antibodies (LA + antibody to cardiolipin + antibody to β2-glycoprotein 1) Isolated constant ACL positivity at high and medium levels for systemic lupus erythematosus
Low risk Isolated periodic increase in each of the antiphospholipid antibodies at medium and low levels

Diagnosis example

1. Antiphospholipid syndrome, recurrent femoral vein thrombosis, recurrent fetal loss syndrome (intrauterine fetal death and spontaneous abortions), category I (positive anti-cardiolipin antibodies and antibodies to β2-glycoprotein 1).
2. Antiphospholipid syndrome, category I, thromboembolism of small branches of the pulmonary artery (date).
3. Probable antiphospholipid syndrome, category IIA, migraine, retinal livedo.
4. Thrombocytopenia associated with antiphospholipid antibodies, category IIA (LA, antibodies to β2-glycoprotein 1).

APS treatment

Patients with APS should exclude causes that may complicate the course of the disease:

- quitting Smoking and other bad habits,
- the decrease in body mass index,

- exclude the use of estrogens-containing contraceptive drugs,
- secondary APS requires treatment of the underlying disease,
- in the presence of arterial hypertension, it is necessary to select antihypertensive therapy.

Anticoagulants are used in APS treatment. Usually, heparins are first prescribed: unfractionated (normal), or low-molecular (most preferred), or pentasaccharides, followed by transfer to vitamin K antagonists (warfarin).
There is no universal treatment regimen for APS due to the variability in the course of APS, the severity and prevalence of thrombotic processes. General recommendations for the management of patients with APS in table 19.

Tactics of APS maintaining in women

- A history of pregnancy complications, moderate/high afla titer — low doses of aspirin (75-100 mg/day). Against the background of therapy, gestation is 50%.
- Women with APS who have a history of thrombosis in previous pregnancies are treated with low-dose aspirin before, during pregnancy, and for 6 weeks after delivery.

Table 19-Management tactics for patients with APS

Symptoms	**Management tactics**
Asymptomatic course	If the APL titer is low, follow-up is recommended, low doses of aspirin (75-100 mg/day) are prescribed for medium or high afla titers), (+ hydroxychloroquine 100-200 mg / day for secondary APS, such as SLE)
Venous thrombosis	Warfarin (INR-international normalized ratio = 2.0-3.0)
Arterial thrombosis	Warfarin (INR = 3.0-3.5)
Recurrent thrombosis	Warfarin (INR = 3.0-4.0) + low-dose aspirin (75-100 mg / day)
Catastrophic APS	Anticoagulants, GCS, intravenous immunoglobulin or plasmapheresis with replacement of a single group of freshly frozen plasma, on the background of SLE+ cyclophosphamide
Thrombocytopenia	Mild to moderate-recommended observation Heavy (less than 50x109/l) — GCS, intravenous immunoglobulin

Refractory APS	Some patients may experience recurrent thrombosis during warfarin therapy. For the treatment of refractory APS use: • direct thrombin inhibitors (dabigatran etexilate); • low molecular weight heparins (dalteparin sodium, enoxaparin sodium, nadroparin); • direct inhibitors of factor Xa (rivaroxaban, edoxaban, betrixaban, apixaban); • hydroxychloroquine; • statins (atorvastatin, rosuvastatin).

• For APL and pregnancy, a combination of low-dose aspirin and low-molecular-weight heparin is recommended: dalteparin 200 u / kg subcutaneously in 1 or 2 injections, or enoxaparin 1 mg / kg every 12 hours or 1.5 mg/kg every 24 hours, or nadroparin 171 / u/kg subcutaneously in 1 or 2 injections). Low-molecular-weight heparin is the anticoagulant of choice, since it does not pass through the placenta. It does not cause osteoporosis and thrombocytopenia in the mother, which may develop due to prolonged (≥6 months) use of unfractionated heparin. Cancellation of low-molecular-weight heparins is performed 2-3 days before cesarean section, and in the postpartum period is resumed, then switch to taking indirect anticoagulants. Warfarin is not prescribed because it penetrates the placenta and can cause fetal abnormalities or death.

In APS, warfarin, a vitamin K antagonist, is used to maintain hypocoagulation and prevent the development of thrombosis.

Each patient's dose of warfarin is selected individually depending on the level of international normalized ratio (INR). The scheme for selecting the dose of warfarin depending on the level of INR is presented in table 20.

Table 20-Warfarin dose selection Scheme (2.5 mg tablets)

Day of treatment	**Level of INR**	**Adjusting the warfarin dose**
1-2 days	Inside, 1 time a day 5 mg	
Day 3	MHO<1,5	Increase the daily dose by 1/2 tablet. Then determine the INR after 1-2 days.
	MHO=1,5-2,0	Increase the daily dose by 1/4 tablet. Then determine the INR after 1-2 days.
	MHO=2,0-3,0	Leave the daily dose unchanged. Determine the INR in 1-2 days.
	MHO=3,0-4,0	To reduce the daily dose by a quarter pill. Then determine the INR after 1-2 days.

	MHO>4,0	Skip one appointment. Then reduce the dose by ¼ tablet. Determine the INR in 1-2 days.
4-5 days	In the morning, determine the level of INR. The actions correspond to the scheme of the 3rd day. If you need more than 5 days to select a dose, the multiplicity of determining the INR dose is 1 every 2-3 days using the 3-day scheme.	

6. SYSTEMIC SCLEROSIS/SYSTEMIC SCLERODERMA

Systemic sclerosis/Systemic scleroderma – progressive systemic sclerosis, characterized by connective tissue fibrosis with lesions of the skin, blood vessels, musculoskeletal system and internal organs (lungs, heart, digestive organs, kidneys).

ICD code 10

- M 34-Systemic sclerosis
- M34. 0-Progressive systemic sclerosis
- M34. 1-CREST Syndrome
- M34. 2-Systemic sclerosis caused by drugs and chemical compounds
- M34. 8-Other forms of systemic sclerosis

Classification of systemic scleroderma

There are clinical forms of SS/SSD (table 21).

Etiology and pathogenesis

- The disease occurs mainly in women (M:F=1:4).
- There is a genetic predisposition: HLA-antigens of type B35 and Cw4.
- Inductors and triggers of systemic sclerosis:

- unknown RNA-containing virus, parvovirus B19;
- long-term professional contact with benzene, polyvinyl chloride, silicon dust, epoxy resins, toxic oils, paraffin;
- working under intense vibration conditions;
- drugs: tryptophan, bleomycin, cocaine.

In systemic scleroderma, activation of CD4+T cells that infiltrate mainly the connective tissue zone and the area around the vessels leads to the secretion of proinflammatory (IL-1, IL-6, IL-8, etc.) and fibrosis-inducing cytokines (IL-17, IL-4, IL-6). Endothelial cells and fibroblasts produce cytokines and type I and III collagen. Growth factors – platelet growth factor, TFR-β, released from platelets and lymphocytes, and tryptase, histamine, and eosinophilic cationic protein of mast cells are involved in the process of fibrogenation. Muscle fiber degeneration, perivascular lymphoplasmocytic infiltration, and interstitial fibrosis develop.

Table 21-Clinical forms of systemic scleroderma (Guseva N. G., 2008), [2]

Clinical form	**Characteristic feature**
Prescleroderma	Raynaud's syndrome, capillaroscopic changes, ANA (antibodies to topoisomerase 1-Scl-70, anticentromeric, antinucleolar)

The diffuse form	• Development of skin changes within 1 year after the appearance of Raynaud's syndrome • Involvement of the skin of the distal and proximal (above the elbow and knee joints) parts of the limbs and trunk • The presence of a symptom of the friction of the tendons • Early development intestinalnogo lung disease, oligonicella renal lesions, diffuse lesions of the gastrointestinal tract and the involvement of the myocardium • Antibodies to topoisomerase 1
A limited form	• Raynaud's symptom precedes other symptoms of the disease for many years • Skin involvement is limited to the distal parts of the extremities (distal to the elbow and knee joints) and the face • Late development of pulmonary hypertension with or without interstitial lung disease, calcifications, gastrointestinal tract damage • Expansion of the capillaries of the nail bed, usually without reduction • High frequency of anti-centromeric antibodies
Scleroderma without scleroderma (visceral form)	• Raynaud's Syndrome + • No skin tightening • Onset of the disease with pulmonary fibrosis, scleroderma renal crisis, heart damage and gastrointestinal tract • Possible detection of antinuclear antibodies, anti-Scl-70
Cross form (overlap-syndrome)	Combination of clinical signs of scleroderma and one or more ARD
Juvenile form	• Onset of illness before age 16 • The skin lesion is often the type of focal or linear (hemiform) scleroderma • Tendency to form contractures, possible abnormalities of limb development • Moderate visceral pathology according to instrumental methods
Induced SSD	Common, often diffuse skin lesions (induration),

	sometimes in combination with vascular pathology, developed after exposure to chemical and other environmental factors

There is a thickening of the intima walls, mainly vessels of the microcirculatory bed, which leads to vasculopathy: occlusion of the vascular lumen, adventitia fibrosis, thrombosis. Fibrous and vascular changes occur in the skin, gastrointestinal tract, lungs, heart, kidneys, nervous and endocrine systems, and the musculoskeletal system. This leads to thickening of the skin, violation of the functions of internal organs and heart attacks associated with vascular obliteration. At the onset of the disease, Raynaud's syndrome develops – a violation of the microcirculation of the distal parts of the limbs, accompanied by painful swelling of the fingers, often ulceration of the fingertips.
Characterized by Hyper-production of antinuclear autoantibodies.

Clinical picture of systemic scleroderma
The localization of lesions and symptoms of systemic scleroderma are presented in table 22.

Table 22-Clinical symptoms of systemic scleroderma

Localization of lesions	**Symptoms**
Skin and vascular lesions	In local skin scleroderma-morphea (ring-shaped, teardrop-shaped, linear), unlike SSD, there is no vascular spasm and damage to internal organs. In SSD-Raynaud's syndrome in 95% of patients, dense skin edema, induration, atrophy, hyperpigmentation, depigmentation, digital ulceration, telangiectasia
Defeat of the musculoskeletal system	Polyarthritis with contractures, polymyositis, calcinosis, osteolysis of the nail phalanges
Defeat of the gastrointestinal tract	In terms of the frequency of visceral lesions, it ranks first. Reduced motility of the esophagus, small intestine, colon, esophagitis, stomach ulcers, duodenitis, malabsorption syndrome, colitis
Lesion of lungs	Second place by frequency after lesions of the gastrointestinal tract. Fibrosing alveolitis, and diffuse bilateral basal pulmonary fibrosis, adhesive pleurisy, pulmonary hypertension
Heart failure	Interstitial myocarditis, cardiosclerosis with rhythm and conduction disorders, endocarditis with the

	formation of a heart defect, pericarditis
Kidney damage	Acute nephropathy (sclerodermic renal crisis), chronic nephropathy
Damage to the nervous system	Neuritis of the trigeminal nerve, carpal tunnel syndrome, polyneuritis
Defeat of the endocrine system	Hypothyroidism
Other defeats	Sjogren's syndrome, primary biliary cirrhosis, fibrosis of the cavernous arteries

The limited form of scleroderma includes *CREST syndrome (Calcinosos, Raynaud's syndrome, Esophagitis, Sclerodactyly, Teleangiectasia)* - calcinosis, Raynaud's syndrome, decreased esophageal motility, sclerodactyly, telangiectasia. Anti-centromeric antibodies are detected in 70% of patients with CREST syndrome. Patients with CREST syndrome often have primary biliary cirrhosis.
Variants of the course: acute (rapidly progressive), subacute (moderately progressive), chronic (slowly progressive).

Stages of SSD: initial (the number of localizations of lesions of organs and systems from 1 to 3), generalized (polysyndromic nature of the process), terminal (failure of one or more organs).

Evaluation of SSDS activity in accordance with the recommendations of the European group for the study of SSDS is carried out in points. An alternative option is to evaluate the degree of SSD activity according to Guseva N. G. (2004), taking into account the localization of clinical manifestations, the severity of the course and laboratory markers of inflammation (table 23). At the first initial stage of SS, treatment is most effective, at the second (generalization stage) it is reduced, and at the third (terminal) symptomatic and supportive therapy is performed.

Table 23-Degree of activity of systemic scleroderma (Guseva N. G., 2004), [3]

Degree of activity	Characteristic
Minimum (I)	• Prevalence of functional vasospastic (Raynaud's syndrome), dystrophic, and sclerotic changes of various localization in the disease picture • Usually a chronic course of the disease • ESR<20 mm / h, level of γ-globulins up to 25%
Moderate (II)	• Prevalence of proliferative changes (skin induration, indurative-proliferative polyarthritis, adhesive pleurisy,

	interstitial myocarditis, cardiosclerosis, esophagitis, duodenitis, etc.) • For acute, sub-acute or exacerbation of chronic • ESR - 20-35 mm / h, the level of γ-globulins up to 25-30%
Maximum (III)	• Fever, predominance of exudative phenomena (dense edema of the skin, capillaries, exudative polyarthritis, pneumonitis, myocarditis, duodenitis, acute sclerodermic nephropathy, etc.) • Usually acute current • ESR>35 mm / h, PSA>4 g / l fibrinogen >50 g / l, CIC>30 units, gamma globulin level >30%

Diagnostics of SSD

American rheumatological Association's clinical criteria for recognizing systemic scleroderma (1980)

• *"Large" criteria:*

-Proximal scleroderma – bilateral, symmetrical thickening, compaction, induration, sclerosis of the dermis of the fingers, skin of the extremities proximally from the metacarpal and metatarsophalangeal joints, involvement of the skin of the face, neck, chest, and abdomen.

• *"Small" criteria:*

- Sclerodactyly-induration, sclerosis, osteolysis of the terminal phalanges, deformity of the fingers of the hands.
- scars, tissue defects on the fingertips of the hands.
- basal pulmonary fibrosis on both sides.

For the diagnosis of systemic scleroderma, either one "large "or 2 "small" criteria must be present.

Laboratory and instrumental studies

- General analysis of blood, urine, biochemical analysis of blood, creatinine clearance (Rehberg test, glomerular filtration rate).
- Biopsy of the skin and muscle flap: obliterating vasculitis of small vessels, fibrotic sclerotic changes.
- Puncture biopsy of the thyroid gland: identification of morphological signs of autoimmune thyroiditis, vasculitis of small vessels, fibrous atrophy of the organ.
- Research of thyroid hormones.
- X-ray examination (for the early diagnosis of interstitial lesions of the lung - computed tomography high resolution):

- calcinates in the tissues of the end phalanges of the fingers, elbows, and knees;
- osteolysis of the distal phalanges of the fingers;
- osteoporosis, narrowing of the joint gap, sometimes ankylosis of the affected joints.
- chest - interpleural adhesions; basal, diffuse, often cystic (cellular lung) pneumofibrosis.
- chest x-Ray with esophageal contrast (act of swallowing).

- Fibrogastroduodenoscopy (FGDs).
- Study of external respiratory function (ERF).
- ECG, echocardiography.
- Capillaroscopy.
- Tests for malabsorption diagnosis: determination of fecal fat, xylose absorption, Shilling test to assess the absorption of vitamin B12, secretin test, serum carotenes, vitamin A, prothrombin time, radiography and biopsy of the small intestine, etc.

