BULGARIAN SOCIETY OF RHEUMATOLOGY

CONSENSUS SYSTEMIC LUPUS ERYTHEMATOSUS

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March, 2019

DEFINITION AND GENERAL CHARACTERISTICS

Systemic lupus erythematosus (SLE) is a chronic, autoimmune, multisystem connective tissue disease. SLE is more common in females (female to male ratio is approximately 9: 1), with a peak incidence between 20 and 40 years of age.

THE ASSESSMENT OF A PATIENT WITH SLE INCLUDES THE FOLLOWING FIVE MAIN STEPS

1. Diagnosis – the classification criteria of the American College of Rheumatology (ACR), 1982, modified in 1997, are generally accepted.

2. Assessment of the degree and type of involvement of various organs and systems – disease staging – SLICC/ACR Damage Index.

3. Evaluation of activity – various indices of activity have been created, as the most common and available for use in clinical practice is the so-called. SLEDAI (Systemic Lupus Erythematosus Disease Index).

4. Assessment of the probable prognosis of the disease and its severity – prognostic tables are used.

5. Choice of therapy.

Diagnosis of SLE

Given the variety of clinical symptoms for the diagnosis of SLE must have at least 4 of the 11 criteria (ACR, 1997), presented in table. 1

Table 1. ACR classification criteria (1982) for systemic lupus erythematosus.

1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Oral ulcers
5. Non-erosive arthritis/Arthralgia
6. Serositis <ul style="list-style-type: none">• Pleuritis• Pericarditis
7. Renal disorder <ul style="list-style-type: none">• persistent proteinuria ≥ 0.5 g/l/24 h• cylindruria – cellular and/or erythrocyte
8. Neurologic disorder <ul style="list-style-type: none">• seizures• psychosis
9. Hematologic disorder <ul style="list-style-type: none">• Haemolytic anemia < 8.5 g% Hb• Leukopenia < 3000 mm³• Lymphopenia < 1500 mm³• Thrombocytopenia $< 100,000$ mm³
10. Immunological abnormalities <ul style="list-style-type: none">• anti-dsDNA• anti-Sm• antiphospholipid antibodies
11. Antinuclear antibodies

ANA – antinuclear antibodies; anti-dsDNA – anti-double stranded DNA antibodies

In 2012, the so-called SLICC criteria for SLE (Systemic Lupus International Collaborating Clinics), which include two groups of criteria, respectively: clinical and immunological criteria (Table 2).

Table 2. SLICC (Systemic Lupus International Collaborating Clinics) criteria, 2012

Clinical criteria
<ol style="list-style-type: none"> 1. Acute/Subacute skin lupus 2. Chronic cutaneous lupus 3. Nonscarring Alopecia 4. Ulcerations in the nasal and/or oral cavity 5. Synovitis ≥ 2 joints or pain in ≥ 2 joints accompanied by morning stiffness ≥ 30 minutes. 6. Serositis 7. Renal involvement <ol style="list-style-type: none"> a. proteinuria > 500 mg/24 h b. erythrocyte cylinders 8. Neurological manifestations <ol style="list-style-type: none"> a. psychosis, multiple mononeuritis, myelitis, peripheral or cranial b. neuropathy, acute period of confusion. 9. Haemolytic anemia 10. Leukopenia $< 4000/\text{mm}^3$ at least once or lymphopenia $< 1000/\text{mm}^3$ at least once 11. Thrombocytopenia $< 100,000/\text{mm}^3$ at least once.
Immunological criteria
<ol style="list-style-type: none"> 1. ANA – value above the reference limit for the respective laboratory. 2. Anti-dsDNA antibodies – value above the reference limit; in ELISA method 2x above the reference limit. 3. Anti-Sm antibodies 4. Antiphospholipid At – some of the following: <ol style="list-style-type: none"> a. LAC b. false positive RPR test c. ACL (IgG, IgM, IgA) – in moderate or high titer d. Anti-b2 glycoprotein (IgG, IgM, IgA) 5. Low complement <ol style="list-style-type: none"> a. low C3 b. low C4 c. low CH50 6. Positive direct Coombs test without haemolytic anemia.

LAC – lupus anticoagulant; ACL – anticardiolipin antibodies; RPR – rapid plasma reagin

At least 4 criteria are required, of which at least 1 must be clinical and at least 1 must be immunological.

* The presence of lupus nephritis as an independent clinical criterion in the positive of ANA or α -dsDNA is considered to be a sufficient condition for the diagnosis of SLE.

Clinical picture

SLE is characterized by extreme diversity in the clinical course.

1. Manifestations on the part of the musculoskeletal system:

- Arthralgia; arthritis; aseptic necrosis; tenosynovitis with M-finger and swan neck type

- Arthritis is usually symmetrical, distal; rarely erosive (10-30%) of patients

- A rare late consequence is the so-called. “Jacoud’s rheumatism”, which is a ulnar deviation of the fingers in the absence of erosions in the joints

- Osteoporosis occurs late in the course of the disease and is most often corticosteroid-induced

- Myositis/myalgias

- Fibromyalgic syndrome.

2. Lesions of the skin and visible mucous membranes (together with lesions of the musculoskeletal system are most common and most often demonstrated as the first manifestations of the disease):

Specific skin lesions in Lupus erythematosus (LE):

- Acute skin lesions

- “butterfly” rash or “malar rash”

- generalized erythema

- Exacerbate skin lesions

- annular/cyclic lesions

- papulosquamous (psoriasiform) rash

- Chronic skin lesions

- localized discoid LE

- disseminated discoid LE

- hypertrophic (verrucous) LE

- lupus profundus

- lupus thymus

- chilblains lupus

Nonspecific skin lesions in Lupus erythematosus:

- Skin vascular manifestations

- vasculitis

- vasculopathy – livedo reticularis, Raynaud’s phenomenon, thrombophlebitis, periungual telangiectasias

- Alopecia

- Calcinosis

- LE-nonspecific bullous lesions – bullous LE

- Other non-specific skin manifestations.

