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V. N. Karazin Kharkiv National University

MANAGEMENT OF A PATIENT WITH ARTHRALGIA / MYALGIA (SYSTEMIC LUPUS ERYTHEMATOSUS)

Methodical recommendations
for the preparation of students of higher education in the 6th year of study
in the discipline «Internal Medicine»

Electronic resource

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M 24

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M 24 **Management** of a patient with arthralgia / myalgia (systemic lupus erythematosus) : methodical recommendations for the preparation of students of higher education in the 6th year of study in the discipline «Internal Medicine» [Electronic resource] / compil. T. M. Tykhonova, M. Yu. Gorshunska, N. V. Lysenko, N. Ye. Barabash, L. O. Martymianova. – Kharkiv : V. N. Karazin KhNU, 2025. – (PDF 33 p.)

The methodical recommendations outline the main aspects of managing patients with arthralgias and myalgias using the example of systemic lupus erythemasus.

For students of the 6th year to prepare for practical classes in the discipline «Internal Medicine».

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CONTENT

LIST OF CONVENTIONAL ABBREVIATIONS

ANA	antinuclear antibodies
AZA	azathioprine
APLAs	antiphospholipid antibodies
APS	antiphospholipid syndrome
BLM	belimumab
LN	lupus nephritis
LA	lupus anticoagulant
IVIG	intravenous immunoglobulin
GCs	glucocorticoids
HCQ	hydroxychloroquine
ECG	electrocardiography
IV	intravenous (infusion)
CT	computer tomography
CNS	central nervous system
MP	methylprednisolone
MTX	methotrexate
MRI	magnetic resonance imaging
MMF	mycophenolate mofetil
NSAIDs	nonsteroidal anti-inflammatory drugs
PZ	prednisolone
RIX	rituximab
SCTD	systemic connective tissue diseases
SLE	systemic lupus erythematosus
US	ultrasound examination
CP	cyclophosphamide
anti-dsDNA	anti-double-stranded deoxyribonucleic acid antibodies
anti-Sm	anti-Smith antibodies

Anti-β2GP1	beta-2 glycoprotein 1 antibodies
ACA	anti-cardiolipin antibodies
ACR	American College of Rheumatology
EULAR	European League Against Rheumatism
ISN/RPS	International Society of Nephrology (ISN)/Renal Pathology Society (RPS)
SELENA–SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
ACEi	angiotensin-converting enzyme inhibitors
ARB	angiotensin receptor blockers
ANI	anifrolumab
BSA	body surface area
CNI	calcineurin inhibitor
eGFR	estimated glomerular filtration rate
PO	per os
SGLT2i	sodium glucose transporter 2 inhibitors
TAC	tacrolimus
Upr	urine protein
VKA	vitamin K antagonists
VOC	voclosporin
PLTs	platelet count
BILAG	British Isles Lupus Assessment Group
ALT	alanine aminotransferase
AST	aspartate aminotransferase
RA	rheumatoid arthritis
TTP	thrombotic thrombocytopenia purpura

INTRODUCTION

Arthralgias and myalgias are the most frequent complaints in systemic connective tissue diseases (SCTD). In the early stages of the disease, patients can turn to specialists of various specialties and they should pay attention to general complaints to perform early diagnosis and timely treatment appointment. SCTD are diseases with severe damage to internal organs, a polysyndromic clinic, the beginning of which can be precisely pains in the joints and muscles. Most often in clinical practice, doctors encounter these symptoms against the background of such diseases as systemic lupus erythematosus (SLE).

SLE is a multisystem disease, sometimes limited to one or more organs. The pathogenesis of SLE includes a complex interaction of genetic and environmental factors, various disorders of innate and acquired immunity, hyperproduction of cytokines, pathological activation of B cells, disruption of intracellular signaling of T cells, defects in apoptosis and cell necrosis.

1. BASIC KNOWLEDGE, SKILLS, ATTAINMENTS NECESSARY FOR THE TOPIC STUDYING

Names of previous disciplines	Acquired skills
Foreign language	To be able to work with foreign literature to obtain data on modern methods of diagnosis and treatment of rheumatological patients
Medical informatics	Apply modern computer programs and be able to work with them, have statistical methods for processing the results of clinical studies, analyze the results of studies, be able to evaluate and interpret the results of clinical research from information sources, have the ability to work with electronic databases
Human anatomy. Normal physiology. Histology, cytology and embryology	Know the normal structure and functions of the musculoskeletal system, understand and determine the relationship of its structure and function with other organs and systems of the human body
Microbiology, virology and immunology	To be able to analyze the peculiarities of the microorganisms vital activity, to know the basics of antibiotic therapy, the conditions for the development of microorganisms resistance Understand the pathogenesis of infectious diseases of the body as well as musculoskeletal system pathology, evaluate the effectiveness and safety of antimicrobial agents
Pathomorphology Pathophysiology	Know typical pathological processes in the human body: mechanisms of development, changes, compensatory reactions, the development of «cause-effect» relationships in the pathology of the whole body Describe and schematically represent the mechanism of development of typical pathological syndromes in rheumatological diseases, justify pathogenetic approaches to drug therapy

Pharmacology	Be able to navigate in the nomenclature of medicines. Know the mechanism of action of medicines, their pharmacodynamics, indications and contraindications for their use Know the features of the clinical pharmacology of drugs used in the treatment of rheumatological diseases, the features of the pharmacological action of these drugs in different categories of patients Make a reasonable choice of individual drugs and therapy schemes in accordance with the principles of evidence-based medicine, optimization of treatment schemes, evaluate the effectiveness and safety of pharmacotherapy taking into account the individual characteristics of the patient, the presence of concomitant diseases
Propaedeutics of internal medicine	Conduct a physical examination of patients, analyze the results of basic laboratory and instrumental research methods To determine the leading syndromes and symptoms in rheumatological patients. To be able to make a differential diagnosis, justify and formulate a diagnosis on the basis of a physical examination and the data of additional methods

The student should know:

- the difference between arthralgias and arthritis, myalgias and myositis;
- mechanisms of connective tissue damage, including - autoimmune;
- classification of SCTD, according to the international recommendations;
- diagnostic standards (diagnostic criteria) of SCTD, according to the international recommendations;
- main risk factors and etiological factors, pathogenesis, clinic, differential diagnosis, medical and social expertise, prevention of SLE;
- quality of life of patients with SCTD;
- standards of treatment of SCTD, according to the international recommendations;
- prophylactic methods aimed at SCTD prevention;

– prognosis of SCTD in a patient.