Immunodiagnosis of SSD

- Screening test for the presence of ANF positive. For differential diagnostics with other ARD, RF, dsDNA antibodies, antimitochondrial antibodies, and cryoglobulins are determined.
- In SS, the presence of sclerodermic antibodies is determined, which include *anti-centromeric antibodies (CENP-A, CENP-B, etc.), antibodies to Scl-70, and anti-nucleolar antibodies*.
- *ACA (antibodies to the CENP-B protein*) are detected in a limited form of scleroderma-CREST syndrome in 50% of patients, in systemic sclerosis-in 5-20%, in idiopathic Raynaud's syndrome in combination with arthralgias - in 20% of cases, in isolated Raynaud's syndrome - in 10%. ACA in Raynaud's syndrome is a precursor to scleroderma in a few years. In healthy individuals, they are not detected even in low titles. ACAS do not reflect the activity of the disease, it is recommended to determine them once.
- *Antibodies to Scl-70 (topoisomerase I-the main non-histone chromosomal protein)* are a serological marker of SS with proximal scleroderma and diffuse lesions of the skin and internal organs. They are present in 70% of patients with SS, 30% of patients with CREST syndrome, and 10% of patients with localized forms of scleroderma. A single detection of Scl-70 antibodies is recommended.
- *Antinucleolar antibodies - antibodies to PM-Scl, to U3-RNP (fibrillarin), to Th/To, to the family of RNA polymerases I, II, III.* They have high specificity (94-98%), but low sensitivity (12-50%).

- *Antibodies to PM-Scl100 and to PM-Scl75* are often detected (50%) in cross-syndrome (CC+PM), and may occur in idiopathic polymyositis. PM in

combination with SS is characterized by myalgia, skin lesions (periorbital edema, Gottron papules), Raynaud's syndrome, sclerodactyly, interstitial pneumonitis.
- *Antibodies to fibrillarin (U3-RNP)* are found in 5-15% of patients with SS, indicating the involvement of internal organs, the progressive course of the disease.
- *Antibodies to RNA polymerases I, II, and III* occur in isolation without antibodies to centromeres and to Scl-70 in 20% of patients with SS, CREST syndrome, and cross syndrome. Indicate a high risk of involvement of internal organs.
- *Antibodies to the Th/To antigen* are found in 5% of cases in SS. They are detected in limited skin forms of scleroderma, there is a relationship with lung damage.

- *Antibodies to the Ku / Ka antigen* are rarely detected in SS (<5%). They are a marker of a combination of scleroderma and polymyositis. There are SLE in 10-40% of patients, primary pulmonary hypertension in 20%, diffuse toxic goiter (graves ' disease) - in 30%, less often in Sjogren's syndrome, PM, RA.

SSD monitoring

- General blood, urine, biochemical blood analysis, creatinine clearance.
- Computed tomography of the lungs.
- External respiration functions.
- Echocardiography.
- Research of thyroid hormones.
- Tests for the diagnosis of malabsorption.

Diagnosis Examples

1. Systemic scleroderma, diffuse form, acute course, grade III activity, stage III, with skin lesions (swelling and induration of the skin of the trunk, shoulder girdle, sclerodactyly), joints (polyarthritis, functional insufficiency II), blood vessels (Raynaud's syndrome, telangiectasia), lungs (interstitial pneumonia, II), gastrointestinal tract (esophagitis, duodenitis), nervous system (polyneuropathy).
2. Systemic scleroderma, diffuse form, subacute course, grade II activity, stage II, with skin lesions (sclerodactyly, "pouch" mouth), blood vessels (Raynaud's syndrome), lungs (diffuse pneumosclerosis, respiratory failure I), gastrointestinal tract (esophagitis, stomach ulcers), Sjogren's syndrome.
3. Systemic scleroderma, limited form, chronic course, activity of the first degree, stage I, with skin lesions (edema and induration of the hands), blood vessels (Raynaud's syndrome).

The treatment of SSD

- Anti-fibrosis therapy. D-penicillamine (penicillamine, cuprenil) - 500-1000 mg/day for 6-12 months, then gradually reduce to 250-500 mg/day, take for a long time (2-5 years); lidase, ronidase, dimexid, colchicine, unitiol.

- GCS. Prednisone 15-20 mg/day in acute, subacute course, exacerbation of the chronic course of SSD. When the clinical effect is achieved, the dose of GCS is reduced to the maintenance dose (5-10 mg/day). The course of treatment is long in acute and subacute course, in chronic form-short (1-2 months). In the presence of fibrosis of various organs, GCS is combined with D-penicillamine and cyclophosphamide.
- Immunosuppressants. Methotrexate 15 mg / week, or cyclosporine 2-3 mg / kg / day; or cyclophosphamide in the pulse therapy scheme, or aminoquinoline drugs (chloroquine, plakvenil).
- Immunoglobulins for intravenous administration in the active course, the addition of severe infections in a dose of 0.4-2G/kg / day for 2-5 days daily, then monthly.
- NSAIDs are prescribed to relief the joint syndrome, muscle pain: selective COX-2 inhibitors (meloxicam, nimesulid); in the absence of gastrointestinal pathology-non-selective Cox-1 and COX-2 inhibitors.
- Vasodilator therapy:

- calcium antagonists (dihydropyridine-nifedipine group; nifedipine 30-60 mg/day, or amlodipine 5-10 mg/day inside), with poor tolerance-benzodiazepine group);
- angiotensin converting enzyme inhibitors (captopril, enalapril, ramipril, perindopril, spirapril, lisinopril);
- prostaglandin E1 (alprostadil);
- the prostacyclin (iloprost, beraprost, epoprostenol);
- endothelina receptor antagonists (bosentan, sitaxentan);
- phosphodiesterase type 5 inhibitors (sildenafil);
- antiplatelet agents (acetylsalicylic acid, dipyridamole);
- angioprotectors (emoxipin).

- Antioxidant therapy (Actovegin, N-acetylcysteine).
- Extracorporeal treatment methods.
- Physiotherapy (electro -, heat -, balneo -, ultrasound -, laser therapy courses number 7-10 sessions), massage.

Differential treatment of lesions in SSD

- Raynaud's syndrome-prostaglandins, calcium antagonists, prostacyclines, if ineffective – finger sympathectomy.
- Skin lesions in diffuse SSD-methotrexate.
- Interstitial lung disease – penicillamine, cyclophosphamide, corticosteroids.
- Pulmonary arterial hypertension-prostacyclines (iloprost, beroprost, epoprostenol), endothelin I receptor antagonists (bosentan, syntaxentan), type V phosphodiesterase inhibitor (sildenafil), anticoagulants.

- Renal crisis – ACE inhibitors, slow calcium channel blockers, prostacyclin, an antagonist of transforming growth factor beta (pirfenidone); hemodialysis in the progression of renal failure.
- Gastrointestinal disorders-procinetics, proton pump inhibitors, rotating antibiotics, pancreatic enzymes, nutritional support, surgical treatment for esophageal strictures, fecal incontinence.

7. DERMATOMYOSITIS, POLYMYOSITIS

Dermatomyositis or polymyositis (DM/PM) belongs to a group of autoimmune inflammatory myopathies, the main manifestation of which is progressive muscle weakness of the proximal extremities associated with inflammation of the striated muscles, skin, small vessels, and replacement of affected tissues with fibrous structures.

Classification of inflammatory myopathies [16]

- Primary idiopathic polymyositis
- Primary idiopathic dermatomyositis (polymyositis with skin lesions)
- Juvenile polymyositis/dermatomyositis.
- Myositis, combined with MCTD (cross syndrome, frequency is 20%)
- Myositis, combined with malignant tumors (20-30%)
- Myositis with intracellular inclusions (15-28%)
- Rare forms of inflammatory myopathies (granulomatous, eosinophilic, myositis in vasculitis, focal (nodular), orbital)

DM/PM is most common among myopathies.

ICD code 10: M33-Dermatopolymiositis; M33. 2-Polymyositis.

Epidemiology, pathogenesis

The peak incidence is 45-60 years. Women get sick 2 times more often in myositis, combined with cancer, and 5 times more often in childbearing age.

- Infiltration of the muscle with CD4-lymphocytes, B-lymphocytes, macrophages, activation of complement and, as a result, vascular damage (vasculopathy) of the muscles in DM. tissue Ischemia leads to necrosis of perivascular muscle fibers.
- Due to a genetic predisposition or as a result of exposure to an unknown factor, HLA class I antigens are expressed on the surface of muscle fibers. The result of this abnormal expression is infiltration of the muscle by cytotoxic CD8 lymphocytes, their secretion of perforins, and necrosis of the muscle fiber in PM.
- In the later stages of DM / PM, muscle fibrillation, fibrosis, and adipose tissue replacement develop.

The clinical picture of PM/DM is shown in table 24.

Table 24 - Clinical symptoms of PM/DM

Symptoms	**Signs**
Common	Weakness, weight loss, fever (40%), Raynaud's syndrome
Myositis	Muscle weakness of the proximal muscles of the lower extremities (thighs), pelvic girdle, neck muscles, shoulders, trunk; shortness of breath - with weakness of the intercostal muscles and the diaphragm Myalgia (50%), muscle pain on palpation Muscle atrophy, contractures
Skin lesion	Heliotropic rash (30-60% of cases) - purple staining of the skin of the periorbital zone, often with edema Macular spots (Gottron sign) or erythematous papules or plaques on the skin of the extensor surface of the hands, elbow and knee joints (gottron papules) - 80% V-syndrome-macular rashes at the base of the neck and a "shawl" symptom on the back of the neck and shoulders Rarely in juvenile DM, skin vasculitis, ulceration Peeling and cracking of the skin of fingers and palms ("mechanic's hand»)
Injuries of the musculoskeletal system	Arthropathy (remember RA), strain, calcification of subcutaneous or connective tissue in the areas of microtraumatic
Lesion of lungs	Interstitial fibrosis (20%), aspiration pneumonia, respiratory failure, rarely-pulmonary vasculitis, pulmonary hypertension, hypersensitive pneumonitis, opportunistic infections
Heart lesions	Cardiomyopathy (5%), pericarditis (20%), blockages and arrhythmias
Lesions of the gastrointestinal tract	Dysphagia (30%), dysfunction of striated muscle tissue, cricopharyngeal dysfunction, lower esophageal dysfunction, impaired motility of the stomach and intestines
Kidney damage	Proteinuria, nephrotic syndrome, myoglobulinuria (very rare)
Tumors	High risk in men over 45 years of age with DM without autoantibodies In 15% of patients with DM, in 9% - with PM

Diagnostics and monitoring of DM / PM

- General analysis of blood and urine.
- Biochemical blood analysis: bilirubin, AST, ALT, creatine phosphokinase (CPK), MB fraction of CPK, glucose, total protein, CRP, creatinine, urea, electrolytes;
- Serum myoglobin, myoglobin in the urine.

- External respiration functions
- Computed tomography – cancer search, diagnosis of interstitial lung diseases.
- MRI muscles.
- Electromyography.
- Muscle biopsy.
- Additional research methods for the diagnosis of cancer: examination of the rectum, prostate-specific antigen in men, fecal examination for hidden blood; smear from the cervix, mammography, pelvic ultrasound, CA-125 in women-ovarian tumor antigen.
- Immunological diagnostics of inflammatory myopathies includes determination of ANA, myositis-specific antibodies to extracted nuclear antigens-Jo-1, RNP, Mi-2, etc.

  - Myositis-specific antibodies-a group of autoantibodies (to tRNA synthetases (Jo-1, PL-7, PL-12, EJ, OJ), to the Mi-2 protein, to the SRP-signal recognition particle) detected in 40% of inflammatory myopathies.

  - Antisynthetase antibodies are found in 20-30% of patients with PM/DM and are markers of antisynthetase syndrome, a form of myositis. It is characterized by the presence of anti-Jo-1 antibodies directed to histidyl-tRNA synthetase. Clinical manifestations of antisynthetase syndrome are interstitial lung disease, arthritis, Raynaud's disease, skin manifestations, fever and muscle weakness, and low effectiveness of immunosuppressive therapy.

  - Antibodies to the Mi-2 protein are found in DM in 10% of patients, characterized by a favorable course of the disease.

  - Antibodies to the SRP signal-recognizing particle are detected in 3% of cases in PM, and have a severe course with damage to the myocardium and respiratory muscles.

  - In 20-30% of patients with cross syndrome (PM+SS). Myositis-associated antibodies are detected - antibodies to PM-Scl, U1-RNP, SS-A.

- **Monitoring of indicators for DM/PM**: General blood test, creatinine, electrolytes, MRI (muscle).

International criteria for diagnosing DM/PM [17]

1. Skin lesions: heliotropic rash, a sign of Gottron, erythema on the skin of the extensor surface of the elbow and knee joints.
2. Proximal muscle weakness of the upper and lower extremities.
3. Myalgia or muscle pain on palpation.
4. Increased activity of CPK and / or aldolase in blood serum.
5. Myogenic changes on the electromyogram (short polyphase potentials with spontaneous fibrillation potentials).

6. Antibodies to histidyl-tRNA synthetase-ajo-1 (detected in 50% of patients, other antisynthetic antibodies-in 5%).
7. Non-destructive arthritis or arthralgia.
8. Signs of systemic inflammation: body temperature above 370C, increase in CRP or ESR more than 20 mm / hour.
9. Morphological examination of the skin-muscle flap: infiltrates in skeletal muscles with degeneration or necrosis of fibers, active phagocytosis or signs of active regeneration.

The presence of at least one type of skin lesion and at least 4 signs from 2 to 9 p. correspond to the diagnosis of DM (DH-94.1%, DS-90.3%).

The presence of 4 or more signs of 2-9 points correspond to PM (DH-98.9%, DS-95.2%).

Diagnosis examples

1. Idiopathic dermatomyositis, acute course, grade 3 activity with muscle damage (proximal myositis), skin (paraorbital edema, Gottron syndrome in the metacarpophalangeal and proximal interphalangeal joints, neck erythema), heart damage (myocarditis with rhythm and conduction disorders by type of atrial fibrillation, H2A, 2 functional class by NYHA (classification of chronic heart failure of the new York cardiological Association), lesions of the lungs (pneumonitis, DN II), the nervous system (polyneuropathy), joints (polyarthritis, functional class II).

2. Idiopathic dermatomyositis, chronic course, activity of 1 degree with damage to the joints (polyarthralgia, functional class I), lungs (fibrotic alveolitis, respiratory failure II).

3. Paraneoplastic polymyositis against the background of bladder cancer, subacute course, activity of the 1st degree with damage to the muscles of the upper and lower extremities, pharyngeal muscles, diaphragm, and skin (Gottron syndrome in the metacarpophalangeal joints).

Treatment of PM/DM

- First – line GCS: prednisone at a dose of 1 mg/kg/day, if there is no effect for 4 weeks-2 mg/kg/day; treatment for 2-3 months or more until clinical effect is achieved. Reduce by ¼ tablet in 30 days.
- Immunosuppressants in combination with GCS: methotrexate 7.5-15 mg/week or cyclosporine 2.5-3.5 mg/kg/day, or azathioprine 2-3 mg/kg/day, or mycophenolate mofetil 1g /day.
- Combined pulse therapy for progressive lung damage: GCS 1g/day +cyclophosphamide 2 mg/kg/day.

- Aminoquinoline compounds: plakvenil 200-400 mg/day (for skin manifestations of DM).
- Immunoglobulin for intravenous administration (for refractory course).
- Rituximab, infliximab (effectiveness is being studied).
- Plasmapheresis (4-5 procedures for severe, refractory to therapy).
- NSAIDs (for muscle and joint pain).
- Improvement of muscle metabolism (retabolil, Riboxin, ATP).
- Treatment of calcification (disodium salt of ethylenediaminetetraacetic acid, colchicine).
- Physical therapy, massage, physiotherapy.

8. MIXED CONNECTIVE TISSUE DISEASE

Mixed connective tissue disease (MCTD), or Sharpe's syndrome is characterized by the presence of symptoms of various autoimmune diseases - SLE, scleroderma, PM/DM, RA, Sjogren's syndrome. It has a more favorable course and forecast in comparison with other ARD. To date, there is no clear answer as to whether the SPST is an independent nosological form or a variant of a single disease in a group of autoimmune systemic connective tissue diseases.

Code according to ICD-10:
M. 35 Other systemic connective tissue lesions.
M 35.1 Other cross syndromes. Mixed connective tissue disease.