3. Manifestations of the respiratory system. The most common manifestations are pleurisy and planar atelectasis, as the most dangerous and life-threatening – pulmonary vasculitis, with the development of alveolar hemorrhage, thrombosis; pneumonitis; acute respiratory distress syndrome.

Pulmonary manifestations resulting from an induced autoimmune response in SLE:

- Pleurisy with or without effusion

- Planar atelectasis

- Acute lupus pneumonitis

- Diffraction dysfunction

- Alveolar hemorrhage in vasculitis

- Pulmonary arterial hypertension

- Acute respiratory distress syndrome (ARDS)

- Diffuse interstitial pulmonary fibrosis

Pulmonary complications in patients with SLE

- Infections – bacterial, viral, fungal
- Pulmonary thromboembolism
- Pulmonary edema, uremic with renal involvement (development of renal failure) and acute heart failure.

4. Manifestations of the cardiovascular system – lupus carditis is typical.

- **Lupus carditis** with or without signs of heart failure:

- Endocarditis type Libman-Sacks (valvulitis, defects rarely develop);
- Myocarditis;
- Pericarditis – has a transient nature, rarely leads to adhesions or tamponade;
- Vasculitis of the vessels of the heart (coronary).

- **Vasculitis** – palpable purpura; lived reticularis; periungual lesions; paniculitis; necrotic lesions; phlebotrombosis; Raynaud's syndrome.

- **Arterial hypertension**, often associated with glomerulonephritis (GN)

- **Congenital heart defects** developing in children born to mothers with SLE and positive anti-Ro (SSA); anti-La (SSB) antibodies.

5. **Lupus nephritis (LN)** – this is the only manifestation of SLE, the presence of which only diagnoses in the presence of positive ANA > 1: 160 or positive anti-dsDNA antibodies

Classification of LN according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS), 2003:

Class I: Normal or minimal finding

Class II: Mesangial proliferative LN

Class III: Focal proliferative LN (< 50% damaged glomeruli)

Class IV: Diffuse proliferative LN

Class V: Membranous LN

Class VI: Advanced Sclerosing LN (> 90% of glomeruli are sclerotically altered)

In widespread practice, mixed forms of LN are most common. The therapeutic approach depends on the clinical picture of nephritis and the biopsy finding. Therefore, puncture kidney biopsy (PKB) is mandatory for persistent proteinuria above 0.5 g/l.

6. **Manifestations of the nervous system.** Along with epileptiform seizures and psychosis,

which are criteria for diagnosis in SLE, there is a significant variety of neurological manifestations:

- Lupus headache
- Psychosis
- Epileptiform seizures
- Damage to the cranial nerves
- Peripheral neuropathy
- Cerebrovascular accidents
- Paralysis, paresis
- Sensory disturbances
- Transverse myelitis
- Aseptic meningitis
- Pseudotumor of the brain
- Cerebral atrophy
- Disorders in coordination
- Lacunar infarcts
- "Organic brain syndrome"

The described manifestations often occur in combination. They are usually an expression of vasculitis (cerebrovasculitis) or vasculopathy and are a sign of disease activity. They respond favorably to treatment and are largely reversible.

7. **Hematological manifestations** – after the skin and musculoskeletal system, blood tissue is the third system involved in the onset of the disease:

- Anemia – HB < 85 g/l – with haemolytic origin (positive direct and/or indirect Coombs test) and/or anemia in the course of the chronic inflammatory response;

- Leukopenia – Leu < 4000/mm³ or < 3000/mm³;
- Lymphopenia – Lym < 1500/mm³ or < 1000/mm³;

- Thrombocytopenia – Plt < 100 000/mm³

Cytopenias are autoimmune and are due to erythro-, leuko- and platelet antibodies. Patients with arthritis, skin manifestations and leukopenia are suspected to be SLE.

8. **Manifestations of the gastrointestinal tract** – they are rare and are thought of in the presence of SLE with vasculitis and abdominal pain.

9. **Manifestations of the reticuloendothelial system**

- Lymphadenomegaly

Moderate hepatosplenomegaly, hypersplenism is possible.

The SLICC/ACR Damage Index is used to assess the degree of damage (Table 3).