The student should be able to:

– collect complaints, anamnesis;
– carry out the method of objective examination of a patient with SLE;
– diagnose SLE using diagnostic criteria;
– carry out differential diagnosis of SLE;
– establish a clinical diagnosis of SLE on the basis of these complaints, anamnesis, objective examination of the patient, laboratory and instrumental diagnostics, using diagnostic criteria;
– prescribe treatment for SLE, according to the international algorithms;
– conduct a medical and social examination of patients with SLE.

2. DIAGNOSTIC ALGORITHM OF SYSTEMIC LUPUS ERYTHEMATOSUS

Considering the variety of systemic clinical manifestations of SLE and the difficulties of diagnosis in the early stages, it is recommended to use the following algorithm. If the patient has 2 or more symptoms: constitutional, lesions of the musculoskeletal system, skin, kidneys, gastrointestinal tract, lungs, cardiovascular, reticuloendothelial system, hematological syndromes, psychoneurological manifestations, he should be sent for an antinuclear antibodies (ANA) test. If the result is negative, the immunoreactivity of SLE is very low and it is necessary to extend the diagnostic search in another direction. If there is a positive result, the patient should be referred for specific immunological tests such as anti-double-stranded deoxyribonucleic acid antibodies (anti-dsDNA) and anti-Smith antibodies (anti-Sm). It should be taken into account that even with their positive result and the absence of organ involvement or typical laboratory signs, the diagnosis of SLE is unlikely. In the case of obtaining high titers and at least 10 points according to the EULAR/ACR

(European League Against Rheumatism / American College of Rheumatology) 2019 criteria presented in Table 1, a diagnosis of SLE can be established.

When calculating the criteria, the following manifestations are taken into account:

- ANA in a titer ≥1:80 on cells of the transplantable epithelioid line of human laryngeal adenocarcinoma HEp-2 or an equivalent positive test at least once;
- fever – temperature > 38.3ºC;
- leukopenia – number of leukocytes < 4×10^9/l;
- thrombocytopenia – the number of platelets < 100 thousand units/μl;
- autoimmune hemolysis – reticulocytosis, low haptoglobin, elevated indirect bilirubin, elevated lactate dehydrogenase, and positive Coombs test;
- delirium – 1) change in consciousness or level of agitation with reduced ability to focus, 2) development of symptoms within an hour to < 2 days, 3) fluctuating symptoms throughout the day, 4) or 4a) acute / subacute change in cognition (eg, memory deficits or disorientation) or 4b) change in behavior, mood, or affect (eg, restlessness, inversion of the sleep/wake cycle);
- psychosis – 1) delusions and/or hallucinations without awareness and 2) absence of delirium;
- convulsions – primary generalized convulsions or partial / focal seizures;
- non-scarring alopecia - recorded by a doctor;
- ulcers in the oral cavity recorded by a doctor;
- subacute cutaneous or discoid lupus erythematosus observed by a doctor, cutaneous or papulosquamous (psoriasiform) skin rash. Discoid lupus erythematosus, erythematous-purple skin lesions with secondary changes of atrophic scarring, dyspigmentation, often follicular hyperkeratosis / hemato-logic resulting in scarring alopecia on the scalp. Subacute cutaneous lupus: a vacuolar dermatitis presentation consisting of a perivascular

lymphohistiocytic infiltrate, often with 64 marked cutaneous mucin. Follicular keratin plugs may be visible on the scalp;

- acute cutaneous lupus – a rash on the cheeks or a generalized maculopapular rash, which was recorded by a doctor. If a skin biopsy is performed, typical findings should be present: vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with marked cutaneous mucin;
- pleural or pericardial effusion – imaging evidence (such as ultrasound (US), X-ray, computed tomography (CT), magnetic resonance imaging (MRI)) of pleural or pericardial effusion or both;
- acute pericarditis – ≥ 2 of 1) pericardial chest pain (usually sharp, worse with inspiration, improved forward tilt), 2) pericardial friction murmur, 3) pericardial scar, electrocardiogram (ECG) with new episode of ST elevation or depression PR, 4) occurrence of new or worsening pericardial effusion during imaging (for example, US, X-ray, CT, MRI);
- joint damage or synovitis of two or more joints characterized by swelling or effusion, or pain in two or more joints and at least 30 minutes of morning stiffness;
- proteinuria – more than 0.5 g / 24 hours / urine per day or an equivalent of protein / creatinine ratio in urine;
- lupus nephritis (LN) type II or V on renal biopsy according to the ISN/RPS (International Society of Nephrology (ISN) / Renal Pathology Society (RPS)) 2018 classification – class II: mesangial proliferative LN – mesangial hypercellularity of any degree or expansion of the mesangial matrix by light microscopy with mesangial immune deposit. Class V: membranous LN – global or segmental subepithelial immune deposits or their morphological consequences by light microscopy and immunofluorescence;
- ISN/RPS 2018 classification of LN – class III or IV. Class III: LN: active or inactive segmental or global endocapillary or extracapillary glomerulonephritis involving < 50 % of all glomeruli, typically with focal

subendothelial immune deposits. Class IV: diffuse LN: active or inactive diffuse, 65 segmental or global endocapillary or extracapillary glomerulonephritis involving ≥ 50 % of all glomeruli, usually with diffuse subendothelial immune deposits, with or without mesangial changes;

- positive antiphospholipid antibodies (APLAs) – ACA (IgA, IgG or IgM) in medium or high titer (> 40 upper limit of normal Ig G, Ig M or APLAs Ig M or > 99th centile) or positive anti-β2GP1 (IgA, IgG or IgM) or positive LA;
- low C3 or C4–C3 or C4 below the lower limit of normal;
- anti-ds DNA or anti-SM antibodies – anti-ds DNA in an enzyme-linked immunosorbent assay with demonstrated ≥ 90 % specificity for SLE relative to appropriate controls or anti-Sm antibodies.