Etiology and pathogenesis. Mostly women get sick, the peak of the incidence is observed in 20-30 years. The role of infectious antigens and genetic predisposition is assumed in the occurrence of MCTD.
Immune inflammation develops in blood vessels and tissues, mediated by the formation of anti-nuclear antibodies, mainly to the nuclear antigen-ribonucleoprotein U1-RNP, as well as hypergammaglobulinemia, hypocomplementemia, and an increased content of circulating immune complexes.

Clinical symptoms

- More often reminds SLE, SSD, PM.
- Skin lesions: scleroderma-like changes-mild swelling of the hands-in 88%, rare therapeutic induration, skin atrophy and flexor contractures; telangiectasia, erythematous and Hypo - or hyperpigmented spots, discoid lupus, alopecia, periorbital pigmentation.
- Arthritis (erosive in 30%) and arthralgia in 96%.
- Raynaud's syndrome-in 84%, is an early symptom, but less pronounced than in MCTD.
- Myositis (myalgia, muscle weakness mainly in the proximal extremities, increased CPK, aldolase, AST) - in 72%
- Enlarged lymph nodes - in 68%.
- Fever, serositis (effusion pericarditis, pleurisy), hepatosplenomegaly-in 20-33%.
- In 75% of cases, lung damage develops (diffuse fibrosis with impaired restrictive function and pulmonary hypertension), or esophageal hypokinesia.
- Secondary Sjogren syndrome - in 50%.
- Kidney damage (glomerulonephritis) is rare-in 10%.
- Polyneuropathy, often a lesion of the trigeminal nerve.

MCTD diagnosis

- Presence of characteristic clinical symptoms of SS, SLE, and PM that appear simultaneously or sequentially.
- High antibody titer to the soluble nuclear antigen - ribonucleoprotein U1-RNP (more than 1:100,000) is detected in 100% of cases, high titer of ANA (more than 1:1000) of speckled glow type. Anti-nuclear antibodies to other soluble nuclear antigens (anti-dsDNA, Scl-70, Ro, La) are negative, and RF antibodies to nucleosomes can be detected.
- There is an increase in ESR and CRP, hypergammaglobulinemia, hypocomplementemia, and an increased content of circulating immune complexes.
- The presence of signs of myositis, kidney and lung damage requires CT, MRI, electromyography, and muscle biopsy.

Diagnostic criteria for MCTD [27]

- *Serological criteria:* high (>1:2000) antibody titers to the nuclear ribonucleoprotein-U1-RNP antigen (DH: 95-100%, DS: 98%).
- *Clinical criteria:*

  2A-Raynaud's syndrome;
  2B-synovitis;
  2C-myositis;
  2D - swelling of the fingers.

To make a diagnosis of MCTD, you must have a serological criterion, criteria 2A and 2-3 criteria from 2b to 2d (DS-62.5%; DS-86.2%).

Diagnosis examples

1. Mixed connective tissue disease: Raynaud's syndrome, swelling of the skin of the hands, esophagitis, myopathy, exudative pleurisy, pericarditis.
2. Mixed connective tissue disease: Raynaud's syndrome, myalgia, arthralgia, antiU1-RNP (titer).

MCTD treatment

• In the *mild form* of the disease - NSAIDs and aminoquinoline drugs, in some cases - low doses of GCS (prednisone at a dose of 5-15 mg per day).

• In a *moderately severe* and *severe* form of MCTD, prednisone is prescribed at a dose of 1 mg/kg / day orally, then the dose is gradually reduced to a maintenance dose (5-10 mg/day).

• The use of immunosuppressants (cyclophosamide, azathioprine, methotrexate) or the appointment of combination therapy with corticosteroids and immunosuppressants is possible.

• If signs of myositis or systemic scleroderma appear, they should be treated accordingly.

The ten-year survival rate is 80%. The main causes of death are pulmonary hypertension, renal failure, myocardial infarction.

Cross-forms of systemic connective tissue diseases

The term *"cross-sectional forms of MCTD - cross syndrome"* is used when a patient has two or more systemic connective tissue diseases. The most common are: SS and DM / PM, SS and RA, SLE and RA, SLE and PM, RA and PM, RA and systemic vasculitis.

Diagnosis is based on the identification of clinical, laboratory, immunological and other diagnostic criteria for both diseases. Treatment is determined by the predominance of the symptoms of one of the diseases, the activity and prognosis of its course.

9. Sjögren’s syndrome

Sjögren’s syndrome is an autoimmune systemic inflammatory disease of unknown etiology, in which exocrine glands are affected and other organs are involved.
Distinguish between primary and secondary secondary school.
Primary secondary or Sjogren’s disease is an independent noslogic form.
Sjogren's syndrome (secondary Sjogren's syndrome in foreign literature) develops in about 30% of cases with ARD (RA, SLE, SSD, PM / DM, MCTD), as well as with Hashimoto's thyroiditis, primary biliary cirrhosis, chronic autoimmune hepatitis.
The incidence of secondary infections ranges from 4 to 250 cases per 100,000 population, most often between the ages of 35-50. The ratio of women to men with secondary school is 8-10 / 1.

ICD-10 code: M 35.0 - dry syndrome (Sjogren)

Etiology, pathogenesis
The relationship of the disease with HLA antigens DR3, DQ1, DQ2, B8 and others was revealed. Viral infections (herpes viruses, retroviruses, cytomegaloviuses), dysregulation of the immune response, and imbalance of sex hormones (androgens/estrogens) are important in *Sjögren’s syndrome* development. There is lymphocytic infiltration of exocrine glands - lacrimal, salivary and others, the result of which is their inflammation and destruction. T-lymphocytes, infiltrating glandular tissue, produce pro-inflammatory cytokines (IL-1, IL-2, IL-6, IFN-γ, etc.), activate B-cells. In turn, polyclonal B-cell activation is accompanied by the synthesis of autoantibodies against Ro (SS-A) and La (SS-B), RF, antinuclear antibodies antigens. The proliferation of cells of the exocrine gland ducts, obstruction of their ducts occurs, in the future - atrophy of the glands and a pronounced violation of their function. There is dryness of the mucous membranes of the eye, oral cavity, gastrointestinal tract, etc., a third of patients develop extragranular lesions of internal organs (arthritis, Raynaud's syndrome, lymphadenopathy, interstitial pneumonia, etc.).

Clinical symptoms of SS associated with glandular lesions

- Due to a decrease in production of tears and mucins, changes in the quality of the tear fluid (the content of lysozyme, lactoferrin, secretory IgA, etc. decreases), *dry keratoconjunctivitis* develops. The patient is concerned about dry eyes - xerophthalmia (dry eye syndrome), sensations of "sand" in the eyes, photophobia, pain and burning in the eye area, the appearance of discharge in the form of long

mucous filaments. With the development of keratitis, vision deteriorates, ulcers and perforation of the cornea develop.

- Damage to the salivary glands - *chronic sialadenitis*, accompanied by a decrease in salivation (xerostomia), impaired chewing, swallowing, formation of calculi of the salivary ducts, and decrease in the perception of smell and taste. The parotid salivary glands, sublingual, small salivary, submandibular glands are affected. A characteristic sign of the disease is recurrent mumps. Approximately 30% of patients have an increase and slight pain on palpation of the parotid/submandibular salivary glands, which have a dense texture and a smooth contour. Violation of the qualitative composition of saliva leads to a decrease in local anti-infection protection of the mucous membranes of the oral cavity and lips, the development of recurrent aphthous/fungal stomatitis, multiple caries, cheilitis.
- Dry skin and mucous membranes of another location might be developed - the nose, larynx, pharynx (dry subatrophic/atrophic rhinopharyngolaryngitis), bronchi, vulva and vagina, the occurrence of chronic arthrophic gastritis with secretory insufficiency, chronic pancreatitis.
- In Sjögren's disease, three main symptoms are detected: parenchymal sialadenitis with xerostomia, dry keratoconjunctivitis, and morphological changes in the small salivary glands.
- In Sjögren's syndrome, one, two, or three symptoms may be present at the same time (sialodenitis, dry keratoconjunctivitis, arthritis/arthralgia, lymphocytic infiltration of exocrine glands).

Clinical out-of-body (systemic) manifestations of Sjogren's Syndrome

• Weakness, fatigue, fever, often associated with exacerbations of mumps.

• Arthralgia occurs in approximately 70% of patients, and in 33% of patients - arthritis with localization, as in RA, but without erosion.

• Raynaud's syndrome is often detected.

• Generalized lymphadenopathy.

• Interstitial pneumonia, alveolar pulmonary fibrosis.

• Biliary damage to the liver, pancreas.

• A third of patients have vasculitis (lymphocytic, leukocytoclastic) with damage to the skin and mucous membranes, peripheral nerves, central nervous system, and kidneys.

• Kidney damage - interstitial nephritis, tubular acidosis, the formation of calculi in the kidneys.

• Perhaps the development of pseudolymph (accumulation of lymphoid cells without histological signs of malignancy), malignant lymphomas, Waldenstrom macroglobulinemia. The likelihood of developing non-Hodgkin lymphomas in SS is 40 times higher than in healthy people.

Diagnosis of Sjogren's syndrome [13]

Tests that determine the level of secretion of the lacrimal glands. The function of the lacrimal glands can be assessed by the Schirmer test: the degree of wetting of a strip of filter paper placed on the lower eyelid is determined in 5 minutes. Normally, the wetting is 15 mm, while the SS is less than 10 mm.

A more highly specific test is eye staining when instilling a 0.1% solution of fluorescein or lissamine green. Determine the time of rupture of the fluorescent film by the appearance of a "dry spot" after the last blink. Normally, it is 10 seconds, while the time indicator is significantly reduced.

Ophthalmoscopy at different stages of SS reveals dystrophy of the conjunctival and corneal epithelium of the I-III degree, filamentous keratitis, corneal xerosis, and corneal ulcer.

Tests that determine the level of salivary gland secretion. Sialometry is used to objectify the degree of xerostomia. When the salivary glands are affected, the unstimulated saliva flow is less than ≤1.5 ml for 15 minutes, the stimulated (lemon juice, 5% ascorbic acid, 40% ethyl alcohol) saliva secretion is also reduced - <2.5 ml/5 min.

Sialography - examination of the salivary gland ducts with x-ray contrast material allows detecting the expansion of the ductal system. Cavities >1 mm in diameter are found, which is typical for parenchymal mumps.

Salivary gland scintigraphy reflects the rate of saliva release by determining the capture and secretion of the radioactive technetium nuclide (Tc99) within 60 minutes after its intravenous administration.

Ultrasound and MRI of the salivary glands allow us to assess the structure, size of the glands, localization and degree of gland damage.

Presence of autoantibodies

Antibodies to the Ro nuclear antigen (SS-A) or to La (SS-B) are detected in 85-100% of patients with SS: simultaneously, both antigens are detected in 40-50% of cases, to one Ro antigen (SS-A) - much more often than to La (SS-B).

Antibodies to the Ro antigen (SS-A) have limited sensitivity and specificity, they are found in other ARD, whereas to the La antigen (SS-B) they are more specific for SS.

The antibody titer to the soluble nuclear antigens Ro (SS-A) and La (SS-B) does not reflect the activity of the pathological process.

ANA and RF are determined in 95-100% of patients. High RF numbers are typical for patients with cryoglobulinemic vasculitis and morphological signs of MALT-tissue formation (mucosa-associated lymphoid tissue) in the salivary/lacrimal glands and lungs. MALT lymphomas are the most common form of non-Hodgkin's

lymphoma in Sjogren's disease. Cryoglobulins are detected in a third of patients with SS, while there is no link between the disease and hepatitis b and C viruses.

Other laboratory indicators. In 50% of cases, antithyroid antibodies are detected, and hypothyroidism often develops. In 70% of cases, there is an increase in ESR, total protein, hypergammaglobulinemia (due to an increase in IgG and IgA, less often IgM). Monoclonal secretion of immunoglobulins (more often IgM) is detected in 20%, while in half of cases non-Hodgkin's lymphomas are diagnosed. In 33% of cases, anemia is detected, in 25% - leukopenia.

A biopsy of salivary glands. In complex diagnostic cases, a salivary gland biopsy is performed, revealing characteristic histological changes – lymphohistioplasmocytic infiltration, multiple large clusters of lymphocytes (often follicle-like) with acinus atrophy.

European-American criteria for SS diagnosis [12]

- *Eye* symptoms (1 of 3):
- dry eyes for more than 3 months;
- feeling of a foreign body in the eyes;
- using artificial tears more than three times a day.

- *Oral symptoms (1 of 3):*

- dry mouth for more than 3 months;
- swelling of the salivary glands;
- the need to wet the mouth.

- *Eye tests (1 of 2):*

- unstimulated Schirmer test <5 mm/5 min;
- vitally colored spots on the cornea.

- Positive labial biopsy (number of foci >1 in 4 mm2).

- *Oral tests (1 of 3):*

- unstimulated salivary secretion <0.1 ml / min;
- deviation from the norm on the sialogram of the parotid salivary gland and the salivary Scintigram.
- Positive Ro (SSA) and/or La(SSB) antibodies are detected during immunological blood tests.

Classification criteria for Sjogren's syndrome (Sjogren's International Collaborative Clinical Alliance [13]

- Presence of anti-SS-A/Ro and/or anti-SS-B/La anti-nuclear antibodies or positive RF and ANF.

- Focal lymphocytic infiltration is detected in the biopsy of small salivary glands – ≥1 focus in 4 mm2 (focus is a cluster of at least 50 lymphoid cells in 4 mm2 of the surface of the salivary gland, the average focus is estimated for 4 small salivary glands).
- Dry keratoconjunctivitis - ≥3 points on the scale of color of the eye epithelium with fluorescein and lissamine green (exclude the use of anti-glaucoma eye drops that inhibit the production of intraocular fluid, corneal surgery and blepharoplasty).
The disease can be classified as *Sjogren's syndrome if two of the three criteria points are met*, excluding head and neck radiation, hepatitis C, HIV infection, sarcoidosis, amyloidosis, IgG4-related disease, RA, SLE, SSD, and other autoimmune diseases.

Diagnosis Examples

1. Sjogren disease, acute period, severe stage, the activity of III degree, with the defeat of the salivary glands hypofunction III degree (Cialdini, xerostomia, grade II stomatitis, cervical caries with loss of teeth), with damage to the lacrimal glands with hyponatremia III degree, the eyes (dry keratoconjunctivitis, corneal dystrophy II degree), joints (non-erosive arthritis, functional class II), gastrointestinal tract (atrophic gastritis, pancreatic insufficiency), generalized lymphadenopathy.
2. Sjogren's disease, subacute course, grade II activity with lesions of the salivary glands (bilateral mumps, paradontosis, cervical caries with tooth loss), lacrimal glands (dry keratoconjunctivitis), joints (polyarthritis, functional class II), with vascular lesions (Raynaud's syndrome), and the gastrointestinal tract (atrophic gastritis).
3. Sjogren's disease, chronic course, initial stage, activity of I degree, with damage to the salivary glands with hypofunction of I degree, (stomatitis), with damage to the lacrimal glands with hypolacrimia of I degree, eyes (dry keratoconjunctivitis), joints (polyarthralgia, functional class I).

Treatment of Sjogren's syndrome

General recommendation. Avoid factors that lead to dryness of the mucous membranes of the eye and mouth (air conditioning, cigarette smoke, strong wind, prolonged visual, speech or psycho-emotional load), alcohol consumption, Smoking, taking drugs that reduce salivation (antidepressants, antihistamines, anticholinergics).
If the oral mucosa is dry, it is recommended to drink the liquid in small sips and chew sugar-free chewing gums. Careful oral hygiene and regular dental supervision are necessary.

Treatment of dry keratoconjunctivitis

- Artificial tears containing 0.1-0.4% sodium hyaluronate, 0.5-1% hydroxypropylmethylcellulose, 0.5-1% carboxymethylcellulose, 0.1-3% dextran 70, apply 3-4 or more times a day.
- Eye drops are recommended on the basis of blood serum of cattle (of Adgelon). Assign 1-2 drops to the conjunctival SAC 3-6 times a day for 14 days. Drainage of the lacrimal ducts is performed.
- The use of NSAIDs (0.1% indomethacin, 0.1% diclofenac) reduces discomfort in the eyes, but may provoke corneal damage.
- Drugs that increase the amount of mucin-like substances and lacrimal fluid – 2% ophthalmic emulsion of rebamipid, 2% solution of dikvafozol-an agonist of purine P2Y2 receptors.
- Cyclosporine-0.05% eye drops 2 times a day for 6-12 months.
- GCS in low doses in short courses (up to two weeks) with exacerbation of dry keratoconjunctivitis.