SLICC/ACR DAMAGE INDEX

Table 3. Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index

Item	Score (max.)
Ocular (each of the eyes, by clinical examination)	
Cataract	1
Retinal damage or atrophy of the optic nerve	1
Neuropsychic	
Cognitive impairment (ie memory deficits, difficulty calculating, impaired concentration, speech and writing difficulties, impaired level of efficiency/performance) or significant psychosis	1
Seizures requiring therapy for 6 months	1
Cerebrovascular accident, whenever	1 (2)
Cranial or peripheral neuropathy (excluding optic)	1
Transverse myelitis	1
Renal	
Calculated or measured glomerular filtration rate <50%	1
Proteinuria ≥ 3.5 g/24 hours	1
or	
Terminal kidney disease (independent of dialysis or transplantation)	3
Lungs	
Pulmonary hypertension (right ventricular protrusion, or accentuated P2)	1
Pulmonary fibrosis (physical examination and radiography)	1
Pulmonary cirrhosis (radiography)	1
Pleural fibrosis (radiography)	1
Pulmonary infarction (radiography)	1
Cardiovascular	
Angina or coronary artery bypass grafting	1
Myocardial infarction at any time (score 2 if > 1)	1 (2)
Cardiomyopathy (ventricular dysfunction)	1
Valve disease (diastolic murmur or systolic murmur > 3/6)	1
Pericarditis lasting 6 months, or pericardectomy	1
Peripheral vasculitis	
Claudication lasting 6 months	1
Minimal tissue loss (pulp space)	1
Significant tissue loss whenever (ie loss of finger or limb) (score 2 if > 1 place)	1 (2)
Venous thrombosis with edema, ulceration or venostasis	1
Gastrointestinal	
Infarction or resection of the intestine below the duodenum, spleen, liver, or gallbladder, at any time, for any reason (score 2 if it is > 1 place)	1 (2)
Mesenteric insufficiency	1
Chronic peritonitis	1
Stricture or surgery of the upper gastrointestinal tract at any time	1
Musculoskeletal	
Muscle atrophy or weakness	1
Deforming or erosive arthritis (including reduced deformities other than avascular necrosis)	1
Osteoporosis with fracture or collapse of the vertebral body (excluding avascular necrosis)	1
Avascular necrosis (score 2 > 1)	1 (2)
Osteomyelitis	1
Skin	
Chronic alopecia with scars	1
Extensive scarring of the panniculus outside the scalp and pulp spaces	1
Cutaneous ulceration (excluding thrombosis) for > 6 months	1
Premature gonadal insufficiency	1
Diabetes (regardless of treatment)	1
Malignant disease (excluding dysplasia) – score 2 if > 1 place)	1 (2)

Possible maximum of the total score: 46 points.

Definition of **damage** (irreversible change not related to active inflammation) occurring after the onset of lupus, established by clinical examination and available for a period of at least **6 months**, unless otherwise indicated. Repeated episodes mean an interval of at least 6 months to give a score of 2. The same lesion cannot be counted twice.

10. Antiphospholipid syndrome (APS)

APS is an autoimmune, multisystemic disease characterized by thrombocytopenia, venous and/or arterial thrombosis, pathological pregnancy in women (preeclampsia, eclampsia, miscarriage) and the presence of a heterogeneous group of antibodies – antiphospholipid antibodies. Various pathogenetic mechanisms are involved in the process of thrombosis in APS, affecting natural anticoagulants and stimulating the procoagulant phenotype. Antiphospholipid antibodies (aPL) play a key role. They act directly on natural anticoagulants, disrupting their physiological role, affecting the platelet-dependent phase of the coagulation cascade.

In most cases, APS is associated with another autoimmune disease, most commonly SLE, then classified as secondary APS (sAPS). Less commonly, it appears as a separate disease – primary APS (pAPS). In recent years, the division of APS into primary and secondary has been rejected due to the lack of pathogenetic differences between them.

Criteria for classifying antiphospholipid syndrome (Sapporo, 1999; updated Sydney, 2006)

1. Clinical criteria

• *Vascular thrombosis*

– One or more episodes of arterial, venous and/or minor vascular thrombosis in any tissue or organ.

– Thrombosis must be proven by an objective validated method or histologically. On histological evidence, any possibility of an inflammatory process in the vessel wall must be ruled out.

• *Pathological course of pregnancy*

– One or more miscarriages after 10 weeks. In morphologically healthy fetus, this should be documented by ultrasound or direct examination of the fetus.

– One or more births of a morphologically healthy fetus before 34 g.s. due to pre – eclampsia, documented according to the accepted criteria for placental insufficiency.

– Three or more miscarriages before 10 g.s. to the exclusion of any maternal anatomical, hormonal and chromosomal pathology.

2. Laboratory criteria

• Lupus anticoagulants detected two or more times in the last 12 weeks, tested according to the

guideline of the International Society of Thrombosis and Hemostasis.

• Anticardiolipin antibodies IgG, IgM or both in medium and high titers at least twice in the last 12 weeks detected by ELISA.

• Anti – β – 2 glycoprotein I antibody, IgG, IgM or both isotypes detected two or more times in the last 12 weeks by plasma ELISA.

When there is more than one clinical or one clinical and one laboratory criterion, the diagnosis is considered certain.

Vascular thrombosis in APS must be proven by a reliable, validated method, and any other causative agent, including vascular wall inflammation, must be ruled out.

Another characteristic clinical manifestation of APS is the pathological course of pregnancy in women: miscarriages in late gestational week (after 10), eclampsia, preeclampsia, HELLP syndrome.

In case of pathological pregnancy, a genetic abnormality of the fetus, infection, gynecological cause, etc. must be ruled out. Genetic defects causing congenital thrombophilia are not uncommon and are expressed in a clinical picture similar to APS.

Antibodies to APS can be grouped into two separate groups, those directed against individual anionic phospholipids (Table 1) and/or those against their protein co-factors (Table 2).

In clinical practice, the most commonly used and best studied are antibodies directed against: cardiolipin (aCL), 2GPI, annexin V, protein C and protein S.

The most clinically important antibodies against phospholipids are those against cardiolipin – anticardiolipin antibodies (aCL). They belong to the class of immunoglobulins IgG, IgM, IgA, which have the ability to recognize anionic phospholipids. This type of antibody is strongly correlated with venous thrombosis and miscarriage. As IgG and IgM are of greater clinical importance, the role of IgA is debatable.

The diagnosis of APS is a combination of clinical and immunological manifestations. Antibodies play an important role in the pathogenesis of the disease and therefore it is necessary to use a standardized methodology for their study.

The method originally used to test anti-cardiolipin antibodies is the radio-immunological method. Subsequently, the much more specific enzyme-linked immunosorbent method (ELISA) for the study of antibodies directed against CL and β 2GPI has been implemented in practice. Despite the high specificity, some infectious diseases (tuberculosis, HCV, HIV, Lyme disease, etc.), as well as the intake of some drugs can positively antiphospholipid antibodies,

without being associated with autoimmune rheumatic disease.