Table 1

Classification criteria of systemic lupus erythematosus

(EULAR /ACR, 2019)

Entry criteria
ANA at a titer ≥ 1:80 on cells of the transplantable epithelioid line of human laryngeal adenocarcinoma HEp-2 or an equivalent positive test, at least once.
↓
If absent, do not classify as SLE If present, apply additive criteria
↓

Additive criteria			
Do not count a criterion if there is a more likely explanation than SLE. Occurrence of a criterion on at least one occasion is sufficient. SLE classification requires at least one clinical criterion and ≥ 10 points. Criteria need not occur simultaneously. Within each domain, only the highest weighted criterion is counted toward the total score.			
Clinical domains and criteria	**Weight**	**Immunology domains and criteria**	**Weight**
Constitutional Fever	2	***Antiphospholipid antibodies*** ACA *OR* Anti-β2GP1 antibodies *OR* LA	2

Hematological		***Complement proteins***	
Leukopenia	3	Low C3 OR low C4	3
Thrombocytopenia	4	Low C3 AND low C4	4
Autoimmune hemolysis	4		
Neuropsychiatric		***SLE-specific antibodies***	
Delirium	2	Anti-dsDNA antibodies* *OR*	
Psychosis	3	Anti-Sm antibodies	6
Seizure	5		
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous *OR* discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria > 0.5 g/24 h	4		
Renal biopsy Class II *OR* V lupus nephritis	8		
Renal biopsy Class III *OR* IV lupus nephritis	10		

↓

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

(Anti-β2GP1**,** beta-2 glycoprotein 1 antibodies; ACA, anti-cardiolipin antibodies; LA, lupus anticoagulant.)

Note:

* In an assay with ≥ 90 % specificity against relevant disease controls Additional criteria items within the same domain will not be counted.

The algorithm for diagnosis of SLE is presented in Fig. 1.

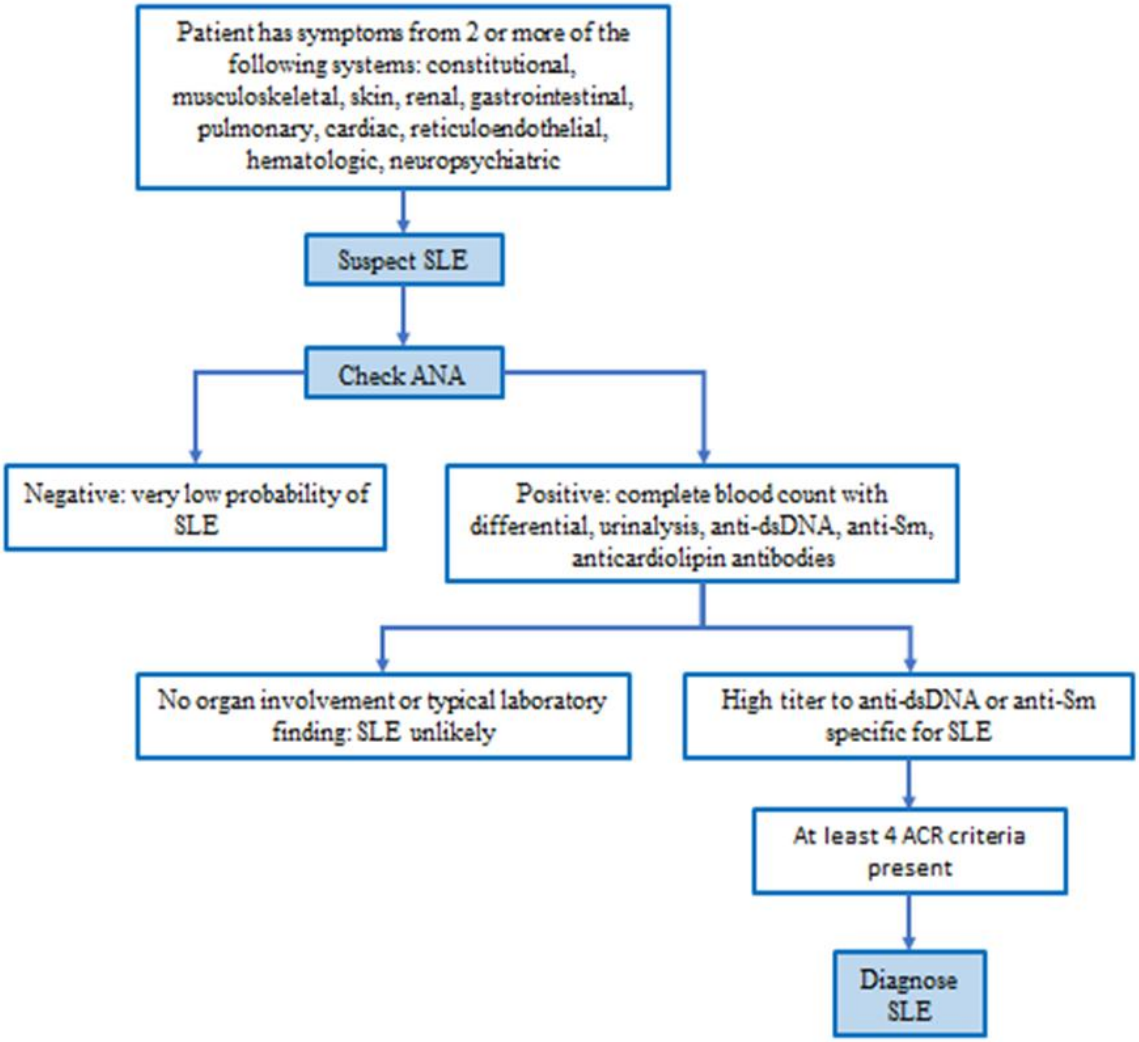

Fig. 1. Algorithm for diagnosis of SLE

3. TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

The treatment of SLE should be a common decision of the patient and the doctor, taking into account medical, social and individual costs. Currently, the optimal therapy of this disease is based on a combination of non-pharmacological and pharmacological treatment methods. The main directions of treatment are long-term survival of patients, prevention of damage to target organs and improvement of life quality.«Treat to target» begins from the moment of diagnosis with the immunosuppressive therapy prescription, while frequent (every 3 months before achieving remission, every 6 months after achieving remission) and objective control of the patient's condition is necessary. In the absence of an effect from the treatment, the schemes are changed until the goals are achieved, against the background of constant dynamic monitoring. In severe cases, in order to quickly achieve control over the activity of the disease, high-intensity immunosuppressive therapy is used, followed by a long period of less intensive therapy to prevent relapses. At this point, it should be noted that the «feeling bad» of SLE patients does not always correlate with an increase in the activity of the disease, and may not require a change in immunosuppressive therapy, but symptomatic treatment.