In case of dryness of the mucous membrane of the oral cavity is recommended:

- Use of artificial saliva substitutes based on mucin and carboxymethylcellulose in the form of mouthwash.
- Cholinergic drugs-pilocarpine (inside 5 mg 3-4 times a day) or cevimelin hydrochloride 30 mg 3 times a day to stimulate salivation. Contraindicated in bronchospasm and angle-closure glaucoma.
- Warm compresses, analgesics, and NSAIDs are used to relieve pain caused by swelling of the salivary gland.
- When infection develops, local and systemic antifungal treatment (nystatin, clotrimazole, fluconazole), and antibacterial therapy are indicated.

If the *upper respiratory tract is dry* (rhinitis, sinusitis, laryngitis, bronchitis), Bromhexine or acetylcysteine is prescribed.

If the *skin and vagina are dry*, lubricants are used.

Treatment of extra-vascular manifestations of SS

- To reduce arthralgia, NSAIDs, hydroxychloroquine 200-400 mg/day, small doses of GCS (prednisone 5 mg/day or every other day) are prescribed.
- In the absence of severe systemic manifestations of SS, but there are moderate and significant changes in laboratory indicators of disease activity, small doses of GCS are prescribed in combination with leuceran 2-4 mg/day for 12 months, with the transition to a dose of 6-14 mg/week for several years.
- In vasculitis, when there are no life-threatening systemic manifestations, low doses of GCS are prescribed in combination with cyclophosphane 200 mg/week for 3 months, with a transition to 400 mg/month.

- For vasculitis with severe systemic manifestations, GCS therapy (20-60 mg/day) is performed in combination with leuceran (6-10 mg/day), or cyclophosphan (0.8-3.0 g/month) and intensive therapy (pulse therapy of GCS in combination with cyclophosphan and extracorporeal methods).
- Treatment with rituximab is performed in severe systemic manifestations of SS and in cases of resistance to therapy.
- Intravenous immunoglobulin is prescribed for autoimmune thrombocytopenia, hemolytic anemia, agranulocytosis, sensory neuropathy resistant to therapy.

VASCULITIS ASSOCIATED WITH ANTINEUTROPHILIC CYTOPLASMIC ANTIBODIES (ANCA-VASCULITIS)

ANCA-associated vasculitis belongs to the group of systemic vasculitis (SV) - a heterogeneous group of diseases that are based on generalized immuno-inflammatory damage to blood vessels of different calibers with subsequent involvement in the pathological process of organs and tissues supplied by the corresponding vessels.

Classification of systemic vasculitis

- Primary (as independent nosological units).
- Secondary vasculitis or vasculopathy associated with infections, tumors, systemic diseases of connective tissue, drugs, deficiency of components of the complement system, organ transplantation.

The current classification of SV takes into account the caliber of affected vessels and the mechanisms of their damage (table 25).

ANCA-associated SV vasculitis includes 3 nosological forms: granulomatous polyangiitis (GPA), formerly known as Wegener's granulomatosis; microscopic polyangiitis (MP), eosinophilic granulomatosis with polyangiitis (EGPA), formerly – Churge-Strauss syndrome.

GPA occurs in about one in 25,000 people, and can occur at any age, most often at 40.

MP is rare (approximately 13-19 cases per million), and the average age of onset is 50 years.

The incidence of EGPA is approximately 3 cases per million, and the average age for the onset of the disease is 48 years.

Code according to ICD:

M 30.1-Eosinophilic granulomatosis with polyangiitis
M 31.1-Granulomatous polyangiitis
M 31.7-Microscopic polyangiitis

Etiology and pathogenesis of SV

The association of SV with viruses (HBV infection, HIV infection, Parvovirus B19, Epstein-Barr virus), bacteria (streptococci, staphylococci), fungi (aspergillus), drugs, malignant diseases, and systemic diseases of connective tissue was revealed.

The basis of SV pathogenesis is inflammatory infiltration and necrosis of the vessel wall, leading to rupture and hemorrhage in the surrounding tissue, the formation of blood clots and ischemic tissue damage. Pathological changes are

associated with immune mechanisms mediated by autoantibodies, immune complexes, T-lymphocytes.

With ANCA vasculitis, autoantibodies to specific neutrophil cytoplasm antigens are formed - proteinase 3 (PR-3) and myeloperoxidase (MPO). Under the influence of pro-inflammatory cytokines, neutrophil cytoplasm antigens move to the cell membrane, neutrophils are activated and adhere to vascular endothelial cells. The subsequent binding of ANCA to neutrophil enzymes leads to their degranulation, release of inflammatory mediators and cytokines, lysis of endothelial cells and necrotic vasculitis, accompanied by the formation of granulomas.

With MPA, ANCA can be detected, but there is no granulomatous inflammation in contrast to GPA and EGPA.

Table 25-Current classification of systemic vasculitis (Chapel Hill Consensus Conference, 2012), [11]

Vasculitis with large-caliber vascular lesions • Takayasu arteritis (non-specific aortoarteritis) • giant cell arteritis (Horton's disease) and rheumatic polymyalgia
Vasculitis with lesions of medium-sized vessels • nodular polyarteritis • Kawasaki disease
Vasculitis with small-caliber vascular lesions Vasculitis associated with antineutrophilic cytoplasmic antibodies (ANCA): • microscopic polyangiitis • granulomatosis with polyangiitis (Wegener) • eosinophilic granulomatosis with polyangiitis (Churg-Strauss) Immunocomplex vasculitis: • iseases associated with antibodies to GBM (Goodpasture syndrome) • cryoglobulinemic vasculitis • IgA-associated vasculitis (hemorrhagic vasculitis, Shenlein-Genoch purpura) • hypocomplete urticarial vasculitis (anti-C1q vasculitis)
Variable vasculitis • Behcet's disease • Cogan syndrome
Vasculitis with vascular lesions of a single organ • cutaneous leukocytoclastic angiitis • cutaneous arteritis

• primary vasculitis of the central nervous system • isolated aortitis • others
Vasculitis associated with systemic diseases • vasculitis in SLE • rheumatoid vasculitis • sarcoid vasculitis • others
Vasculitis associated with certain etiological factors • cryoglobulinemic vasculitis associated with hepatitis C virus • vasculitis associated with hepatitis B virus • aortitis associated with syphilis • drug immunocomplex vasculitis • medicinal ANCA-associated vasculitis • paraneoplastic vasculitis • others

Clinical symptoms of systemic vasculitis

Common symptoms: fever, weight loss, general weakness.
Signs of a systematic pathological process: damage to several organs and systems: arthralgia, myalgia, damage to the skin, lungs, cardiovascular system, gastrointestinal tract, kidneys, and nervous system.
Clinic SV significantly varies depending on the location and degree of damage to the vessel. The main clinical manifestations of SV depending on the caliber of the affected vessel are shown in table 26.
Clinical symptoms of granulomatosis with polyangiitis (Wegener)
• A triad of organ damage involving the upper respiratory tract, lungs and kidneys is characteristic. GPA may manifest as an isolated lesion of the upper respiratory tract or a combination of these lesions.

Table 26 - The main clinical manifestations of SV depending on the caliber of the affected vessel

Affected vessel	Possible clinical manifestations
Systemic vasculitis of large / medium vessels	
Common carotid artery	Dizziness, headache, syncope
Maxillary artery	Intermittent muscle pain when chewing
Ocular artery	Vision loss

Renal artery	Hypertension, renal failure
Mesenteric arteries	Ischemic Enterocolitis
Coronary arteries	Angina pectoris, myocardial infarction
Pulmonary artery	Cough, bloody sputum, shortness of breath, pulmonary infarction
SV vessels of small caliber	
Leather	Mesh livedo, subcutaneous nodules, purpura, skin ulcers, finger necrosis
Peripheral nerves	Mononeuritis
Muscle	Myalgia
Joints	Arthralgia
Kidney	Necrotizing glomerulonephritis
Gastrointestinal tract	Ulcers, bleeding
Heart	Myocarditis, arrhythmia
Lungs	Pulmonary Alveolar Hemorrhage
Serous membranes	Pericarditis, pleurisy
Eyes	Retinal hemorrhages, scleritis

• The upper respiratory tract is most often affected (90%): ulcerative necrotic rhinitis, sinusitis, damage to the organ of hearing, trachea, and larynx with the formation of sub-follicular granulomas. Perforation of the nasal septum with the formation of a saddle-shaped deformation of the nose, destructive pansinusitis with the spread of granulomatous tissue into the orbit, hearing loss, stenosis of the larynx may develop.
• Lung damage (50-70%): multiple nodes or infiltrates, prone to disintegration and cavity formation, atelectasis, pneumonia. Often, lung damage is asymptomatic.
• Kidney damage (80-90%): proliferative focal glomerulonephritis with half moon, necrosis and thrombosis of individual loops and large segments of glomeruli. Acute nephritic syndrome, renal failure, or asymptomatic proteinuria, microhematuria, less often macrohematuria may develop.
• Lesions of the organ of vision (50%): periorbital granuloma, leading to blindness in every fifth patient, episiscleritis, optic vasculitis, occlusion of the retinal arteries.
• Skin lesion (25-35%): hemorrhagic or ulcerative hemorrhagic rashes, reticular liver, gangrenous pyoderma.
• Damage to the peripheral nervous system (20-30%): sensory-motor multiple mononeuritis, less commonly distal symmetric polyneuropathy, neuritis V, VII pair of cranial nerves.
• Heart damage (20%): coronary heart disease, high risk of myocardial infarction, stroke, peripheral arterial occlusion.

• Damage to the gastrointestinal tract (5%): abdominal pain, nausea, vomiting, diarrhea, bleeding.
• With HPA, in comparison with other ANCA vasculitis, the highest risk of developing exacerbations and relapses, even at high doses of immunosuppressants.

Clinical symptoms of microscopic polyangiitis
• Clinical symptoms are similar to GPA, but there is no or minimal upper respiratory tract damage, no destructive granulomas in the lungs.
• In 50% of patients a severe pulmonary-renal syndrome is developed: necrotizing alveolitis (antibodies to PR-3 are detected), fibrosing alveolitis (antibodies to MPO), kidney damage (40-55% - rapidly progressive glomerulonephritis).
• Skin lesion (70%): ulcerative hemorrhagic rashes, mesh retinitis, skin and tissue necrosis.
• Lesions of the organ of vision (30%): scleritis and episcleritis.
• Damage to the nervous system (30%): multiple mononeuritis with damage to the peripheral and cranial nerves, cerebral vasculitis.
• Damage to the gastrointestinal tract (10%): abdominal pain, nausea, vomiting, diarrhea, bleeding.
• A more aggressive course is characteristic than with GPA or EGPA.

Clinical symptoms of eosinophilic granulomatosis with polyangiitis (* Churg-Strauss*)
• EGPA is combined with eosinophilia, bronchial asthma, allergic rhinitis, nasal polyposis, or a combination of both.
• Clinical development goes through 3 stages. At the first stage for several years there are symptoms of bronchial asthma, allergic rhinitis, sinusitis, drug intolerance, an increase in the number of eosinophils in the blood. At the 2nd stage, eosinophilic pneumonia or gastroenteritis joins, often eosinophilia of blood more than 10%. Stage 3 - the development of necrotizing vasculitis.
• Lung damage (70%): migratory infiltrates (eosinophilic pneumonia) or nodes without decay cavities, eosinophilic pleurisy, moderate enlargement of intrathoracic lymph nodes.
• Kidney damage 20-45%: glomerulonephritis.
• Heart damage (30-50%): pericarditis, endomyocarditis, coronary artery disease, heart failure, rhythm and conduction disturbances.
• Skin lesion (64%): hemorrhagic or ulcerative hemorrhagic rashes mainly on the skin of the limbs, urticaria rashes.
• Damage to the peripheral nervous system (64%): sensory-motor multiple mononeuritis.

• Damage to the central nervous system (10%): neuritis of the cranial nerves, acute cerebrovascular accident, convulsions, coma.
• Lesions of the organ of vision (30%): scleritis and episcleritis.
• Damage to the gastrointestinal tract (10%): eosinophilic gastroenteritis, vasculitis of the intestinal wall.

Diagnosis of systemic vasculitis [31, 32, 33]

Diagnosis of SV is based on a comprehensive assessment of the clinical picture, data from laboratory, instrumental, and morphological studies. An exclusion of all causes that can lead to the development of secondary vasculitis is required.

Laboratory indicators specific to SV

• Complete blood count: normochromic anemia, thrombocytosis, neutrophilic leukocytosis, increased ESR, for EGPA, eosinophilia above 1.5 x 109 / l is characteristic.
• Urinalysis: proteinuria, hematuria, cell cylinders. The level of serum creatinine, GFR, electrolyte levels are determined, a study of daily urine is conducted, etc.
• Markers of inflammation - the content of CRP and ESR correlate with the activity of the disease.

Immunological studies for SV diagnosis

• Detection of ANCA confirms the diagnosis of ANCA-associated vasculitis. Antibody content correlates with disease activity.
• ANCA screening test - IIF response. There are two main types of luminescence of ANCA: cytoplasmic (c-ANCA) and perinuclear (p-ANCA).
• After receiving a positive response in the IIF method, the specificity of antibodies is determined by ELISA: cytoplasmic antibodies react with proteinase-3, perinuclear antibodies with myeloperoxidase.
• The frequency of detection of ANCA in ANCA-SV and their specificity are different (table 27):

- in GPA, antibodies to PR-3 (c-ANCA) are detected in most patients in 90% of cases, while to MPO (p-ANCA) in only 10% of cases.
- with EGPA, antibodies to MPO are detected in 50-75% of patients, while to PR-3 in only 10% of cases;
- with MP with equal frequency, antibodies to PR-3 and to MPO are detected in 50% of cases.

Table 27 - Frequency of ANCA detection in systemic vasculitis

Glow Type (IIF)	**Antibody Specificity (ELISA)**	**Disease**	**Occurrence (%)**
c-ANCA	Anti-proteinase-3 antibodies	• Granulomatosis with polyangiitis (Wegener)	• 90

	detected	• Microscopic polyangiitis • Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	• 50 • 10
p-ACCA	Antibodies against myelopyroxidase detected	• Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) • Microscopic polyangiitis • Granulomatosis with polyangiitis (Wegener) without antibodies against proteinase-3 (c-ANCA)	• 75 • 50 • 10

Other diseases and SV in which ANCA is detected

• Perinuclear ANCA (p-ANCA) include antibodies to other components of neutrophil cytoplasmic granules (elastase, cathepsin, lactoferrin) along with antibodies to MPO. Some p-ANCA are not characteristic of vasculitis, but are found in other diseases. For this reason, in the diagnosis of vasculitis, obtaining the perinuclear type of luminescence in the IIF reaction is always supplemented by a study for antibodies to myeloperoxidase using ELISA or a comprehensive study of several ANCA.

• P-ANCA can be detected with IgA-associated vasculitis (hemorrhagic vasculitis, in 20-30% of cases), nodular periarteritis (2%), rarely with SLE, RA.

• P-ANCA (more often for MPO) is found in patients with Goodpasture syndrome (10-15%) together with antibodies to the glomerular basement membrane (anti-BMC).

• P-ANCA can be detected with rapidly progressive glomerulonephritis (in 50% of cases), idiopathic alveolar hemorrhagic syndrome, ulcerative colitis (40-50%), Crohn's disease (10-20%), primary biliary cirrhosis, chronic hepatitis, paraneoplastic vasculitis.