Lupus anticoagulants are a heterogeneous group of antibodies that cause a variety of clinical and laboratory phenomena, one of which is prolonged time of activated thromboplastin (aPTT). There are various methods for their registration, with the highest diagnostic value being: dilute Russell viper venom time (dRVVT), silicaclottingtime (SCT), kaolinclottingtime (KCT). Currently recognized by the International Society for Thrombosis and Hemostasis, the validated methods for LAC testing are dilute Russell viper venom time (dRVVT) and aPTT.

Treatment of APS

Prevention of thrombosis is the main goal of therapy in patients with antiphospholipid syndrome. This predetermines different therapeutic behaviors in: 1) patients with APS who have had a thrombotic event and 2) asymptomatic patients with positive aPL, patients with SLE and positive aPL, or women with obstetric pathology in the context of APS.

Secondary thromboprophylaxis

Anti-thrombotic therapy is recommended before immunosuppressive therapy. In patients with APS and first thrombotic events, it is recommended that the International normalized ratio (INR) be maintained between 2.0 and 3.0. In recurrent thrombosis, the target INR value is 3.0 or combination antithrombotic therapy.

In patients with a history of thrombosis and positive for aPL but not meeting the criteria for APS, thromboprophylaxis is recommended.

Primary thromboprophylaxis

The risk of developing thrombosis in asymptomatic patients with positive for aPL is low. In SLE-positive patients with aPL, the probability of a thrombotic event is about 3% to 4%.

Observational studies have not shown a statistically significant difference between low-dose aspirin therapy in thrombotic pathology and placebo. In women with obstetric pathology, a protective effect of low-dose aspirin treatment has been reported.

Treatment of APS during pregnancy

With appropriate therapy, more than 70% of women with antiphospholipid syndrome give birth to healthy children. [Hochberg Mrac C. et al. Elsevier] During pregnancy, treatment of women with APS with Heparin and low-dose aspirin is accepted. It is recommended to start it early, in the first trimester, immediately after the ultrasound registration of the presence of a live embryo.

Immunological abnormalities in SLE

SLE is the disease with the most immune phenomena, it is also called the “**showcase of antibodies**”. The listed (Table 4) immunological tests are essential for the diagnosis and illustrate the increased synthesis of antibodies against various antigens.

1. **Positive LE cells** – these are segmental leukocytes (Neu) phagocytosed LE masses

2. **Positive lupus band test LBT (+)** – matters in suspicious cases; illumination of the dermoepidermal border in direct immunofluorescence, result of deposition of immune complexes, complement fractions

3. **Positive antibodies against double-stranded DNA (anti-dsDNA), native DNA (anti-nDNA); nucleosomes (anti-nucleosomes); against extractable nuclear antigens – Sm, SSa (Ro60), SSb (La), RNP, RibP** – some or all of them are positive

4. **Positive antiphospholipid antibodies** – ACL, anti-β2GPI, anti-prothrombin, anti-annexin; presence of LAC; positive Wasserman test

5. **Positive antierythro-, leuko-, thrombo-antibodies, lymphocytotoxic At**

6. **Positive antinuclear antibodies ANA titer> 1:80**, the type of glow in indirect immunofluorescence is important, it is related to the type of antibodies

7. **Positive antihistone antibodies** – associated with drug-related lupus

8. **Reduced fractions of complement – C3, C4, C1q.**

Table 4. Immunological abnormalities in SLE

Interpretation of serial serological changes in SLE			
Anti-dsDNA	C3	C4	Interpretation
↑	No change	No change	↑ activity, probable change in clinical condition
No change	↓	↓	probable renal involvement
↓	↓	↓	probable renal involvement
↑/no change	↑	↑	Probably an infection, a study of ESR, SRS is needed

3. SLE activity

Different measuring systems are used to measure the disease activity: SLEDAI, SELENA-SLEDAI, BILAG. SLEDAI-2K (Table 5) was created as a modification of SLEDAI, which includes assessment of persistently active SLE. In particular, SLEDAI-2K allows persistent active disease to be noted in alopecia, mucosal ulcers, rash and proteinuria.

SLEDAI 2K

(valid for evaluation for 4 weeks or 10 days evaluation)

The points in the SLEDAI Score column are enclosed if the description is available during the visit or in the previous 4 weeks.

SLEDAI-2K is based on the presence of 24 points in nine organs and systems in the previous 30/10 days. SLEDAI-2K descriptions are documented as present or absent. Each of the indicators has a certain number of points, and the total score of SLEDAI-2K is the sum of the points in all 24 points. The overall score of SLEDAI-2K varies between 0 and 105, with higher scores indicating higher disease activity.

Disease activity is defined in SLEDAI-2K ≥ 6 .

SELENA SLEDAI FLARE INDEX (SFI)

(Can be used with any version of SLEDAI)

Global doctor's assessment (10 cm Visual analog scale)

0 1 2 3
Absent | _____ | Severe
Mild Moderate

Mild or moderate seizure

☐ Change in SELENA-SLEDAI score of 3 or more points (but not more than 12)

☐ New/worse:

Rash (discoid, photosensitive, deep, bullous lupus)