A very important point is the education of patients regarding the mechanisms of disease development, visits to schools of health for patients with SLE, forums as well as psychological consultations of specialists. In addition all the family members should be involved in counseling regarding the disease; family must have a thorough understanding of the disease, its potential severity and complications of the disease and treatment.

Non-pharmacological methods of SLE treatment include sun protection, smoking cessation, weight control and regular exercise.

The updated EULAR guidelines (2019) for the management of patients with non-renal systemic lupus erythematosus are presented in Fig. 2.

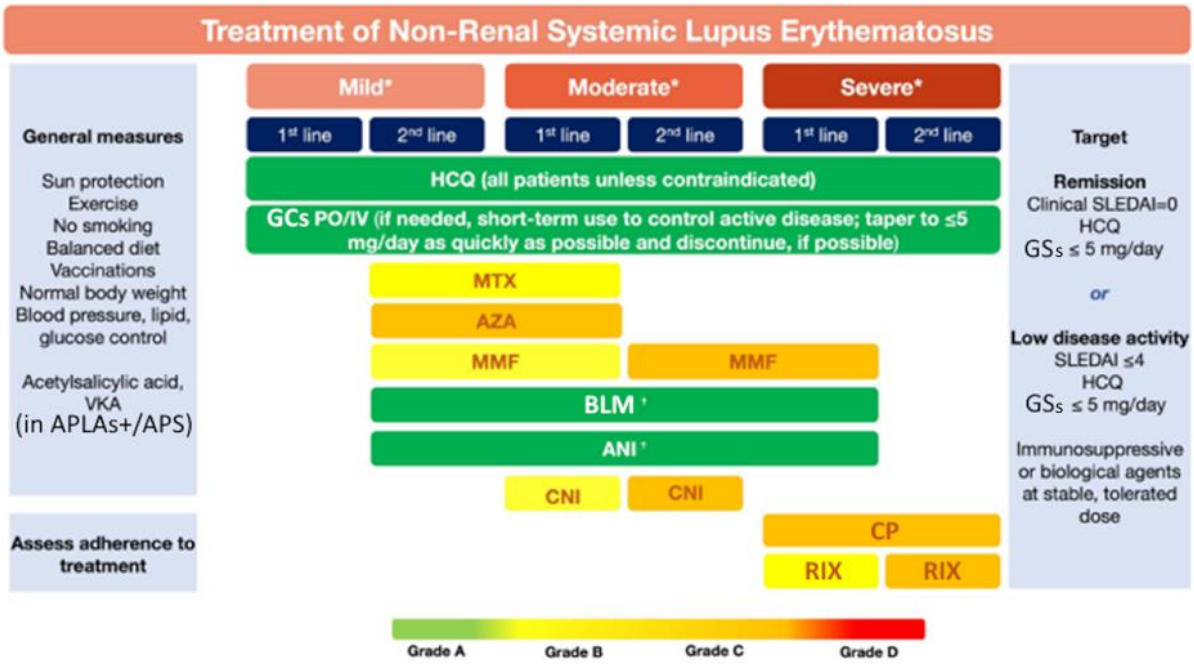

Fig. 2. Treatment of non-renal systemic lupus erythematosus (ANI, anifrolumab; aPLAs, antiphospholipid antbodies; APS, antiphospholipid syndrome; AZA, azathioprine; BLM, belimumab; BILAG, British Isles Lupus Assessment Group; CNI, calcineurin inhibitor; CP, cyclophosphamide; GCs, glucocortocoids; HCQ, hydroxychloroquine; IV, intravenous; MMF, mycophenolate mofetil; MTX, methotrexate; PO, per os; RIX, rituximab; SLEDAI, SLE Disease Activity Index; VKA, vitamin K antagonists).

Note:

Top-to bottom sequence does not imply order of preference (eg, MTX, AZA and MMF are equal options for second-line therapy in mild disease or first-line therapy in moderate disease).

*Mild disease: constitutional symptoms; mild arthritis; rash ≤ 9 % body surface area (BSA); platelet count (PLTs) 50–100× 10^9 /L; SLEDAI ≤ 6; BILAG C or ≤ 1 BILAG B manifestation.

*Moderate disease: moderate–severe arthritis (‘RA (rheumatoid arthritis)-like’; rash 9 %–18 % BSA; PLTs 20–50×10^9 /L; serositis; SLEDAI 7–12; ≥ 2 BILAG B manifestations).

*Severe disease: major organ threatening disease (cerebritis, myelitis, pneumonitis, mesenteric vasculitis); thrombocytopenia with PLTs < 20×10^9 /L; TTP (thrombotic thrombocytopenia purpura) -like disease or acute haemophagocytic syndrome; rash > 18 % BSA SLEDAI > 12; ≥ 1 BILAG A manifestations.

† Recommendation of belimumab and anifrolumab as first-line therapy in severe disease refers to cases of extrarenal SLE with non-major organ involvement, but extensive disease from skin, joints, and so on. The use of anifrolumab as add-on therapy in severe disease refers mainly to severe skin disease. For patients with severe neuropsychiatric disease, anifrolumab and belimumab are not recommended.

Conservative treatment of systemic lupus erythematosus

Medicines used in the treatment of SLE:

– glucocorticoids (GCs);
– antimalarial drugs;
– cytotoxic drugs;
– nonsteroidal anti-inflammatory drugs;
– immunobiological drugs.

Glucocorticoids (GCs). Doses and method of application depend on the type and severity of organ damage, preference is given to short-acting drugs (prednisolone (PZ), methylprednisolone (MP)). The initial dose of GCs is selected according to the activity of the disease and the individual characteristics of the patient (age, weight, concomitant pathology). Schematically, the choice of the dose of GCs depending on the activity of the disease (index (SELENA–SLEDAI) presented in table 2.