The defeat of small vessels of the skin and internal organs is often secondary and occurs when the antigen is kept in the body for a long time (infections, tumors, drugs, etc.). For differential diagnosis between primary and secondary SV (vasculopathy) laboratory, instrumental, histological studies are performed.

Laboratory studies used for SV differential diagnosis:

• determination of antibodies to dsDNA, ANA, RF, antibodies to phospholipids to exclude ARD;

• determination of concentration of creatinine, liver enzymes, CPK (exclusion of inflammatory myopathy);

• bacteriological blood test; determination of markers of hepatitis B virus, C, HIV, syphilis;
• electrophoresis of serum and urine proteins, analysis of sternal punctate to exclude lymphoproliferative diseases;
• identification of tumor markers.

Instrumental research methods used for differential diagnosis of SV:
• rhinoscopy, laryngoscopy, bronchoscopy, radiography of lungs and sinuses, CT, high-resolution CT, MRI;
• determination of external respiration functions;
• FGDs, colonoscopy;
• ultrasound dopplerography of blood vessels, heart,
• ultrasound of internal organs,
• angiography of the celiac trunk and renal arteries,
• MRI of large blood vessels and aorta,
• electromyography.

Histological examination in SV. Due to the large number of cases of seronegative variants of SV, a biopsy is an obligatory component of diagnosis in ANCA vasculitis, giant cell arteritis, and polyarteritis nodosa. A biopsy of the most accessible affected tissue is performed.

Histological signs of vasculitis:
• Vascular wall infiltration with various combinations of white blood cells and lymphocytes.
• Fibrosis and intimal hypertrophy, secondary thrombus formation, fibrinoid necrosis - destruction of all wall layers.
• Leukocytoclasia - the detection in vessels and around them of small fragments of nuclei ("nuclear dust") of destroyed inflammatory cells due to the destruction of white blood cells.
• Perivascular infiltration.
• There may be (during immunofluorescence research) a small number of deposits of immunoglobulins and complement in the walls of blood vessels or their complete absence.
• None of pathomorphological changes is specific to individual vasculitis. Interpretation of biopsy data should be done only taking into account the clinic.

When making a diagnosis of ANCA vasculitis, an analysis is made of the compliance of the data from the above studies with classification criteria (table 28). An important aspect of diagnostics is the knowledge of age-related priorities of SV (table 29). If SV symptoms appear in an age group uncharacteristic for it, secondary vasculitis should be suggested.

Table 28 - ANCA-SV classification criteria

Nosological Form	Criteria	Characteristic
Granulomatosis with polyangiitis (Wegener)	1. Inflammation of the nose and mouth	Oral ulcers; purulent or bloody discharge from the nose
	2. Changes in the lungs during x-ray examination	Nodules, infiltrates or cavities in the lungs
	3. Changes in urine	Hematuria (> 5 red blood cells in sight) or erythrocyte cylinders in urine sediment
	4. Biopsy data	Granulomatous inflammation in the artery wall or in the perivascular and extravascular space
	The presence of 2 or more criteria allows you to diagnose with a sensitivity of 88% and a specificity of 92%	
*Eosinophilic granulomatosis with polyangiitis (*Churg-Strauss*)*	1. Bronchial asthma	Difficulty breathing or diffuse wheezing when inhaling
	2. Eosinophilia	Eosinophilia> 10% of the total white blood cell count
	3. Mono-or polyneuropathy	Mononeuropathy, multiple mononeuropathy or polyneuropathy by the type of gloves or stockings
	4. Radiological signs of pulmonary infiltrates	Migratory or transient pulmonary infiltrates detected by x-ray
	5. Pathology of the maxillary sinuses	Pain or radiological changes
	6. Extravascular eosinophilia according to biopsy	Accumulation of eosinophils in extravascular space
	The presence of 4 or more criteria allows you to diagnose with a sensitivity of 85% and a specificity of 99%	
Microscopic polyangiitis	No classification criteria developed	

Table 29-Age priorities of systemic vasculitis

Age of patients	**Name of systemic vasculitis**
Childhood	Shenlein-Genoa vasculitis, Kawasaki vasculitis
Young age	Nodular periarteritis, Behcet's disease, Takayasu disease
Average age	Granulomatous polyangitis (Wegener), microscopic polyangiitis, eosinophilic polyangiitis (Churg-Strauss)
Elderly age	Horton's giant cell arteritis, rheumatic polymyalgia

Often there is a need for differential diagnosis of ANCA-associated vasculitis with immunocomplex, less often with vasculitis of vessels of medium and large caliber. The differential diagnosis algorithm for systemic vasculitis is presented in Figure 3.

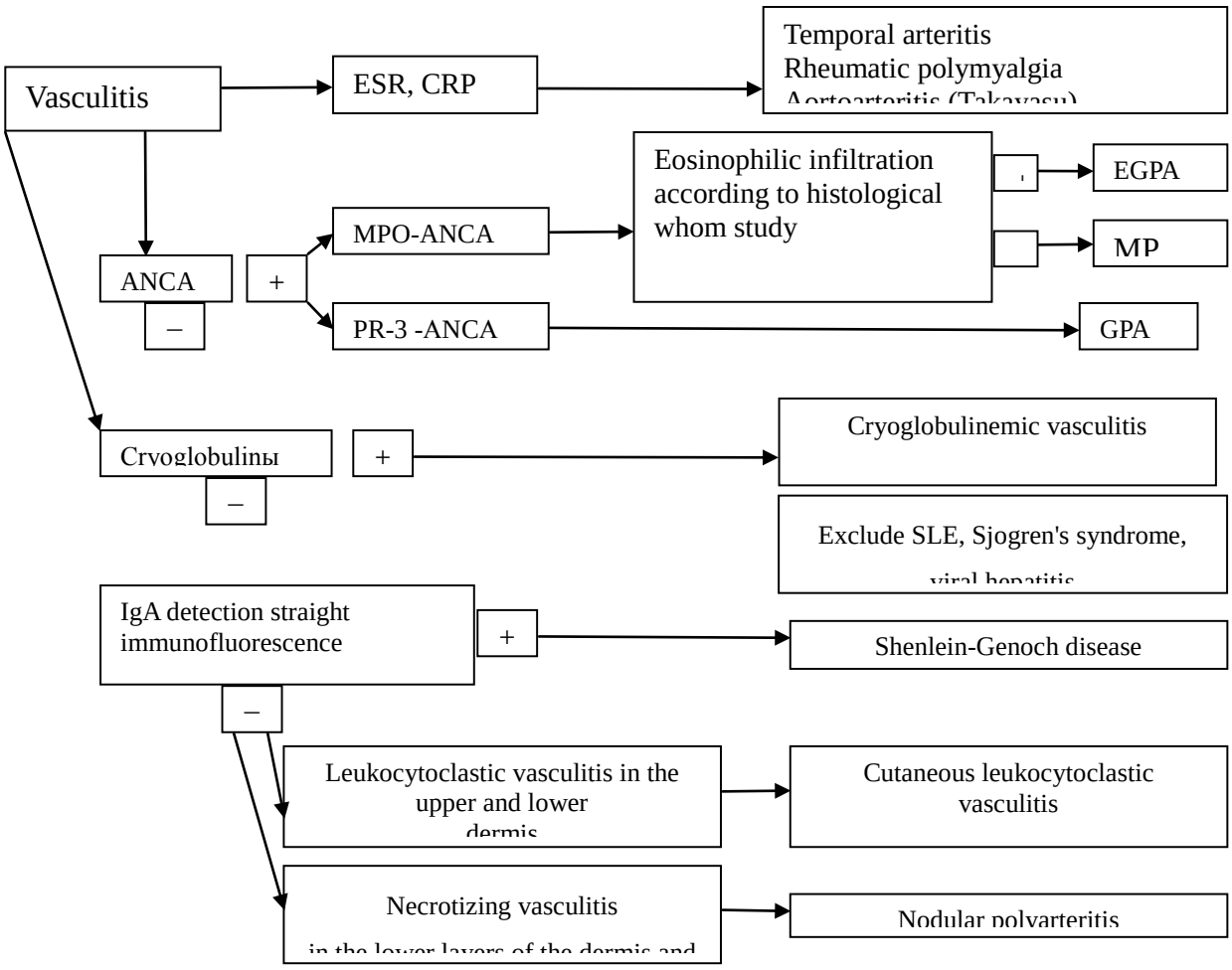


Figure 3 - Algorithm for differential diagnosis of systemic vasculitis

Diagnosis example

1. Granulomatosis with polyangiitis, chronic course, advanced stage, grade 1 activity with lung damage (infiltrative lung damage, respiratory failure I), organs of vision (right-sided exophthalmos, complete atrophy of the optic nerve of the right eye, partial atrophy of the optic nerve of the left eye), kidney (nephropathy, chronic kidney disease C3a).
2. Granulomatosis with polyangiitis (Wegener's granulomatosis), acute course, advanced stage, 3 degree activity with damage to the upper respiratory tract (rhinitis, purulent hemorrhagic sinusitis), oral mucosa (ulcerative stomatitis), hearing organs (ossifying labyrinthitis), organs of vision (bilateral keratitis), lungs (infiltrative lung lesion, pleural empyema, respiratory failure III), kidneys (nephropathy with progressive renal failure), heart (pericardial effusion), gastrointestinal tract (heart attack echeni), nervous system (polyneuropathy), skin (hemorrhagic rash), joints (arthritis, functional class II).

Treatment of ANCA-associated vasculitis [18]

Treatment is carried out in 3 stages.

• *Stage 1* - induction of remission lasting 3-6 months. Used drugs and treatment methods: GCS, GCS + cytostatics, cytostatics, immunoglobulins for intravenous administration, biological drugs, plasmapheresis, escalation therapy (pulse therapy with methylprednisolone + cyclophosphamide + plasmapheresis).
• *Stage 2* - maintaining remission: therapy with cytostatics + GCS for 2-5 years (until clinical and laboratory remission is achieved).
• *Stage 3* - treatment of relapses of SV.

To induce remission of generalized ANCA-SV, it is recommended to use a combination of cyclophosphamide + GCS (methylprednisolone or prednisolone).
The tactics of treatment vary depending on the severity of SV and the response to the therapy. There are 2 treatment regimens that differ in the way of administering drugs - intravenous or oral.
1 circuit. Cyclophosphamide in pulse therapy: intravenously 15 mg / kg (not more than 1 g) at intervals between the first 3 courses of 2 weeks, then every 3 weeks.
+ Methylprednisolone in pulse therapy mode: intravenously 0.5-1 g / day for 3 consecutive days, followed by the administration of prednisolone orally 1 mg / kg / day (no more than 80 mg) once in the morning until the effect is achieved, usually at least a month. After the effect is achieved, they begin to gradually reduce the dose of prednisone at 1.25 mg by 25% per month until the dose of prednisolone

reaches 20 mg / day, then by 10% every 2 weeks to 10 mg / day. In the future, it is possible to reduce the dose of GCs at 1.25 mg every 4 weeks.
With an increase in serum creatinine or in an elderly patient, lower doses of cyclophosphamide are used (Table 30).

Table 30 - modification of intravenous cyclophosphane dose depending on the patient's age and serum creatinine level

Age	**Creatinine <300 mmol / l**	**Creatinine 300-500 mmol / L**
< 60	15 mg / kg / pulse	12.5 mg / kg / pulse
60- 70	12.5 mg / kg / pulse	10 mg / kg / pulse
> 70	10 mg / kg / pulse	7.5 mg / kg / pulse

2nd scheme. Cyclophosphamide inside 2 mg kg/day (no more than 200 mg/day) with a dose reduction to 1.5 mg/kg/day when remission is achieved (within 3-12 months).
In the presence of renal failure, the dose of cyclophosphamide inside should be reduced by 25-50%. Additionally, prednisolone is prescribed orally 1 mg/kg/day (no more than 80 mg) once in the morning (after eating) until the effect is achieved, usually at least a month. After the effect is achieved, a dose reduction of prednisolone is carried out according to the scheme described above
The combination of methotrexate + GCS. It is prescribed for ANCA-associated limited vasculitis (local pathology of the upper respiratory tract), without rapidly progressing nephritis (creatinine <150 mmol/L) and severe lung damage. The dose of methotrexate is 15-25-30 mg week.
The combination of mycophenolate mofetil + GCS. Mycophenolate mofetil has renoprotective properties. Assign 1-2 g/day in one or more doses with a duration of at least 6 months. GCS is prescribed in a standard dose.
A refractory variant of the course of SV is distinguished, in which there is no reverse development of the clinical manifestations of the disease or an increase in clinical activity is observed, despite standard pathogenetic therapy being carried out for 6 weeks.

Treatment of refractory SV and SV with recurrent course

• Genetically engineered biological drugs. Rituximab is a chimeric monoclonal antibody to the CD20 receptor for B-lymphocytes. Dosage regimen: intravenously 375 mg/m2 once a week for 4 weeks. Treatment is combined with the administration of corticosteroids in a standard dose, supporting therapy with azathioprine, mycophenolate mofetil. A combination of rituximab and cyclophosphamide in a standard dose is possible for one or several months in

severe cases of the disease, including the development of rapidly progressive glomerulonephritis.

With the development of relapse after remission induced by rituximab, a second course is recommended. Lower doses of rituximab (500-1000 mg) may be effective. To reduce the risk of relapse, a preventive prescription of a second course of rituximab can be considered.

It is possible to use *infliximab* (chimeric antibodies to TNF-α, etanercept (antibodies to soluble TNF-α), with EGPA - *omalizumab* (chimeric antibodies against the IgE receptor).

• *Normal human immunoglobulin* for intravenous administration is prescribed for the refractory course of ANCA vasculitis, if there are contraindications for cytostatics (infectious complications, pregnancy, before and after surgery). Dosage regimen: slowly intravenously (20 drops per minute) 0.4-2g/kg 1 time/day, 3-5 days. It is possible to conduct repeated courses once a month for 6 months. Side effects: flu-like syndrome.

• *Plasmapheresis*. Mechanism of action: suppression of immune inflammation by removing antibodies, immune complexes, pro-inflammatory cytokines, inflammatory mediators, prostaglandins.

Dosage regimen: 7-10 procedures for 14 days with removal of 60 ml/kg of plasma and replacement with an equal volume of 4.5-5% of human albumin.

It is attached due to ineffectiveness of induction therapy, in cases of active severe illness with an increase in creatinine levels of more than 500 mmol/l, as well as with hemorrhagic alveolitis.

• *Escalation therapy*: plasmapheresis + GCS + cytostatics. Dosage regimen: 7-10 plasmapheresis procedures for 14 days (60 ml / kg/day) with plasma replacement with an equal volume of 4-5% albumin in combination with pulse therapy with methylprednisolone (15 mg kg/day) and cyclophosphamide (10 mg/kg/day).

Additional drugs. In the complex treatment of ANCA vasculitis, antiplatelet agents are used - low doses of acetylsalicylic acid, dipyridamole; anticoagulants (heparin, warfarin); vasodilators; ACE inhibitors.

With gPA in cases with proven carriage Staph. aureus, as well as for the prevention of pneumocystis infection in patients receiving cyclophosphamide, trimethoprim/sulfamethoxazole is prescribed.

If the patient has impaired renal function due to severe renal failure, programmed hemodialysis is performed.

The ANCA-associated vasculitis management algorithm developed by the British Society of Rheumatology [18] is shown in Figure 4.

Maintenance of remission

• The duration of treatment is from 2 to 5 years.