Table 5. SLEDAI-2K

SLEDAI SCORE	Description	Definition
8	Seizures	Newly emerged, exclude metabolic, infectious causes or drugs.
8	Psychosis	Altered ability to function under normal conditions due to severe impairment of perception of reality. It includes hallucinations, incoherence, pronounced free association, poor mental content, overt illogical thinking, strangeness, disorganization, or catatonic behavior. Excludes uremia and medical causes.
8	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, sudden onset and variable clinical characteristics, inability to concentrate on the environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime sleepiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.
8	Visual impairment	Retinal changes from SLE. These include cytoid bodies, retinal haemorrhages, serous exudates or choroidal haemorrhages, or optic neuritis. Exclude hypertension, infection, or medical cause.
8	Damage to the cranial nerve	Newly developed sensory or motor neuropathy affecting the cranial nerves.
8	Lupus headache	Severe, persistent headache; it may be migraine, but it must be non-responsive to narcotic analgesia.
8	Cerebrovascular accident	New cerebrovascular accident (s). To exclude arteriosclerosis.
8	Vasculitis	Ulceration, gangrene, painful nodes on the fingers, periungual infarction, bleeding fissures or biopsically or angiographically proven vasculitis.
4	Arthritis	≥ 2 joints with pain and signs of inflammation (ie tenderness, swelling or effusion).
4	Myositis	Proximal muscle pain/weakness associated with elevated creatine kinase (CK)/aldolase, or EMG changes or biopsy showing myositis.
4	Cylinders in the urine	Granular or erythrocyte cylinders.
4	Hematuria	> 5 Air per field of view. Stones, infection or other cause are excluded.
4	Proteinuria	> 0.5 g/24 hours.
4	Pyuria	> 5 leuk. in the field of view. Infection is ruled out.
2	Rash	Inflammatory type of rash.
2	Alopecia	Abnormal focal or diffuse hair loss.
2	Mucosal ulcerations	Oral or nasal ulcers.
2	Pleurisy	Pleuritic chest pain or pleural rubbing with effusion, or thickening of the pleura (requires objective evidence).
2	Pericarditis	Classical pericardial pain and/or friction, ECG effusion or echocardiographic confirmation (requires objective component).
2	Low complement	Decrease of CH50, C3 or C4 below the lower limit of the norm for laboratory testing.
2	Increased DNA binding	Increased DNA binding above the normal limit for laboratory testing.
1	Fever	$> 38^{\circ}\text{C}$. Excludes infectious cause.
1	Thrombocytopenia	$< 100 \times 10^9$ platelets/L, excludes drug causes.
1	Leukopenia	$< 3 \times 10^9$ leukocytes/L, excludes drug causes.

Nasopharyngeal ulcerations	Vasculitis
Pleurisy	Jade
Pericarditis	Myositis
Arthritis	Platelets <60,000
Fever (SLE)	Haemolytic anemia: Xb < 70 g/l or decrease in
□ Increase the dose of prednisone, but not > 0.5 mg/kg/day	Xb > 30 g/l
□ Addition of NSAIDs or hydroxychloroquine due to SLE activity	Requiring: doubling the dose of prednisone, or increasing the dose of prednisone to > 0.5 mg/kg/day, or hospitalization
□ ≥ 1.0 increase in score from the Global Physician Assessment, but not more than 2.5	□ Increasing the dose of prednisone to > 0.5 mg/kg/day
Severe attack □	□ Appointment of cyclophosphamide, azathioprine, methotrexate or mycophenolate due to SLE activity
□ Change in SELENA-SLEDAI score greater than 12	□ Hospitalization due to SLE activity
□ New/worse:	□ Raising the score from the Global Physician Assessment > 2.5
CNS – SLE	
Skin vasculitis	

BILAG 2004 INDEX

Only items due to SLE disease activity are recorded and the assessment refers to events present in the last 4 weeks (compared to the previous 4 weeks).

•• to be applied with a glossary ••

Marking the result:

ND – Not done

1 – Improving

2 – No change

3 – It's getting worse

4 – Newly emerged

Yes/No OR Value (where applicable)

□ Indicate if it is not due to SLE activity
(default 0 = not available)

Constitutional manifestations

Pyrexia – documented > 37.5°C ()

Weight reduction – unintentional > 5% ()

Lymphadenopathy/splenomegaly ()

Anorexia ()

Cutaneous-mucosal manifestations

5. Skin rash – severe ()

6. Skin rash – mild ()

7. Angioedema – severe ()

8. Angioedema – cure ()

9. Mucosal ulceration – severe ()

10. Mucosal ulceration – mild ()

11. Paniculitis/Bullous lupus – severe ()

12. Paniculitis/Bullous lupus – cure ()

13. Significant cutaneous vasculitis/thrombosis ()

14. Digital infarcts or nodular vasculitis ()

15. Alopecia – severe ()

16. Alopecia – mild ()

17. Periungual erythema/periostitis ()

18. Bleeding fissures ()

Neuropsychiatric manifestations

Aseptic meningitis	()
Cerebro-vasculitis	()
Demyelinating syndrome	()
Myelopathy	()
Acute state of disorientation	()
Psychosis	()
Acute inflammatory demyelinating polyradiculoneuropathy	()
Mononeuropathy (isolated/multiple)	()
Cranial neuropathy	()
Plexopathy	()
Polyneuropathy	()
Seizures	()
Status epilepticus	()
Cerebrovascular disease (not due to vasculitis)	()
Cognitive dysfunction	()
Motor disorders	()
Autonomous violations	()
Cerebral ataxia	()
Lupus headache – severe continuous	()
Headache from increased intracranial pressure	()

Musculoskeletal manifestations

Myositis – severe	()
Myositis – mild	()
Arthritis (severe)	()
Arthritis (moderate)/Tendinitis/Tenosynovitis	()
Arthritis (cure)/Arthralgia/Myalgia	()

Cardiorespiratory manifestations

Myocarditis – mild	()
Myocarditis/Endocarditis + Heart failure	()
Arrhythmia	()
Newly arising valve dysfunction	()
Pleurisy/Pericarditis	()
Cardiac tamponade	()
Pleural effusion with dyspnea	()
Pulmonary hemorrhage/vasculitis	()
Interstitial alveolitis/pneumonia	()
Pulmonary fibrosis	()
Aortitis	()
Coronary vasculitis	()