Table 2

Selection of the dose of glucocorticoids depending on the activity of SLE

Low activity (SLEDAI–2K or SELENA–SLEDAI 1–5 points)	PZ less than 7.5 mg/day, MP 6 mg/day or cancellation of GCs
Moderate activity (SLEDAI–2K or SELENA–SLEDAI 6–10 points)	PZ 7.5–30 mg/day, MP 6–24 mg/day for 4 weeks with a gradual decrease to low-dose sustaining therapy (PZ 5–7.5 mg/day, MP 4–6 mg/day)
High activity (SLEDAI–2K or SELENA–SLEDAI 11–19 points) and very high (SLEDAI–2K or SELENA–SLEDAI more than 20 points)	PZ 31–100 mg/day, MP 0.5–1 mg/kg body weight 4–12 weeks in combination with cytotoxic drugs

In case of rapidly progressive damage to vital organs (damage to the kidneys, central nervous system (CNS), systemic vasculitis, alveolitis), high doses of GCs (PZ 1 mg/kg per day) are prescribed.

The dose of GCs is gradually reduced to a low sustaining dose of 4–6 mg/day under careful clinical and laboratory control. If the initial dose is higher than 40 mg of PZ, 32 mg of MP is reduced by 5–10 mg every one to two weeks; 40–20 mg of PZ, 32–16 mg of MP – by 5 mg every one to two weeks; 20–10 mg of PZ, 16–8 mg of MP – 2.5 mg every two to three weeks; 10–5 mg of PZ, 8–4 mg of MP – 1 mg every two to four weeks; 5 mg of PZ, 4 mg of MP – 0.5 mg for two to four weeks.

During the long-term GCs treatment, it is necessary to resolve the issue of using a steroid-sparing agent and prevent the development of diabetes mellitus, osteoporosis, atherosclerosis, hyperlipidemia, arterial hypertension, cataracts, glaucoma, and damage to the gastrointestinal tract. When achieving remission with the help of immunosuppressive therapy, it is desirable to cancel GCs.

Pulse therapy in patients with SLE is performed only in hospital, as a method of emergency care for severe manifestations and ineffectiveness of oral GCs. The drug of choice is MP. In the 2019 EULAR guidelines, the cumulative MP dose for pulse therapy is 500–2500 mg, depending on body weight and disease severity. After pulse therapy, it is recommended to switch to oral GCs at a dose of 0.3–0.5 mg/kg/day for 4 weeks with a further decrease to 7.5 mg/day, equivalent to PZ, for 3–6 months. Schemes of pulse therapy are presented in Table 3.

Table 3

Types of pulse–therapy with MP

Mini pulse therapy	250 mg/day IV drips for 3 days
Midi pulse therapy	500 mg/day IV drips for 3 days
Classic pulse therapy	1000 mg/day IV drips for 3 days
Combined pulse therapy	MP at a dose of 1000 mg/day IV drips for 3 days + CP at a dose of 15–20 g/kg (1000 mg) intravenously on the second day
Synchronous pulse therapy	Conducting plasmapheresis with a course of 3–6 procedures every other day followed by combined pulse therapy of MP and CP

***Antimalarial drugs*.** In the absence of contraindications, HCQ should be prescribed to all patients with SLE. The dose is 200–400 mg/day, to prevent ophthalmological complications no more than 0.5 mg/kg. An ophthalmologist's consultation is required both before the start of treatment and once a year thereafter. Regular use of HCQ reduces the frequency of exacerbations and the risk of new organs damage, provides antiplatelet and lipid-lowering effects. HCQ can be used during pregnancy and lactation. If skin manifestations or retinopathy occur, consider an alternative antimalarial drug, quinacrine.

Cytotoxic drugs. In patients who do not respond to HCQ (in monotherapy or in combination with GCs), or patients who cannot reduce the dose of GCs to less than 7.5 mg/day (PZ), the question of prescribing immunosuppressive drugs should be considered. The choice of the drug depends on the prevailing symptoms of the disease, age, reproductive potential and cost. AZA, MTX, MMF, CP are effective in patients with SLE and characterized by steroid-sparing effects. The administration of cytotoxic drugs both in the induction and supportive phases of therapy should be carried out under the control of a rheumatologist, due to the high risk of developing 33 bacterial and viral infections, toxic hepatitis, suppression of bone marrow hematopoiesis. Doses, side effects and the algorithm for managing patients on the background of cytotoxic drugs are presented in the table 4.

Table 4

Cytotoxic drugs for the treatment of SLE

Medicine	Dose	Side effects	Clinical monitoring
AZA	1.5–2.5 mg per 1 kg per day	Dyspepsia phenomena, hepatotoxicity, rash, leukopenia	General and biochemical blood tests every 3 months to monitor myelo-suppression and lympho-proliferative disorders

Continuation of table 4

MTX	15–25 mg per week	Myelotoxicity and interstitial pneumonitis (when taking folic acid, the risk is lower), reverse increase of transaminases, liver fibrosis	Complete blood count and biochemistry every 3 months to monitor myelosuppression, liver fibrosis, chest X-ray every 6–12 months to monitor pulmonary infiltrates and pulmonary fibrosis
MMF	2–3 g per day	Bone marrow suppression, acute diarrhea, pulmonary fibrosis	Complete and biochemical blood tests every 3 months to monitor myelo-suppression and infections
CP	From 1 to 3 mg per 1 kg per day	Leukopenia; hemorrhagic cystitis; reverse alopecia; infertility; leukemia, lymphoma, bladder carcinoma	Complete and biochemical blood tests every 3 months to monitor myelo-suppression, malignancy, immunosuppression, and hemorrhagic cystitis

CP is prescribed 1000 mg intravenously every month for 6 months or 500 mg every 2 weeks, up to 6 infusions. Considering its gonadotoxic effect in patients of childbearing age, this drug is used only in case of damage to vital organs and systems (kidneys, cardio-pulmonary or neuro-psychiatric complications).

MMF is prescribed in a dose of 2–3 g/day for 6 months. It is very effective in kidney damage. MMF is used as supportive therapy at a dose of 1–2 g/day or AZA at 2–3 mg/kg of body weight per day for 6 months.

MTX is used for the ineffectiveness of HCQ and GCs in the recommended dose of at least 15 mg per week, in combination with folic acid 5 mg per week, except on the day of MTX administration. It should be noted the positive effect of this drug on such manifestations of SLE as alopecia and pleurisy. However, the appearance of oral ulcers and cytopenia should be clinically and laboratory monitored.

Nonsteroidal anti-inflammatory drugs (NSAIDs) recommended for use in standard therapeutic doses in a short course for fever, myalgias and arthralgias.