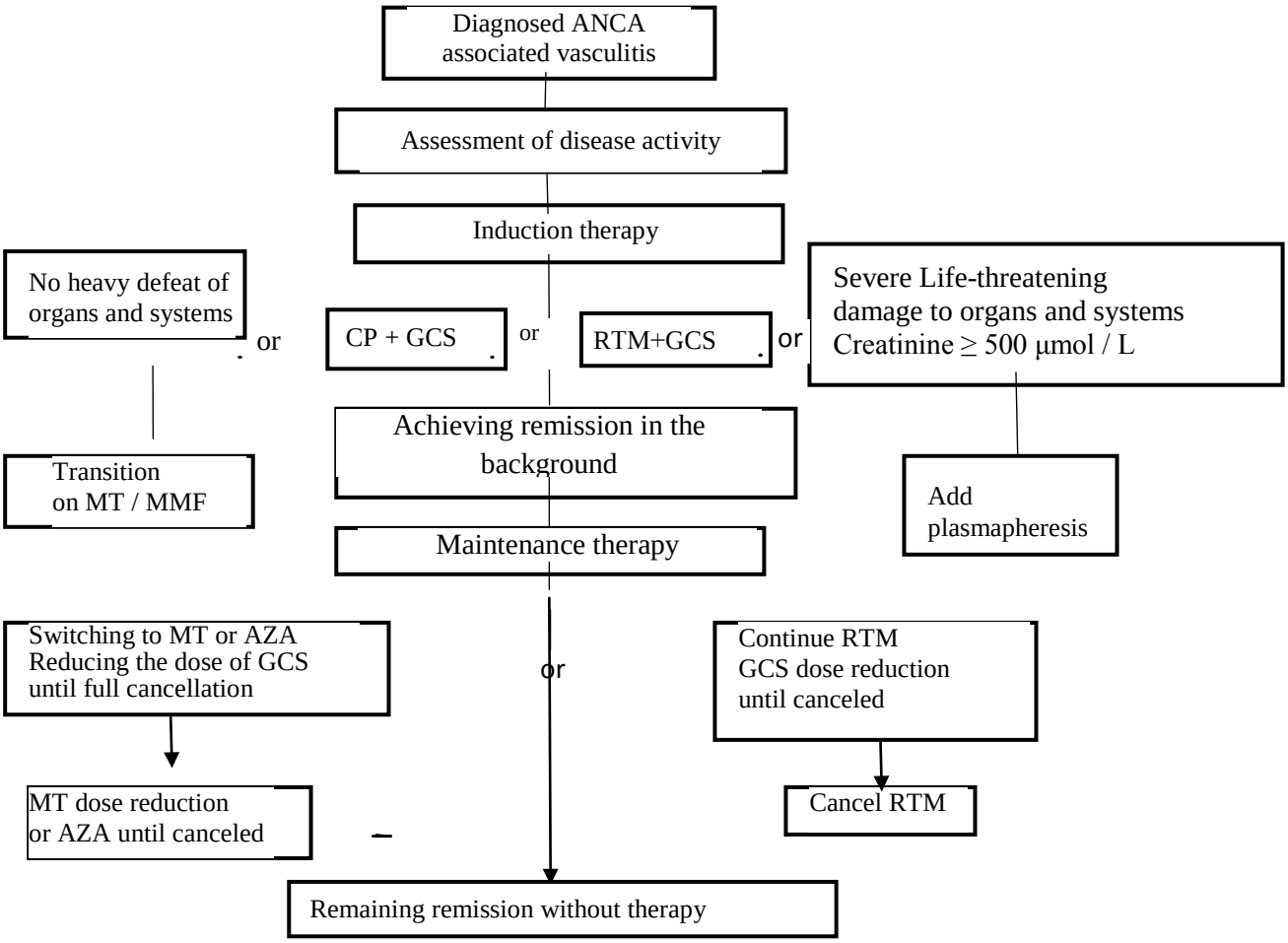
• GCS inside 5-10 mg once in the morning (after eating) + azathioprine 2 mg/kg/day with a possible dose reduction to 1.5 mg/kg/day in a year. If possible, the dose of GCS should be reduced as much as possible or completely abolished. If you need long-term administration of corticosteroids, calcium preparations, vitamin D, bisphosphonates for the prevention of osteoporosis are added to the treatment.

• Instead of azathioprine, you can prescribe leflunomide 20-30 mg/day, or methotrexate 12.5-15 mg/week, or mycophenolate mofetil 1-2 g/day in one or more doses with duration of at least 6 months.

In duration of remission of vasculitis during the year against the background of maintenance therapy, it is recommended firstly to lower the dose of corticosteroids, and then to reduce or cancel immunosuppressive therapy.

Surgery

It is indicated for the development of irreversible tissue changes (peripheral gangrene), subopharyngeal stenosis, stenosis of the bronchi, etc. A kidney transplantation is possible in the stage of terminal renal failure.



AZA - azathioprine, MMF - mycophenolate mofetil, MT - methotrexate, RTM - rituximab, CP – cyclophosphamide

Figure 4 - Algorithm for management of patients with ANCA-associated vasculitis

SECTION CONTROL TESTS

1. What is not typical for antiphospholipid syndrome?
1. The presence of antiphospholipid antibodies
2. Habitual miscarriage
3. Thrombocytosis
4. Arterial thrombosis
5. Venous thrombosis

2. What does not belong to laboratory diagnostic criteria for antiphospholipid syndrome?
1. Antibodies to cardiolipin IgG or IgM isotypes
2. Antibodies to β2-glycoprotein 1 IgG and / or IgM isotypes
3. Lupus anticoagulant in plasma
4. Extension of blood coagulation time in phospholipid-dependent coagulation tests (activated partial thromboplastin time, kaolin test, test with Russell's viper venom)
5. High titer of cryoglobulins in blood serum

3. What is not typical for systemic lupus erythematosus?
1. Photosensitivity
2. Raynaud's syndrome
3. Alopecia
4. Osteolysis of terminal phalanges
5. Erythematous dermatitis of the face

4. What is not typical for systemic lupus erythematosus?
1. Pneumonitis
2. Lupus nephritis
3. Cheilitis
4. Eosinophilic endocarditis
5. Myocarditis

5. Which of the listed hematological parameters is not typical for systemic lupus erythematosus?
1. Leukocytosis
2. Leukopenia
3. Eosinophilia
4. Thrombocytopenia
5. Acceleration of ESR

6. First-choice drugs for SLE are:
1. NSAIDs
2. Aminoquinolines
3. Glucocorticosteroids
4. Cytostatics
5. Gold preparations

7. Which drug is most effective in the treatment of lupus nephritis?
1. Methotrexate
2. Cyclophosphamide
3. Azathioprine
4. Hydroxychloroquine
5. Rituximab

8. The most common manifestation of lupus carditis is:
1. Myocardial infarction
2. Damage to all valves
3. Endocarditis of Liebman-Sachs
4. Myocarditis
5. Pericarditis

9. What antibodies reliably indicate the presence of systemic lupus erythematosus in a patient?
1. Anticentromeric antibodies
2. Antibodies to the J-1 antigen
3. Antineutrophilic cytoplasmic antibodies to proteinase 3
4. Antibodies to cardiolipin
5. Antibodies to double-stranded DNA

10. Name vasculitis that is not granulomatous:
1. IgA-associated vasculitis (hemorrhagic vasculitis, Shenlein-Genoch purpura)
2. Granulomatosis with polyangiitis (Wegener)
3. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
4. Takayasu arteritis (nonspecific aortoarteritis)
5. Giant cell temporal arteritis (Horton's disease)

11. Name vasculitis, which is granulomatous:
1. Obliterating thromboangiitis (Vinivarter-Burger)
2. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

3. Microscopic polyangiitis
4. Essential cryoglobulinemic vasculitis
5. IgA-associated vasculitis (hemorrhagic vasculitis, Shenlein-Genoch purpura)

12. What type of systemic vasculitis affects only medium-sized arteries?
1. Obliterating thromboangiitis
2. Nodular polyarteritis
3. IgA-associated vasculitis (hemorrhagic vasculitis, Shenlein-Genoch purpura)
4. Essential cryoglobulinemic vasculitis
5. With all the mentioned vasculitis, arteries of only medium caliber are affected

13. What type of vasculitis is characterized by vascular lesions of the microcirculatory bed?
1. Essential cryoglobulinemic vasculitis
2. Microscopic polyangiitis
3. Hypocomplementemic urticarial vasculitis
4. IgA-associated vasculitis (hemorrhagic vasculitis, Shenlein-Genoch purpura)
5. With all the mentioned vasculitis, the vessels of the microvasculature are affected

14. What vasculitis is associated with hepatitis B virus infection?
1. Nodular polyarteritis
2. Giant cell temporal arteritis (Horton)
3. IgA-associated vasculitis (hemorrhagic vasculitis, Shenlein-Genoch purpura)
4. Obliterating thromboangiitis
5. With all of the listed vasculitis

15. At what systemic vasculitis antineutrophilic cytoplasmic autoantibodies are detected in the blood serum?
1. Giant cell temporal arteritis of Horton
2. IgA-associated vasculitis (hemorrhagic vasculitis, Shenlein-Genoch purpura)
3. Obliterating thromboangiitis
4. Takayasu arteritis (nonspecific aortoarteritis)
5. Microscopic polyangiitis

16. What systemic vasculitis is characterized by anti-neutrophil cytoplasmic antibodies to proteinase-3?
1. Granulomatosis with polyangiitis (Wegener)
2. Essential cryoglobulinemic vasculitis
3. Giant cell temporal arteritis (Horton)

4. IgA-associated vasculitis (hemorrhagic vasculitis, Shenlein-Genoch purpura)
5. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

17. What systemic vasculitis is characterized by antineutrophilic cytoplasmic antibodies to myeloperoxidase?
1. Essential cryoglobulinemic vasculitis
2. Nodular polyarteritis
3. Granulomatosis with polyangiitis (Wegener)
4. Takayasu arteritis (nonspecific aortoarteritis)
5. Microscopic polyangiitis

18. In what systemic vasculitis can anti-neutrophil cytoplasmic antibodies to myeloperoxidase and proteinase-3 be detected?
1. Takayasu arteritis (nonspecific aortoarteritis)
2. IgA-associated vasculitis (hemorrhagic vasculitis, Shenlein-Genoch purpura)
3. Polyarteritis nodosa
4. Giant cell temporal arteritis (Horton)
5. Microscopic polyangiitis

19. What type of vasculitis is characterized by lung damage?
1. Granulomatosis with polyangiitis (Wegener)
2. Microscopic polyangiitis
3. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
4. With all of the listed vasculitis, the lungs are affected.
5. With all of the listed vasculitis, lung damage is very rare.

20. Which disease is most characterized by an increase in serum creatine phosphokinase?
1. Reactive Arthritis
2. Systemic sclerosis
3. Nodular periarteritis
4. Dermatomyositis
5. Rheumatoid Arthritis

21. What signs are typical for polymyositis?
1. Swelling and skin induction
2. Sharp muscle weakness
3. Cataract
4. Joint deformation
5. Osteolysis of the nail phalanges of the hands

22. The Gottron trait is characteristic of:
1. Dermatomyositis
2. Systemic sclerosis
3. Systemic lupus erythematosus
4. Essential cryoglobulinemic vasculitis
5. Hemorrhagic vasculitis (Schonlein-Genoch purple)

23. Among the systemic manifestations of dermatomyositis following is observed:
1. Myocardiofibrosis
2. Dysphagia
3. Pneumosclerosis
4. Glomerulonephritis
5. All of the above

24. What diseases are associated dermatomyositis with?
1. Bronchial asthma
2. Sarcoidosis
3. Crohn's disease
4. Malignant neoplasms
5. Urticaria

25. A distinctive symptom of Sjogren's syndrome is:
1. Dry keratoconjunctivitis
2. Glaucoma
3. Cataract
4. Astigmatism
5. Optic atrophy

26. For Sjogren's syndrome following is not typical:
1. Severe dryness of the skin
2. Damage to the salivary glands (reduced salivation)
3. Dryness of the mucous membranes of the nose, larynx, pharynx, bronchi
4. Atrophic gastritis with secretory insufficiency, hypokinetic biliary dyskinesia, pancreatitis
5. All of the above is typical

27. Specific markers of Sjogren's syndrome:
1. Antibodies to the nuclear antigen Ro (ass-A/Ro) and La (aSS-B/La)
2. LE cells

3. Antibodies to double-stranded DNA
4. Antineutrophilic cytoplasmic antibodies to myeloperoxidase
5. Anti-neutrophil cytoplasmic antibodies to proteinase 3

28. What does not apply to the radiological signs of rheumatoid arthritis?
1. Osteoporosis
2. Osteophytes
3. Narrowing of the joint gap
4. Usource articular surfaces
5. Ankylosing of joints

29. What complication is most common for rheumatoid arthritis?
1. Renal amyloidosis
2. Secondary infection
3. Antiphospholipid syndrome
4. Gastric ulcer
5. Development of Raynaud's syndrome

30. III degree of activity of rheumatoid arthritis is characterized by the following clinical and laboratory manifestations, except:
1. Erythrocyte sedimentation rate 62 mm/h
2. Pain assessment on a visual analog scale of 8 cm
3. Morning stiffness during the day
4. SRP is 3 times higher than normal
5. The defeat of the periarticular tissues

31. What drug is considered the "gold standard" for the treatment of rheumatoid arthritis?
1. Hydroxychloroquine
2. Methotrexate
3. Cyclophosphamide
4. Sulfasalazine
5. Hlorbutin

32. What immunological indicator is most typical for rheumatoid arthritis?
1. High RF titer
2. Presence of LE cells
3. High titer of antistreptolysin O
4. The presence of antibodies to double-stranded DNA
5. High titers of antinuclear antibodies

33. What immunological indicator is highly specific for rheumatoid arthritis?

1. Antinuclear antibodies
2. Anti-neutrophil cytoplasmic antibodies
3. Antibodies to double-stranded DNA
4. Antibodies to cyclic citrullinated peptide
5. Antibodies to the Scl-70 antigen

34. What kind of disease is characterized by deformation of fingers of the hands like "Swan's neck" and "button loop"?

1. Rheumatoid arthritis
2. Psoriatic arthritis
3. Systemic lupus erythematosus
4. Osteoarthritis's
5. Hemorrhagic vasculitis

35. What is the most common disease that causes hypotrophy of hand muscles?

1. Osteoarthritis
2. Rheumatoid arthritis
3. Systemic sclerosis
4. Systemic lupus erythematosus
5. Microscopic polyangiitis

36. What drug used for the treatment of rheumatoid arthritis is a biologic?

1. Hydroxychloroquine
2. Azathioprine
3. Nimesulide
4. Rituximab
5. Methotrexate

37. What indicators do not determine the degree of activity of rheumatoid arthritis?

1. CRP
2. ESR
3. Duration of morning stiffness
4. The severity of pain on a visual analog scale
5. Uric acid level

ANSWERS TO CONTROL QUESTIONS

1. 3
2. 5
3. 4
4. 4
5. 3
6. 3
7. 2
8. 3
9. 5
10. 1
11. 2
12. 2
13. 5
14. 1
15. 5
16. 1
17. 5
18. 5
19. 4
20. 4
21. 2
22. 1
23. 5
24. 4
25. 1
26. 5
27. 1
28. 2
29. 1
30. 5
31. 2
32. 1
33. 4
34. 1
35. 2
36. 4
37. 5

SITUATIONAL TASKS

Task 1. A 55-year-old woman went to the clinic with complaints of a temperature of 37.2-37.4 ^{o}C for a month, swelling of the joints of the hands, feet, limited mobility in them, morning stiffness in the joints of the upper and lower extremities up to 14 hours. Notes a slight effect from taking NSAIDs.

Objective examination: there is a symmetrical lesion of the wrist, metacarpophalangeal and proximal interphalangeal joints of the hands (except for the 1st metacarpophalangeal joint and the 5th proximal interphalangeal joint), and the metatarsophalangeal joints. Above the surface of these joints, there is hyperemia of the skin, local hyperthermia. Active and passive movements in the joints are limited.

Data from additional surveys. General blood analysis: red blood cells- 4,6x10^{12}//l, HB-118 g / l, white blood cells-- 8,0x10^{9}/l, ESR-35 mm / h.

Radiography of hand joints: periarticular osteoporosis, narrowing of joint slits, single usures in the area of proximal interphalangeal joints is determined.