Gastrointestinal manifestations

Lupus peritonitis	()
Abdominal serositis or ascites	()
Lupus enteritis/colitis	()
Malabsorption	()
Protein-losing enteropathy	()
Intestinal pseudoobstruction	()
Lupus hepatitis	()
Acute lupus cholecystitis	()
Acute lupus pancreatitis	()

Ophthalmic manifestations

Orbital inflammation/myositis/proptosis	()
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Keratitis – severe		()
Keratitis – mild		()
Anterior uveitis		()
Posterior uveitis/retinal vasculitis – severe		()
Posterior uveitis/retinal vasculitis – mild		()
Episcleritis		()
Scleritis – severe		()
Scleritis – mild		()
Retinal/choroidal vascular occlusive disease		()
Isolated stains such as cotton wool (cytoid bodies)		()
Optic neuritis		()
Anterior ischemic optic neuropathy		()
Renal manifestations		
Systolic blood pressure (mm Hg) v	alue	()
Diastolic blood pressure (mm Hg)	value	()
Accelerated hypertension	Yes/No	()
Urine dipstick protein (+ = 1, ++ = 2, +++ = 3)		()
Urine albumin-creatinine ratio mg/mmol		()
Urine protein-creatinine ratio mg/mmol		()
Protein in 24-hour urine (g)	value	()
Nephrotic syndrome	Yes/No	()
Creatinine (plasma/serum) $\mu\text{mol/l}$		()
GFR (calculated) ml/min/1.73 m ²		()
Active urine sediment	Yes/No	()
Active nephritis	Yes/No	()
Haematological manifestations		
Hemoglobin (g/dl)	value	()
Total leukocyte count ($\times 10^9/\text{l}$)	value	()
Neutrophils ($\times 10^9/\text{l}$)	value	()
Lymphocytes ($\times 10^9/\text{l}$)	value	()
Platelets ($\times 10^9/\text{l}$)	value	()
Thrombotic thrombocytopenic purpura		()
Data on active hemolysis	Yes/No	()
Positive Coombs test	Yes/No	()

Weight (kg)	Serum urea (mmol/l)
African ancestry: Yes/No	Serum albumin (g/l)

The index is a standardized measurement of clinical disease activity in SLE. It is a comprehensive score system for assessing both the current disease activity of lupus and the changes in it compared to the previous examination of the patient.

Only events that are due to SLE disease activity and not due to persistent/irreversible damage, infection or other condition are reported. The assessment refers to events that are present for the last 4 weeks, compared to the previous 4 weeks. Activity means a disease process that is reversible. For some manifestations, it may be difficult to differentiate SLE from

other conditions because specific tests are lacking and the decision is then made based on the physician's opinion of the probability ratio.

BILAG was developed and subsequently validated **according to the assumption of the probable treatment** that will be prescribed to patients with a certain group of clinical manifestations in the eight assessed organs and systems.

- **Grade A** – the most active score for all organs and systems is defined as individual clinical manifestations or a combination of them, for which the group considers it necessary to prescribe medium/high

doses of CS (> 20 mg prednisolone or equivalent) and/or initiation of high doses of immunosuppressive drugs or high doses of anticoagulants [INR > 3]. (When the manifestations are unchanged, worsened or new).

- **Grade B** – patients with disease activity requiring the use of low doses of immunosuppressants (ie < 20 mg prednisolone) and/or specific medications such as antimalarials, antiepileptics, antidepressants and NSAIDs or topical CS. (When manifestations improve but are still significant).

- **Grade C** for each system is given to patients with mild persistent activity requiring only symptomatic therapy (ie analgesics or NSAIDs). (When the manifestations improve and do not belong to the more severe manifestations of lupus).

- **Grade D** – when the organ or system was active but no longer active.

- **Grade E** – indicates that the organ or system has never been active.

For the purposes of statistical analyzes, the BILAG index can be converted into a numerical score: **degree A = 9 points, B = 3 points, C = 1 point, D = 0 points, E = 0 points.**

Guide for reflecting BILAG points

(4) Newly emerged

- Manifestations are recorded as new when they are a new episode that occurred in the last 4 weeks (compared to the previous 4 weeks) and do not improve. Includes new episodes (reappearance) of old events.

- New episodes that occur in the last 4 weeks but meet the criteria for improvement (listed below) should be classified as improvement instead of new.

(3) Worsen

- Refers to symptoms that have worsened in the last 4 weeks compared to the previous 4 weeks.

(2) No change

- Refers to manifestations that have been present in the last 4 weeks, as well as in the previous 4 weeks, without significant improvement or deterioration (from the previous 4 weeks)

- Also applies to events that have improved in the last 4 weeks, compared to the previous 4 weeks, but still do not meet the criteria for improvement

(1) With improvement

Definition of improvement

- a) The degree of improvement is sufficient to consider a reduction in therapy and does not justify increasing therapy

- b) The improvement should be available and last ≥ 2 weeks from the last 4 weeks

(0) Missing

If lupus manifestations can be classified as mild or severe (according to the definition of the dictionary) and affect the severe point, the corresponding mild point may also be completed. When the manifestation improves and changes to mild, only the point for mild is filled in (but it will not be new, it will be improved).

If the mild point worsens and becomes severe, the severe point is marked as new and the mild point is marked as worse.

Assessment of the probable prognosis of the disease and its severe

Prognosis in patients with SLE: It is important in view of the early and late strategy for the specific patient.