Intravenous immunoglobulin (IVIG) usually used in a dose of 0.4 to 2 g/kg, the drug is administered 1 g/kg for 2 days or 0.4 g/kg for 4–5 days, treatment courses are repeated monthly. Indications for its prescription may be severe damage to the CNS, bacterial infections and severe thrombocytopenia.

Immunobiological drugs used only in the specialized medical organization with the presence of laboratory and diagnostic departments for timely diagnosis of conditions associated with the development of undesirable phenomena against the background of treatment. Monoclonal antibody BLM inhibits B cell hyperreactivity. Its long-term use contributes to the achievement and maintenance of remission, even in the case of a «refractory» course of the disease, reduces the risk of irreversible organ damage and allows patients to be kept on the minimum supportive dose of GCs.

BLM is prescribed in a hospital at 10 mg/kg of body weight (days 0, 14th, 28th) and then continued in an outpatient setting every month for at least 6 months. In the absence of an effect from treatment with high doses of GCs and cytotoxic drugs, damage to the CNS during the first 3–4 days from the start of induction therapy for LN, experts recommend prescribing RIX at a dose of 500–1000 mg once every 2 weeks (maximum total dose per year – 2000 mg).

Therapy with immunobiological drugs has a number of features:
it is recommended to avoid prescribing during active infections, including skin infections, sepsis, tuberculosis, hepatitis B and C, HIV infection, hypersensitivity to the protein component of the drugs or other components of the solution, in the presence of immunodeficiency states (for example, hypogammaglobulinemia, a low level of CD4 and CB8 lymphocytes, in first of all when planning the appointment of RIX), liver failure (increase in the upper limit of the reference values of alanine aminotransferase (ALT), aspartate aminotransferase (AST)

concentrations > 5 times), oncological diseases (with the exception of non-melanoma skin cancer) in the anamnesis during the last 10 years;

- recommended vaccination only with inactivated vaccines (against influenza virus and pneumococcal infection). It is better for patients over 60 years of age to be vaccinated against herpes zoster virus infection.

Extracorporeal methods of treatment of SLE

Plasmapheresis is performed in the case of such dangerous conditions as coma, progressive myelitis, severe thrombocytopenia, cryoglobulinemic and hypergammaglobulinemic vasculitis. This method of treatment is additional and comprehensive against the background of standard therapy. It is recommended to remove 800 to 1000 ml of plasma, with or without replacement with fresh frozen plasma or albumin solution (depending on the level of total serum protein), at intervals of 2-3 days. To increase efficiency, it can be combined with IV infusions of MP from 250 to 1000 mg after each procedure and/or CP from 200 to 1000 mg once.

Differentiated therapy of SLE

- *Constitutional symptoms* need to take HCQ with or without GCs, in the absence of the effect – AZA, MTX, MMF, if necessary, BLM, RIX.
- *Skin lesions* treated with tacrolimus, GCs or acitretin locally, HCQ with or without GCs (PZ 5–7.5 mg/day, or MP 6–8 mg/day). If necessary, add AZA, or switch to MTX or MMF.
- *Arthralgias and arthritis* HCQ with or without low doses of GCs, in the absence of positive dynamics, add MTX or RIX. NSAIDs therapy in standard doses is possible.
- *Uncomplicated or skin vasculitis* requires treatment with systemic GCs with or without HCQ or MTX. In the absence of the effect of AZA or MMF, CP (IV) is a drug of choice.

- *Alveolitis* – systemic GCs + MMF or CP (IV), with no effectiveness of RIX, IVIG. Maintenance therapy of AZA or MMF.
- *Exudative polyserositis* – medium or high doses of GCs + HCQ, NSAIDs standard doses, colchicine. If there is no effect – pulse-therapy by MP + AZA, or BLM, RIX. In the presence of frequent relapses of IVIG 0.5 mg/kg for 5 days.
- *Myocarditis* – systemic GCs + CP (IV) with or without HCQ, in case of inefficiency – RIX, BLM, IVIG.
- *Pneumonitis* – pulse therapy with MP 1000 mg 3 days + CP 750 mg once a month for six months
- *APS* – anticoagulants with or without HCQ, in severe cases, a direct thrombin inhibitor is used.
- *Mononeuritis/neuronal lupus* systemic GCs with or without CP (IV), in case of ineffectiveness – RIX, IVIG, plasmapheresis.
- *Pulmonary arterial hypertension* systemic GCs + MMF or CP + antagonists of endothelin receptors. In case of ineffectiveness – RIX + inhibitors of phosphodiesterase 5 or prostaglandins.
- *Leukopenia* does not require special treatment. For agranulocytosis, pulse therapy without or with human recombinant granulocyte colony-stimulating factor (100 μg/day, 5 days) is indicated.
- *Thrombocytopenia* – systemic GCs with or without HCQ, in case of ineffectiveness + AZA or MMF, in severe cases RIX, CP or IVIG.
- *Kidney damage*

SLE is the main cause of morbidity and mortality. Constant monitoring of symptoms and manifestations indicating involvement of the kidneys is necessary for long-term preservation of their function. In the treatment of LN, phases of induction and supportive therapy are conventionally distinguished. The choice of drugs depends on the histological class of nephritis and the activity of SLE. The

induction phase is characterized by an intensive treatment regimen of at least 6–12 months. GCs are prescribed in a dose of more than 5 mg/kg and in the form of pulse therapy. With III and IV classes, the Euro-Lupus regimen is used, which includes low doses of CP (6 pulses within 2 weeks at a dose of 500 mg). Today, MMF and CNI, which are not inferior to the effectiveness of CP and are safer, occupy an important place in the treatment of LN.