Questions:

1. Formulate a preliminary diagnosis.
2. What additional tests should be performed to verify the diagnosis?
3. What diseases should be treated with a differential diagnosis?
4. Determine the tactics of managing patients with this pathology.

Task 2. Patient K., 24 years old, went to the clinic with complaints of a slight temperature increase (up to 37.5 ^{o}C), pronounced general weakness, pain in the joints of the hands, knee and ankle joints, and an increase in axillary lymph nodes. She considers herself sick for about six months, and associates the disease with hypothermia.

At objective examination: the state of moderate severity. There is erythema on the face, especially on the cheeks and in the area of the back of the nose. Axillary lymph nodes are enlarged (size exceeds 15 mm in diameter), dense, painless. There is swelling of small joints of the hands, ankle and knee joints, movement in them is limited. The heart rate - 108 beats/min, BP - 140/100 mm Hg. All heart tones are rhythmic, muted. The borders of the heart are not changed. When auscultation of the lungs is determined by hard breathing, in the lower parts - weakened. The abdomen is of the usual shape, participates in the act of breathing, and is soft and painless when palpated. The liver is not enlarged. The symptom of pounding is negative on both sides. Stool and diuresis are normal. Dense edema in the area of the feet and shins.

Data from additional surveys. General blood analysis: red blood cells-2,9x10^{12}/l, Hb-90 g/l, white blood cells-3,1x10^{9}/l, platelets-105x10^{9}/l, ESR-45 mm per hour.
General analysis of urine: protein-3.5 g / l, specific weight 1018, white blood cells-8-10 in the field of view, red blood cells changed-22-24 in the field of view, hyaline cylinders-2-4 in the field of view.
Biochemical analysis of blood: total protein-53 g / l, CRP-16 mg/l, blood urea-11.6 mmol / l, creatinine-113 mmol / l.
Questions:
1. Formulate a preliminary diagnosis.
2. What additional tests should be performed to verify the diagnosis?
3. What diseases should be treated with differential diagnostics?
4. Determine the tactics of managing patients with this pathology.

Task 3. The first-born 26-year-old was admitted to the maternity hospital at full-term pregnancy. She complained on periodic flashing of flies before the eyes, pain in the epigastric region. This third, first, and second pregnancy resulted in a spontaneous miscarriage at 17-18 weeks of gestation. During the pregnancy, she added 9 kg of body weight.
On objective examination: there is no edema, and the peripheral lymph nodes are not enlarged. When the lungs are auscultated, vesicular respiration is determined. The boundaries of the heart correspond to the norm. The heart tones are rhythmic, muted. The number of heartbeats is 95 in 1 min. Blood pressure is 115/65 mm Hg. The face is symmetrical on both hands. The abdomen is soft, painless, and the liver and spleen are not enlarged. The chair is normal. Diuresis is sufficient.
Data from additional surveys. General blood analysis: red blood cells-4,3x10^{12}/l, white blood cells-7,2x10^{9}/l, platelets-105x10^{9}/l. General urine analysis without pathology.
Biochemical blood analysis: total protein-70 g / l, bilirubin-2.2 mmol/l, urea-3.1 mmol/l, creatinine-62 mmol / l. Wasserman's Reaction is weakly positive.
Immunological examination of blood: anti-cardiolipin antibodies and lupus anticoagulant in high titers are determined.
In the emergency room, she was examined by the obstetrician-gynecologist on duty: pregnancy of 37-38 weeks, pelvic presentation of the fetus.
Questions:
1. Formulate a preliminary diagnosis.
2. What additional methods of examination should be performed to verify the diagnosis?
3. Make a differential diagnosis.
4. Determine the tactics of managing patients with this pathology.

Task 4. Patient V. 52 years old, was admitted to the Department of rheumatology with complaints of severe general weakness, loss of body weight, swelling of the skin of hands, tingling sensation in the fingers, paleness and blueness of the fingers in the cold, wounds on the fingertips, pain in the joints of the hands and feet. She considers herself ill for 3.5 years. The disease began with a tingling sensation of the fingertips, whiteness of the fingers in the cold. Over the past few months, the patient has been concerned about severe general weakness, swelling of the hands and non-healing wounds on the fingertips, and an increase in body temperature to 37.2-37.4 ^{o}C. She was sent to the rheumatological department for verification of the diagnosis.

Under objective inspection: asthenic physique, low nutrition. Expression limitee, the mouth slit is narrowed, with wrinkles around. In the area of the hands, there is dense swelling and induration of the skin, the brush does not clench into a fist. Symptom of a "rat bite" on your fingertips. Muscle tone is lowered. When palpated, the muscles are slightly painful. Peripheral lymph nodes are not palpated. The number of heartbeats 95 in 1 min. AD-110/70 mm Hg. Borders of the heart correspond to the norm. The heart tones are rhythmic, muted. Breathing in the lungs is vesicular, crepitation is heard in the lower parts on both sides. The abdomen is of usual shape, participates in the act of breathing, is soft on palpation, and is painful in the epigastrium. The liver is not enlarged. The symptom of pounding is negative on both sides.

Data from additional surveys. General blood test: red blood cells-3,9x10^{12}/l, Hb-110 g/l, color. indicator-0.7, white blood cells-9,2x10^{9}/l, ESR-51 mm / h.

General urine analysis: clear, acid reaction, specific gravity 1015, protein- absent., 1-2 white blood cells in p / s.

Biochemical blood analysis: total protein-76 g / l, CRP-17.4 mg / l.

X-ray examination of the hands: areas of calcification in the subcutaneous tissue, mainly the end sections of the fingers. Osteolysis of the nail phalanges of the fingers of the hands, periarticular osteoporosis.

Questions:

1. Formulate a preliminary diagnosis.
2. What additional tests should be performed to verify the diagnosis?
3. What diseases should be treated with differential diagnostics?
4. What are the diagnostic criteria for this disease?
5. Determine the tactics of managing patients with this pathology.

Task 5. Patient B., 34 years old, came to the clinic with complaints of severe pain in the knee, ankle, and foot joints, severe weakness, and pain in the muscles of the arms and legs, which made self-care difficult. During the month, she had an increased temperature (37.5-37.7 °C), without chills. She considers herself sick for

six months, when there was a general weakness, the joints of the upper and lower limbs began to hurt and swell. She has redness and peeling of the skin over the joints of the hands. After consulting a rheumatologist, the clinic diagnosed rheumatoid arthritis and prescribed prednisone at a dose of 15 mg / day. She took prednisone for about 4 months with a gradual decrease in the dosage until complete withdrawal. She noted a significant improvement in the general condition, joint pain decreased, and skin changes began to pass. In the spring, after hyperinsulemia, again appeared the above complaints, but more pronounced. The patient was unable to get out of bed and had a high fever (38.8 °C). She was taken to the hospital by ambulance and admitted to the rheumatology department.

At objective examination: the state of moderate severity. Body temperature 37.7 °C. The patient is of correct physique and moderate nutrition. She can hardly move, can't keep her arms and legs in the air. Musculature is developed normally. Muscle tone is sharply reduced. The muscles of the shoulder and pelvic girdle are compacted, enlarged in volume, of a testy consistency, and there is marked pain when palpation of the muscles. The joints are not changed, and movements in the joints are limited due to pain. Lymph nodes are not enlarged. On the skin of the chest in the decollete area, in the area of the back of the neck and shoulders, bright erythema, slightly flaking. Erythema and peeling of the skin of the back surface of the hands over the proximal interphalangeal and metacarpal joints, redness and peeling of the skin of the palms. No pathological changes were detected in the cardiovascular system, respiratory system, and gastrointestinal tract.

Data from additional surveys. General blood analysis: red blood cells-- $4,6x10^{12}$/l, hemoglobin-139 g / l, white blood cells-$15,0x10^{9}$/l, ESR - 26 mm/h.

General urine analysis: clear, acid reaction, specific gravity 1015, protein-absent, 2-3 white blood cells in p / s.

Biochemical blood analysis: protein-81 g / l, AST-98 IU / l, ALT-100 IU/ l, CFK-1002 IU / l, cholesterol-5.2 mmol/l, CRP ++, total bilirubin - 12 mmol/l, creatinine - 120 mmol/l, urea - 4.52 mmol/l.

Questions:

1. Formulate a preliminary diagnosis.
2. What additional tests should be performed to verify the diagnosis?
3. What diseases should be treated with a differential diagnosis?
4. Determine the tactics of managing patients with this pathology.

Task 6. Patient A., 54, complained of dry mouth and eyes, and an increase in the size of the parotid salivary glands.

A few years ago, there was a feeling of "sand" in her eyes. When visiting an optometrist, a diagnosis was made: dry keratoconjunctivitis (filamentous keratitis OU), hypolacrimia III art. Then, active destruction of teeth with formation of

cervical caries began, taste perception decreased, and pain appeared in the joints of the hands. About 10 months ago, the left and then the right parotid salivary gland began to increase in size. During this period, the patient noted an increase in temperature to 37.3-37.5 °C, and her vision began to deteriorate.
On objective examination: body temperature 37.2°C. Dry skin. Parotid salivary glands with palpation are enlarged in size, dense in consistency. The oral mucosa is bright red, and there is no free saliva. The tongue is dry, without plaque, there is atrophy of the papillae. The conjunctiva of eyes are dry and hyperemic. No pathological changes were detected in the respiratory system, cardiovascular system, or gastrointestinal tract.
Data from additional surveys. Sialography of the left parotid salivary gland: there is a slight expansion of the parotid duct, single cavities are determined in the parenchyma.
Sialometry-unstimulated saliva secretion <0.1 ml/min.
Results of biopsy of the small salivary glands of the lower lip: there is a preservation of the lobular structure, a decrease in the number of acinuses. In the periductal regions with the transition to stroma, lymphohistiocytic infiltration of 125-250 cells in the field of view is determined.
Questions:
1. Formulate a preliminary diagnosis.
2. What additional tests should be performed to verify the diagnosis?
3. What diseases should be treated with a differential diagnosis?
4. Determine the tactics of managing patients with this pathology.

Task 7. Patient V., 29 years old, went to the emergency room of the hospital with complaints on difficulty in nasal breathing, nosebleeds, cough with the release of viscous sputum mixed with blood, shortness of breath at rest, expressed General weakness. The last 4 years he has high blood pressure and a change in the color of urine. A few months ago, the weakness and headache increased, and in recent days the above-described complaints have appeared.
At objective examination: the state of moderate severity. The skin is pale, dry, there is swelling of the face, minor swelling of the lower extremities. When auscultation of the lungs is determined by hard breathing, in the lower parts on both sides-small-bubble wet rales. The number of breaths is 26 per minute. The borders of the heart are not expanded. The number of heartbeats is 95 per minute. The tones are rhythmic, muted.BP 210/110 mm. Hg. The abdomen is soft and painless. Diuresis is reduced: drinks 1.5 l, allocates urine-800 ml.
Data from additional surveys. General blood analysis: red blood cells-$2,7x10^{12}$/l, hemoglobin-96 g / l, white blood cells-$9,8x10^{9}$/l, ESR-45 mm / hour.

General urine analysis: specific gravity 1008, protein-1.5 g / l, 3-4 white blood cells in the field of view, 12-14 red blood cells in the field of view, 2-4 hyaline cylinders in the field of view.
Biochemical blood analysis: urea - 12.8 mmol/l, creatinine - 126 mmol/l, CRP - 29 mg/l.
X-ray of the lungs: deformation of the pulmonary pattern, reduced transparency of the lung tissue in the lower parts on both sides. In the projection of the lower lobes of both lungs, single areas of infiltration are rounded to 5 cm in diameter.
Questions:
1. Formulate a preliminary diagnosis.
2. What additional examinations should be performed for the patient to verify the diagnosis?
3. Make a differential diagnosis of the disease.
4. Determine the tactics of managing patients with this pathology.

Task 8. Patient B., 22 years old, went to the clinic to the district therapist with complaints of severe headache, rash on the fingertips, palms, nail beds, which appeared about a week ago. She feels whiteness and soreness of fingers and toes, increased when cooled, persistent redness in the area of the back of the nose and cheeks, swelling of the right cheek. About 3 months, there is a subfebrile temperature (up to 37.2 °C), pronounced weakness and pain in the area of the muscles of the shins, elbow and ankle joints. She associates this disease to stress (loss of a relative).
At objective examination: the state of moderate severity. On the face, erythema is defined as a "butterfly", mainly on the cheeks. Slight swelling in her cheeks, slightly larger on the right. On the pads of her fingers, palms, and nail beds, there is a small-point hemorrhagic rash, the second and third fingers of her hands are red and bluish. Movements in the ankle and elbow joints are limited due to pain, slight swelling of the affected joints, and their pain is palpated. On a visual analog scale, the severity of pain is 90 mm. The general assessment of the disease by the patient is 86 mm, by the doctor-74 mm. The number of heartbeats is 102 beats/min. BP is 130/95 mm Hg. All heart tones are rhythmic, muted. The boundaries of the heart are not expanded. No pathological changes were detected on the part of the respiratory system and gastrointestinal tract.
Data from additional surveys. Total blood count: red blood cells-2,6x10^{12}/l, white blood cells-3,1x10^{9}/l, platelets-101x10^{9}/l, ESR-55 mm per hour.
The general analysis of urine: protein - 1.5 g/l, specific weight 1017, leukocytes 12-14 in sight, erythrocytes-changed - 12-14 in sight, hyaline cylinders - 4-6 in the field of view.

Biochemical blood analysis: total protein-76 g / l, CRP-38 mg/l, blood urea-10.5 mmol / l, creatinine-134 mmol / l. CIC-566 Ed. D-Dimers-650 ng / ml, fibrinogen A-5.0 g / l.
Wasserman's reaction is sharply positive (4+).
Antibodies to cardiolipin and lupus anticoagulant are detected in the middle titers.
Questions:
1. Formulate a preliminary diagnosis.
2. What additional tests should be performed to verify the diagnosis?
3. What diseases should be treated with differential diagnostics?
4. Determine the tactics of managing patients with this pathology.

Task 9. Patient V., 45 years old, was admitted to the emergency department of the emergency hospital with complaints of severe abdominal pain, pain in the knee and elbow joints, the appearance of a red rash on his legs and arms, an increase in body temperature to 38.0° C. He associates his disease with a viral infection about 3 weeks ago. The listed symptoms developed within a few days.
An objective examination: patient's condition is moderate. The skin is pale pink, there is a small symmetrical hemorrhagic rash on the legs, hips, forearms, slightly rising above the skin (palpable), not disappearing when pressed. Some rashes have necrosis in the center, covered with hemorrhagic crusts. Symptoms of "pinch" and "tourniquet" are negative. Minor edema in the area of the knee and elbow joints is determined, passive and active movements in these joints are sharply painful. The number of heart contractions is 106 beat/min. BP - 110/70 mm. Hg. Heart sounds are rhythmic, muffled. The boundaries of the heart are not extended. Vesicular breathing is heard above the lungs. The abdomen during palpation is painful in mesogastric pain, there is an increase in pain during palpation. Peritoneal symptoms are absent. The liver and spleen are not enlarged. Once there was a stool with an admixture of fresh blood, the gases escaped.
Data from additional surveys. Complete blood count: red blood cells - - $4,7x10^{12}$/l, hemoglobin - 118 g / l, platelets - $220x10^{9}$/ l, white blood cells - $11,0x10^{9}$/l, e - 1%, st - 10%, s - 70%, l - 16%, m - 3%, ESR - 48 mm / hour. D-Dimers - 660 ng / ml, fibrinogen A - 4.9 g / l.
Questions:
1. Formulate a preliminary diagnosis.
2. What additional examinations are needed to verify the diagnosis?
3. What diseases should be used for differential diagnosis?
4. Determine the tactics of managing patients with this pathology.

Task 10. Patient A., 28 years old. She turned to the local therapist with complaints of severe pain and swelling, stiffness (up to 11 hours) in her knee, elbow and wrist

joints. She has continuous (within 1.5 months) temperature of 37.1ºC - 37.3ºC. She feels expressed weakness, serving herself with difficulty. The disease is associated with a viral infection. She took NSAIDs for a long time.