Signs predicting an unfavorable prognosis

Clinical signs

1. Onset of the disease before 20-25 years of age.
2. Development of clinical manifestations with an unfavorable prognosis in the first 3 years from the onset of the disease.
3. Acute onset with simultaneous presence of 7 or more ACR criteria.
4. Rapid evolution with frequent seizures and high activity, clinical remission cannot be achieved with treatment and immunological remission is almost never achieved.

Immunological marks

1. Persistent hypocomplementemia of C3.
2. Persistent hypocomplementemia of C3 and C4.
3. Detection of elevated anti-dsDNA Aβ and antibodies against extractable antigens in the same serum.
4. Detection of elevated anti-dsDNA Aβ, antibodies against extractable antigens and low C3 fractions of complement in the same serum.
5. Establishment of A1, A28, A32, B8, B21 in the genetic formula.

Signs predicting a favorable prognosis

Clinical signs

1. Onset of the disease after 40 years of age.
2. Gradual onset with a long preclinical period.
3. The course is paroxysmal, with well-formed seizures.
4. Seizures are rare and complete clinical, sometimes immunological, remission is common.
5. Associated complications are rare, mostly intercurrent infections and osteoporosis.

Immunological marks

1. Normal serum C3 levels.

2. Normal serum C3 and C4 levels in the same serum.

3. Elevated anti-dsDNA A β and antibodies against extractable antigens in the same serum are rarely detected.

4. Elevated anti-dsDNA A β , antibodies against extractable antigens, and low C3 fractions of complement in the same serum are rarely detected.

5. Rarely detected antiphospholipid antibodies – LAC, ACL, anti- β 2GPI At.

6. A11 is often found in the genetic formula; B5; DR3.

7. Haplotype A11B5 is often present.

Differential diagnosis of SLE:

1. Rheumatic diseases with symptoms common to those of SLE.

2. Chronic febrile conditions (infectious diseases, tuberculosis, sepsis).

3. Neoplastic processes.

4. Asymptomatic patients with positive ANA.

5. Primary antiphospholipid syndrome.

Choice of therapy

The goal of treatment in patients with SLE is to achieve clinical and immunological remission.

Treatment has two main sides: hygienic-dietary regime and medical treatment. The hygienic-dietary regime is connected with the avoidance of all noxa, which aggravate the disease. Patients with SLE are prohibited from:

- Exposure to **ultraviolet rays** (induce the synthesis of ANA in the skin);

- Administration of **vaccines** (live or killed, bacterial antigens are a powerful inducer of the synthesis of antinuclear and antiphospholipid antibodies);

- **Use of female sex hormones;**

- **Use of certain medications** – penicillins, cephalosporins, tuberculostatics, sulfonamides. The ban is relative.

- **Other drugs** that are known to induce the synthesis of antinuclear, ACL, antihistone antibodies and should be used with caution in patients with SLE are: hydralazine, procainamide, β -blockers, Cuprenil, gold salts and others. The ban is individual and at the discretion of the doctor.

Another important point in patients with SLE is the need to treat focal infections and abscesses, as bacterial antigens are a powerful inducer of the synthesis of antinuclear antibodies, some of the antigens are the so-called superantigens.

Pregnancy, abortion and childbirth are events that worsen the course of SLE. Throughout preg-

nancy, during and after birth, the patient should be monitored by an experienced rheumatologist.

Medications used to treat SLE

I. Corticosteroids (CS)

The use of CS in patients with SLE is determined by their anti-inflammatory and immunosuppressive effect. In the table 6 and table 7 describes the applied dosage regimens of CS, the indications for their use, the most common side effects from their use.

II. Immunosuppressive drugs

1. Cyclophosphamide (Endoxan®, Cytozar®)

1.1. Mechanism of action

- leads to dose-dependent lymphopenia, which occurs through T- and B-lymphocyte depletion

- impairs the function of macrophages

- affects gene transcription, which leads to a decrease in the production of autoantibodies

1.2. Dosage regimens

- high-dose regimen of 1000 mg/m² administered intravenously once a month for at least 12 consecutive months, then continued for 2-3 months for 2-3 years

- low dose regimen (EuroLupus) 500 mg administered every two weeks for six cycles

- ablative regimen – 50 mg/kg daily for four consecutive days, in stem cell transplantation

- 25-100 mg daily administered orally

Cyclophosphamide is used as monotherapy and/or in combination with a corticosteroid and/or other immunosuppressive drug.

1.3. Indications for use of Cyclophosphamide in patients with systemic lupus erythematosus

1. Lupus nephritis

2. Lupus with neurological involvement

3. Alveolar hemorrhage

4. Autoimmune hemolytic anemia

5. Thrombocytopenia

6. Optic neuritis

7. Thrombotic thrombocytopenic

2. Azathioprine (Imuran®)

2.1. Mechanism of action

- imidazole derivative of 6-mercaptopurine, which inhibits purine synthesis, leading to a decrease in circulating T- and B-lymphocytes