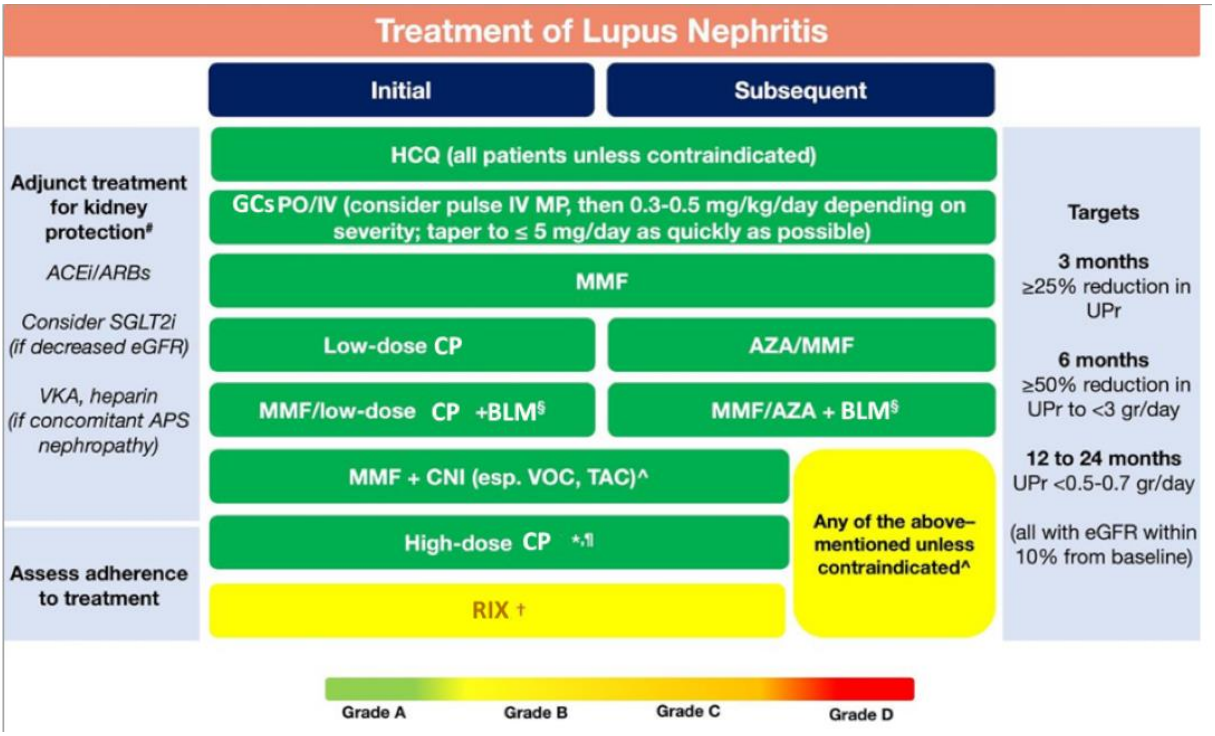

Fig. 3. Algorithm for the treatment of LN (EULAR/ERA–EDTA, 2019) (ACEi, angiotensin-converting enzyme inhibitors; APS, antiphospholipid syndrome; ARB, angiotensin receptor blockers; AZA, azathioprine; BLM, belimumab; CNI, calcineurin inhibitor; CP, cyclophosphamide; eGFR, estimated glomerular filtration rate; GCs, glucocortocoids; HCQ, hydroxychloroquine; IV, intravenous; MMF, mycophenolate mofetil; MP, methylprednisolone; PO, per os; RIX, rituximab; SGLT2i, sodium glucose transporter 2 inhibitors; TAC, tacrolimus; Upr, urine protein; VKA, vitamin K antagonists; VOC, voclosporin.)

Note:

Top-to-bottom sequence does not imply order of preference (similar to figure 2).

#In addition to general protective measures, as outlined in figure 2. BLM should always be given in combination with MMF or low-dose CP as initial therapy, and with MMF or AZA as maintenance therapy.

^CNIs should be given in combination with MMF.

*Particularly recommended in the presence of poor prognostic factors: reduced eGFR, histological presence of cellular crescents or fibrinoid necrosis, or severe interstitial inflammation.

Extension of high-dose CP to subsequent phase refers to severe LN cases, in which bimonthly or quarterly CP pulses may be given following six monthly pulses.

†In relapsing/refractory disease, especially after failure to CP-based regimens.

Induction therapy is not performed if the patient has class I or II hypertension. In the case of detection of proteinuria ≥ 0.5 g/day and erythrocyturia, it is recommended to prescribe GCs in medium and high doses (MP 0.5–1 mg/kg per day) for 4–6 weeks as monotherapy, with subsequent dose reduction to 0.125 mg /kg per day for 3 months or GCs in medium doses in combination with AZA 1–2 mg/kg per day. If there is no effect within 3 months, more intensive treatment regimens are used.

When class III/IV hypertension is detected, induction therapy of CP and MMF is performed against the background of MP pulse therapy (1000 mg per day for 3 days). Then high doses of GCs are prescribed orally (MP 0.5–1.0 mg/kg per day). MMF is used in a dose of 1.5–3 g/day for 6 months.

In patients with IV/V classes of hypertension, especially with rapid deterioration of kidney function, the presence of crescents and/or fibrinoid necrosis in the biopsy, induction therapy is performed with CP or MMF in combination with pulse therapy of MP and GCs internally in high doses (MP at least 1 mg /kg per day).

Induction therapy with the administration of MP 0.5 mg/kg per day in combination with MMF at 2–3 g/day is recommended for Class V LN.

If there is no effect from therapy within 6 months, or an exacerbation has occurred within 3 months from the start of therapy, you should try to change the drug (CP to MMF, or vice versa). RIX in a dose of 500–1000 mg every week (maximum total dose – 2000 mg) is used in case of ineffectiveness of any of the induction therapy schemes mentioned above.

In order to maintain the clinical and laboratory effect, it is recommended to prescribe MMF at a dose of 2 g/day or AZA at a dose of 2 mg/kg per day as a supportive phase of therapy. It should be noted that in addition to the main therapy with GCs and cytostatic drugs, concomitant conditions should be corrected in patients with LN. For the prevention of thrombotic complications, patients with positive APS should take low doses of acetylsalicylic acid, in the presence of nephrotic syndrome with severe hypoalbuminuria – anticoagulants, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers with a nephroprotective purpose, in case of dyslipidemia – statins, to prevent the development of osteoporosis – a calcium preparation and vitamin D.

TEST TASKS FOR SELF-CONTROL

1. Which of the following kidney lesions is most characteristic of SLE?

   A. Interstitial nephritis.
   B. Nephrolithiasis.
   C. Amyloidosis.
   D. Glomerulonephritis.
   E. Nephroptosis.

2. SLE is characterized by:

   A. Septic endocarditis.
   B. Loeffler's endocarditis.
   C. Rheumatic endocarditis.
   D. Libman-Sacks endocarditis.
   E. Infectious endocarditis.