An objective examination: a state of moderate severity. Body temperature 37.2ºC. In the area of the right wrist joint there are 4 subcutaneous dense, painless nodular formations measuring 0.4x0.3 cm. Moderate swelling of the affected joints and skin hyperthermia during palpation are determined. Passive and active movements in the knee, elbow and wrist joints are limited due to severe pain. Lymph nodes are not enlarged. In the lungs, vesicular breathing, no wheezing. The number of breaths is 16 per minute. Heart sounds are muffled, rhythmic. The heart rate is 86 per minute. BP - 129/80 mm. Hg. The abdomen on palpation is soft, painful in the epigastric region. The liver and spleen are not enlarged.

Data from additional surveys. Blood test: red blood cells - $3,2x10^{12}$/l, Hb - 104 g / l, white blood cells - $10,1x10^{9}$/l, platelets - $448x10^{9}$/l, ESR - 38 ml / hour. CRP - 22 mg/l, fibrinogen 4.6 mg/dl, serum iron - 15.2 mg/dl.

X-ray of the knee joints: periarticular osteoporosis, narrowing of the joint gap, single usages are determined.

Esophagogastroduodenoscopy: bright hyperemia of the mucous membrane of the antrum of the stomach with single erosions.

Questions:

1. Formulate a preliminary diagnosis.
2. What additional examinations are needed to verify the diagnosis?
3. Make a differential diagnosis.
4. Determine the tactics of managing patients with this pathology.

ANSWERS TO TASKS

Answer to task 1

1. Diagnosis: rheumatoid arthritis, seropositive/seronegative (depending on the detection of RF in the blood serum), 2nd degree of activity, stage II, FC 1-2.
2. Additional examination plan: general blood analysis, biochemical blood analysis, general urine analysis, determination of rheumatoid factor and antibodies to cyclic citrulline peptide in blood serum, x-ray of foot joints.
3. Differential diagnosis: osteoarthritis, gout, pseudogout.
4. Treatment: NSAIDs for a short time (until joint pain is reduced): diclofenac 50 mg, 1 t. 3 times a day (or diclofenac retard 100 mg a day), or nimesulid 100 mg, 1 t. 2 times a day, or meloxicam 7.5 mg, 1 t. 3 times a day, or etoricoxib 90 mg 1 time a day. Basic drugs: methotrexate 2.5 mg, prescribed from 7.5-10 mg to 25-30 mg per week. When the 2nd degree of RA activity is usually prescribed 10-12. 5 mg per week, the effectiveness of the prescribed dose is evaluated in a month, if necessary, it is increased. After achieving clinical and laboratory remission of RA, the dose of methotrexate is gradually reduced by titrating according to an individual scheme. Folic acid 5 mg / week on days free of methotrexate. With high activity of the disease - prednisone 7.5-10 mg / day inside for 1-1. 5 months. Treatment of NSAIDs and GCS should be performed in combination with the proton pump inhibitor omeprazole at a dose of 20-40 mg/day. It is possible to administer GCS in / articulately: kenalog 1 ml (40 mg), or diprospan 1 ml (7 mg).

***Answer to task* 2**

1. Diagnosis: systemic lupus erythematosus, subacute course, 3rd degree of activity, with skin lesions (erythema of the face according to the "butterfly" type), lymphadenopathy, polyarthritis, serositis (pleurisy?), lupus-nephritis (morphologically unspecified) with nephrotic syndrome, pancytopenia (anemia, leukopenia, thrombocytopenia). Symptomatic arterial hypertension.
2. *Additional tests plan*: general blood analysis, common urine analysis, daily proteinuria, urine analysis according to Nechyporenko, Zimnitskiy, a sample of Rehberg. Biochemical blood analysis (ALT, AST, CPK, glucose, urea, creatinine, total protein, albumin, CRP, potassium, sodium). Immunological markers of the disease: antinuclear antibodies, antibodies to double-chiral DNA, antiphospholipid antibodies. X-rays/ultrasound of the affected joints. Echocardiography, ECG, ultrasound of the abdominal cavity. Kidney biopsy to clarify the morphological variant of nephritis.
3. *Differential diagnosis*: rheumatoid arthritis, mixed connective tissue disease (Sharpe's syndrome), systemic vasculitis.

4. *Treatment*: pulse therapy: methylprednisolone 1000 mg intravenously for 3 days, cyclophosphamide 600-1000 mg intravenously once. Then prescribe prednisone inside 1 mg/kg/day (no more than 60 mg), cyclophosphamide is administered in/in a drip of 600-1000 mg 1 time per month for 6 months. Next, an oral cytostatic is prescribed, the prednisolone dose is reduced to 0.15-0.2 mg/kg / day. ACE inhibitors and diuretic drugs are shown.

Answer to task 3

1. Diagnosis: antiphospholipid syndrome: recurrent fetal loss syndrome (spontaneous abortions), thrombocytopenia, category I (positive anti-cardiolipin antibodies and lupus anticoagulant). Pregnancy 37-38 weeks, pelvic presentation of the fetus.
2. Additional examination plan: determine the dynamics (2 times within 12 weeks) of lupus anticoagulant, antibodies to cardiolipin, antibodies to beta-2-glycoprotein 1, coagulogram.
3. Differential diagnosis: autoimmune thrombocytopenia, gestosis, systemic vasculitis, SLE.
4. Treatment tactics: small doses of aspirin, low-molecular-weight heparin, glucocorticosteroids. The delivery option is determined in conjunction with the obstetrician-gynecologist.

Answer to task 4

1. Diagnosis: systemic sclerosis, 3rd degree of activity, chronic course with skin lesions (edema and induration of the skin of the face, hands, digital ulcers in the area of the fingertips of the hands), blood vessels (Raynaud's syndrome), joints (polyarthralgia), nervous system (polyneuropathy), lungs (interstitial fibrosis?).
2. Additional tests plan: general blood analysis, common urine analysis, daily proteinuria, urine analysis according to Nechyporenko, Zimnitskiy, a sample of Rehberg. Biochemical blood analysis (ALT, AST, CPK, glucose, urea, creatinine, total protein, albumin, CRP, potassium, sodium). Stop x-ray, chest x-ray with esophageal contrast, chest CT, Doppler EchoCG, ECG, coagulogram, FGDs, respiratory function test, immunological examination for antinuclear antibodies, sclerodermic antibodies, skin and muscle flap biopsy, capillaroscopy.
3. Differential diagnosis: rheumatoid arthritis, SLE, dermatomyositis/polymyositis, focal scleroderma.
4. Diagnostic criteria for systemic sclerosis. "Large criteria": proximal scleroderma; "small criteria": sclerodactyly; scars, tissue defects on the fingertips of the hands; basal pulmonary fibrosis on both sides.
5. Treatment. Immunosuppressive therapy: prednisone orally at a dose of 15-20 mg/day; kuprenil 250-500 mg every other day. Vasodilator drugs: calcium

antagonists (nifedipine 10 mg, 1 t. 3 times a day; or diltiazem 60 mg, 1 t. 2-3 times a day). Disaggregants (pentoxifylline-400 mg 3 times a day).

Answer to task 5

1. Diagnosis: dermatomyositis, subacute course, 3rd degree of activity with damage to the muscles of the proximal parts of the upper and lower extremities, joints (polyarthralgia, FC II), skin (Gottron erythema, V-syndrome, "shawl" syndrome, "mechanic's hand").
2. Additional examination plan: general blood analysis, general urine analysis, biochemical blood analysis (ALT, AST, CPK), immunological studies (antinuclear antibodies, myositis-specific antibodies (to the Jo-1, Mi-2 antigen, etc.), electromyography, muscle biopsy, chest x-ray/CT, studies to exclude the paraneoplastic process (ultrasound, FGDs, colonoscopy, etc.).
3. Differential diagnosis: myasthenia gravis, hereditary muscle diseases, drug-induced myopathy. It is necessary to exclude the tumor nature of the process.
4. Treatment. NSAIDs to reduce pain. Prednisone 1 mg/kg/day, in the absence of positive dynamics for a month, the dose should be increased to 2 mg/kg/day. Methotrexate from 25 mg/week inside. Folic acid 5 mg/week on days free of methotrexate. If the disease is highly active, pulse therapy, plasmapheresis, and intravenous immunoglobulin can be used.

Answer to task 6

1. Diagnosis: Sjogren's disease, chronic course, activity of the II degree with damage to the salivary glands (bilateral mumps) with hypofunction of the II degree, the oral mucosa (stomatitis), cervical caries, damage to the lacrimal glands (dry keratoconjunctivitis, hypolacrimia of the III art.), joints (polyarthralgia, FC I).
2. Additional survey plan. General blood analysis, general urine analysis, biochemical blood analysis, RF, ANA, double-chiral DNA antibodies, Ro antigen antibodies (aSS-A/Ro) and more specific La antigen antibodies (aSS-B/La).
3. Differential diagnosis: sarcoidosis, parenchymal mumps, lymphoma.
5. Tactics of treatment. Glucocorticoids and cytostatics (hydroxychloroquine) in small doses for a long time. Intraocular artificial tears, cyclosporine, corticosteroids. Mouthwash, with the development of infection-antibacterial, antiseptic and antifungal drugs.

Answer to task 7

Diagnosis: granulomatosis with polyangiitis (wegenera), subacute course, advanced stage, activity of 3 degrees with damage to the upper respiratory tract (rhinitis), lungs (infiltrative lung damage, hemoptysis, DN I), kidneys (glomerulonephritis, morphologically unspecified, nephrotic syndrome, chronic

kidney disease, C3A - clarification of the stage after determining the glomerular filtration rate). Arterial hypertension, grade 3, risk III. Mild anemia.
Additional survey plan. General blood analysis, general urine analysis, a sample of Rehberg. Biochemical analysis of blood: urea, creatinine, uric acid, total protein, protein fractions, potassium, sodium, CRP, with a decrease in glomerular filtration rate below 60 ml/min – calcium, phosphorus, parathyroid hormone. Immunological studies: rheumatoid factor, ANCA, circulating immune complexes, immunoglobulins. Computed tomography of the lungs. Biopsy of the affected tissues of the upper respiratory tract, kidney biopsy.
Differential diagnosis: other systemic ANCA-associated vasculitis (eosinophilic granulomatous polyangiitis, microscopic polyangiitis), other systemic vasculitis (nodular polyarteritis, hemorrhagic vasculitis, goodpasar's disease), diffuse connective tissue diseases, granulomatous diseases (sarcoidosis, berylliosis, eosinophilic pneumonia, Leffler syndrome, tuberculosis, syphilis), malignant tumors.
Tactics of treatment. Induction therapy: GCS in combination with cyclophosphamide for 3-6 months, with the development of rapidly progressing nephritis, combined with plasmapheresis. When refractional for additionally prescribe infliximab (or rituximab). Maintenance therapy-GCS and cyclophosphamide (or azathioprine, methotrexate) for 2-5 years.

Answer to task 8

1. Diagnosis: systemic lupus erythematosus, acute course, 3rd degree of activity, with skin lesions (erythema of the face according to the "butterfly" type), blood vessels (Raynaud's syndrome, capillaries on the fingertips, palms, nail beds), joints (polyarthralgia), lupus nephritis (morphologically unspecified), antiphospholipid syndrome, category I (antibodies to cardiolipin and lupus anticoagulant), pancytopenia (anemia, leukopenia, thrombocytopenia). Symptomatic arterial hypertension.
2. Additional survey plan. General blood analysis, common urine analysis, daily proteinuria, urine analysis according to Nechyporenko, zimnitskiy, a sample of Rehberg. Biochemical blood analysis: ALT, AST, CPK, glucose, urea, creatinine, total protein, albumin, CRP, potassium, sodium. Immunological markers of the disease: antinuclear antibodies, antibodies to double-chiral DNA, antiphospholipid antibodies (lupus anticoagulant, antibodies to cardiolipin, antibodies to beta-2-glycoprotein 1) after 12 weeks. X-rays/ultrasound of the affected joints. Echocardiography, ECG, ultrasound of the abdominal cavity. Kidney biopsy to clarify the morphological variant of nephritis.
3. Differential diagnosis: rheumatoid arthritis, mixed connective tissue disease (Sharpe's syndrome), dermatomyositis, systemic vasculitis.

4. Treatment. Pulse therapy: methylprednisolone 1000 mg intravenously for 3 days, cyclophosphamide 600-1000 mg intravenously once. Then prescribe prednisone inside 1 mg/kg/day (but not more than 60 mg), cyclophosphamide is administered in / in a drip of 600-1000 mg 1 time per month for 6 months. Next, an oral cytostatic is prescribed, the prednisolone dose is reduced to 0.15-0.2 mg/kg/day. Anticoagulants, antiplatelet agents and vasoprotection are recommended. Angiotensin-converting enzyme inhibitors and diuretic drugs are shown.

Answer to task 9

Diagnosis: IgA-associated vasculitis (hemorrhagic vasculitis, Schenlein-Genoch purpura), acute course, I attack, active phase, activity of 3 degrees, mixed variant (skin, joint and abdominal syndromes).

Additional survey plan. General blood analysis, common urine analysis, daily proteinuria, urine analysis according to Nechyporenko, zimnitskiy, a sample of Rehberg. Biochemical blood analysis: ALT, AST, CPK, glucose, urea, creatinine, total protein, albumin, CRP, potassium, sodium, coagulogram. X-rays/ultrasound of the affected joints. Echocardiography, ECG, ultrasound of the abdominal cavity, FGDs, colonoscopy.

Differential diagnosis: other systemic vasculitis with small vessel damage, intestinal obstruction, peritonitis.

Treatment. Glucocorticoids (prednisolone) and cytostatics (hydroxychloroquine) in small doses for a long time. Disaggregants-kurantil 2-4 mg/kg per day, pentoxifylline 100-300 mg in 250 ml of 0.9% sodium chloride solution intravenously. Heparin in a dosage of 200-300 UNITS/kg of body weight per day, divided into 4 subcutaneous injections, is gradually canceled with a decrease in the single dose. In severe cases, plasmapheresis is prescribed.

Answer to task 10

Diagnosis: rheumatoid arthritis: seropositive (in the presence of RF) polyarthritis of the II x-ray stage, III degree of activity with systemic manifestations (rheumatoid nodules), functional insufficiency of the II art. NSAID-gastropathy. Mild anemia.

Additional survey plan. General blood analysis, biochemical blood analysis, General urine analysis, determination of rheumatoid factor and antibodies to cyclic citruline peptide in blood serum. X-rays/ultrasound of the affected joints. Echocardiography, ECG, ultrasound of the abdominal cavity.

Differential diagnosis: SLE, primary osteoarthritis.

Treatment. Selective COX-2 inhibitors for a short time (until joint pain is reduced): meloxicam (or nimesulide, or celecoxib) in combination with the proton pump

inhibitor omeprazole (20-40 mg/day). Methotrexate 20 mg per week (or methotrexate 20 mg per week intramuscularly), the correction of the dose of methotrexate is carried out depending on the response to treatment, but not earlier than a month. Folic acid 5 mg/week outside of methotrexate. Given the high activity of the disease-prednisone 10 mg/day inside for 1-1. 5 months.

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Учебное издание

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АУТОИММУННЫЕ РЕВМАТИЧЕСКИЕ ЗАБОЛЕВАНИЯ: ПРИНЦИПЫ ДИАГНОСТИКИ И ЛЕЧЕНИЯ

Пособие

Редактор Л.Р. Выхристенко
Компьютерная верстка Л.Р. Выхристенко

Подписано в печать . Формат бумаги 1/16.
Бумага типографская №2. Ризография.
Усл. печ. л. . Уч.-изд. л. . Тираж экз. Заказ № .
Издатель и полиграфическое исполнение Учреждение образования
«Витебский государственный
ордена Дружбы народов медицинский университет»
ЛП №02330/453 от 30.12.2013г.
Пр. Фрунзе, 27, 210023, Витебск