3. What drugs are recommended for SLE?

   A. Glucocorticoids.
   B. Hydroxychloroquine.
   C. None of the above drugs.
   D. All the listed drugs.

4. Who is more likely to suffer from SLE?

   A. Women in menopause.
   B. Elderly men.
   C. Women of childbearing age.
   D. Boys in adolescence.
   E. Children of school age.

5. For SLE, the triad of lesions is most characteristic:

   A. Damage to the heart, blood vessels, nails.
   B. Polyserositis, skin and joint damage.
   C. Damage to joints, heart, eyes.
   D. Damage to the skin, muscles, mucous membranes.
   E. Damage to the skin, liver, spleen.

6. What is characteristic of joint damage in SLE?

   A. Arthritis is usually asymmetric and migratory.
   B. Any joints can be affected, but most often the small joints of the hands, wrist, and knee joints.

C. Usually, the changes are not erosive and do not leave deformations.
D. All the specified changes are typical.
E. True A and B.

7. The most frequent hematological disorders in SLE:

A. Anemia.
B. Leukopenia.
C. Lymphopenia.
D. Thrombocytopenia.
E. All the abovementioned.

8. What is the basis of immunoregulatory disorders in SLE?

A. Phagocytosis disturbances.
B. Changes in the complement system.
C. Deficiency of the suppressive function of T-lymphocytes and anti idiotypes and increased formation of autoantibodies against cell nuclei and their components.
D. Accumulation of circulating immune complexes.
E. Imbalance of T-helpers and T-suppressors.

9. What skin changes are most typical for SLE?

A. Foci of discoid erythema.
B. Inflammatory rashes on the nose and cheeks in the "butterfly" type.
C. Capillaritis on the palms.
D. Phenomena of photodermatosis.
E. Nonspecific exudative erythema.

10. What autoantibodies are found and are pathognomonic for SLE?

A. Antibodies to ribonucleoprotein.
B. Antibodies to cardiolipin.
C. Antibodies to native DNA.
D. Histone antibodies.
E. Antinuclear factor.

KEYS:

1. – A; 2. – D; 3. – D; 4. – C; 5. – B; 6. – C; 7. E; – 8. C; 9. – B; 10. – C.

SITUATION TASKS

1. A 25-year-old woman was hospitalized to the Clinic with complaints of chest pain on the left side, shortness of breath, and fever for two weeks. The patient notes that recently she was suffered from joint pain of the hands, pain in muscles and redness of the skin appeared on both cheeks. Objectively: pulse – 100 bpm, systolic murmur at the apex, pleural friction noise on the left. The joints of the hands are swollen. Blood: WBCs – 2.0×10^9/l, RBCs – 2.7×10^{12}/l, ESR – 59 mm/h. Urinalysis: proteinuria, cylindruria. What is the most likely diagnosis?

B. Rheumatoid arthritis.
C. Acute rheumatic fever.
D. Reactive arthritis.
E. Dermatomyositis.
F. Systemic lupus erythematosus.

2. A 38-year-old woman was admitted to the hospital with complaints of pain in small joints, low-grade fever. She has been sick for 4 years. At first, only repeated attacks of polyarthritis of the small joints of the hand were noted. Objectively: deformation of the proximal interphalangeal joints, expansion of the heart in both directions, systolic murmur at the apex, blood pressure - 150/100 mm Hg. X-ray of the chest shows pleurodiaphragmatic adhesions, enlargement of the left ventricle. Blood analysis: Hb – 98 g/l, RBCs – 3.4×10^{12}/l, WBCs – 4.0×10^9/l, ESR – 50 mm/h. Urinalysis: protein – 1.3 g/l, RBCs – 8–9 / HPF, hyaline casts – 3–4 /LPF. What is the most likely diagnosis?

A. Systemic lupus erythematosus.
B. Rheumatoid polyarthritis.
C. Systemic sclerosis.
D. Chronic glomerulonephritis.
E. Rheumatic fever.

3. A 40-year-old woman complains on weakness, rapid fatigue, an increase in body temperature up to 38 ºC, a rash on the face skin, pain in the wrist and elbow joints. She has been sick for 3 years. Objectively: erythematous rashes in the form of a «butterfly» on the cheeks, radiocarpal and elbow joints are affected symmetrically, swollen; pleural friction noise over the lungs. Anemia, leukopenia, lymphopenia in the blood, proteinuria and cylindruria. The formation of which antibodies is most likely in the mechanism of disease development?

A. Formation of antibodies to native DNA.
B. Formation of antibodies to myositis.
C. Formation of antibodies to endothelial cells.
D. Formation of specific antibodies to myosin.
E. Formation of rheumatoid factor.

4. A 20-year-old patient complains of shortness of breath, fever for two weeks, pain in the chest on the left, stiffness in the joints of the hands, erythema on both cheeks. Objectively: pulse – 94/min, systolic noise at the apex, pleural friction noise on the left. The joints of the hands are swollen. Blood analysis: WBCs leukocytes – 3.7×10^9/l, ESR – 60 mm/h. Urinalysis: protein in urine – 0.4 g/l. What is the most likely diagnosis?

A. Systemic lupus erythematosus.
B. Rheumatic fever.
C. Scleroderma.
D. Reiter's syndrome.
E. Rheumatoid arthritis.

5. Patient M., 22 years old, with suspicion of systemic lupus erythematosus, complains on «flying» pain in the joints of the hands and feet, an increase in temperature up to 38.5-39 ºC for 3 weeks, shortness of breath, palpitations, weakness. Objectively: erythema on the cheeks and nose. Blood analysis: Hb - 90 g/l, platelets – 135×10^9/l, ESR – 43 mm/h. Urinalysis: protein – 2.66 g/l, RBCs – 8–10 / HPF. Which antibodies are most significant for making a diagnosis?

A. To native DNA.
B. To platelets.
C. To phospholipids.
D. Rheumatoid factor.
E. Cryoglobulins.

KEYS:

1. – E; 2. – A; 3. – A; 4. – A; 5. – A.

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Електронне навчальне видання комбінованого використання
Можна використовувати в локальному та мережному режимі

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ВЕДЕННЯ ПАЦІЄНТА З АРТРАЛГІЯМИ ТА МІАЛГІЯМИ (СИСТЕМНИЙ ЧЕРВОНИЙ ВОВЧАК)

Методичні рекомендації
для підготовки здобувачів вищої освіти 6-го року навчання
з дисципліни «Внутрішня медицина»

(Англ. мовою)

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