- reduces the synthesis of immunoglobulins

- suppresses CD28-mediated signaling

2.2. Dosage regimen – 2-3 mg/kg daily

2.3. Indications for use of Azathioprine in patients with systemic lupus erythematosus

1. Lupus nephritis

Table 6. CS – indications for use and side effects

Dosage regimen	Indications	The most common side effects
1. Pulse therapy with CS $\geq$ 250 mg daily for 1-5 days, usually 0.5-1 gr daily, administered intravenously for 1-3 days, 1 x monthly, after which therapy is continued with CS 30-60 mg daily	Organ- and life-threatening complications – myelopathy, cerebrovasculitis, optic neuritis, alveolar hemorrhage, vasculitis, thrombotic thrombocytopenic purpura, Stevens-Johnson-like syndrome, rapidly progressive glomerulonephritis, diffuse/focal proliferative glomerulonephritis Disease refractory to high doses of corticosteroid	– Arterial hypertension – neuropsychiatric manifestations – arrhythmias – myalgias/arthralgias
2. Very high dose of CS $\geq$ 100 mg daily, administered intravenously, in divided doses, for no more than 1-2 weeks	Organ- and life-threatening complications, as in pulse therapy with CS	– psychosis – risk of severe, complicated infections
3. High dose of CS – 1 mg/kg for 2-4 weeks, then reduce the dose by 10% per week > 30 mg and $\leq$ 100 mg daily, administered intravenously or orally	Diffuse/severe focal proliferative glomerulonephritis (less than 6-8 weeks), thrombocytopenia, haemolytic anemia, acute lupus pneumonitis, acute myocarditis, autoimmune pericarditis, optic neuritis, retinal vasculitis	– signs of drug hypercortisolism (Cushing's syndrome) – skin atrophy, acne – hypertension – hypokalaemia, hyperlipidemia, hyperglycaemia – osteoporosis, osteonecrosis
4. Average dose of CS – 0.25-0.5 mg/kg daily for 2-4 weeks, administered intravenously > 7.5 mg and $\leq$ 30 mg daily, administered intravenously or orally	Moderate SLE activity (myositis, severe pleurisy, thrombocytopenia, ophthalmoplegia, excluding optic neuritis) It can be used between pulses with CS, in combination with an immunosuppressive drug in severe SLE	– glaucoma, cataracts – risk of infections – insomnia, psychosis – suppression of the hypothalamic-pituitary-adrenal axis – accelerated atherosclerosis
5. Low dose CS $\leq$ 7.5 mg administered orally	Arthritis, constitutional manifestations that are not affected by the intake of analgesics, NSAIDs as maintenance therapy	– osteoporosis, osteonecrosis – suppression of the hypothalamic-pituitary-adrenal axis – infections, with a lower frequency compared to higher doses of CS
Alternating mode	Membrane glomerulonephritis with nephrotic syndrome – 120 mg. When reducing the dose of CS. As maintenance therapy.	– reduction of side effects – Osteoporosis occurs

Table 7. Corticosteroids – side effects

<ol style="list-style-type: none"> 1. Skin atrophy 2. Fragility of capillaries, ecchymoses 3. Avascular necrosis 4. Corticosteroid-induced osteoporosis 5. Hyperglycemia 6. Hyperlipidemia 7. Risk of infections 8. Arterial hypertension 9. Pancreatitis 10. Glaucoma, cataract 11. Behavior change 12. Fluid retention 13. Stomach/duodenal ulcers 14. Weight gain 15. Accelerated atherosclerosis 16. Hypokalemia, hypocalcemia
--

2. Pulmonitis
3. Hepatitis
4. Autoimmune hemolytic anemia
5. Thrombocytopenia
6. Gastroenteropathy
7. Arthritis, myositis
8. Skin manifestations

Allows it to be combined with other immunosuppressive drugs and targeted therapy.

2.4. Peculiarities before starting treatment in order to limit side effects

- test for thiopurine methyltransferase enzyme deficiency
- gradual increase of the dose

3. Mycophenolate mofetyl (MMF), (Cellcept®)

3.1. Mechanism of action

– inhibits inosine-5'-monophosphate dehydrogenase, inhibits the proliferation of T- and B-lymphocytes, respectively cell-mediated and humoral immune response

3.2. Dosage regimen – 500 mg – 3 gr daily; 1.5-3 gr daily for lupus nephritis

3.3. It is used for lupus nephritis, vasculitis, neurolupus, SLE, resistant to CS.

4. Methotrexate

4.1. Mechanism of action

– inhibits the enzyme dihydrofolate reductase, which in turn inhibits DNA synthesis

4.2. Dosage regimen – 10-25 mg per week, taken orally or parenterally (subcutaneously, intramuscularly)

4.3. Indications for use of Methotrexate in patients with systemic lupus erythematosus

Arthritis

Skin manifestations

Serositis

SLE with leading general, constitutional events

5. Leflunomide (Arava®)

5.1. Mechanism of action

– inhibits the enzyme dihydroorotate dehydrogenase, which in turn leads to inhibition of pyrimidine synthesis and DNA synthesis

5.2. Dosage regimen – 20 mg daily

5.3. It is used for arthritis that develops during systemic lupus erythematosus.

6. Cyclosporine

It is used when the disease does not respond to other immunosuppressive drugs, in complications such as cytopenia, oral ulceration, urticaria, nephritis, some skin lesions.

III. Approximately 10% of patients with systemic lupus erythematosus use medications other than corticosteroids and standard immunosuppressive drugs, as well as some specific interventions.

1. Dapson (Diaminodiphenyl sulfone) – mesenchymal inhibitor

1.1. Mechanism of action

– suppresses inflammatory reactions in the mesenchyme (skin, subcutaneous tissue, vessels, etc.)

– blocks the activation of the alternative complement pathway

– stimulates neutrophil cytotoxicity

– mild anti-TNF effect.

1.2. Dosage regimen – between 50-100 mg daily

1.3. It is used in cases of:

– every vasculitis

– bullous lupus

– Lupus paniculitis

– urticaria

– oral ulcerations

2. Thalidomine, Lenalidomide

Their effect has been proven in refractory skin lupus, but their use is limited due to their teratogenic effect, established procoagulant activity and risk of developing polyneuropathy.

3. Other drugs with immunosuppressive and immunomodulatory effect

3.1. Tacrolimus

– used in lupus nephritis

– local forms of skin lupus

3.2. Rapamycin – phase II clinical study in patients with systemic lupus erythematosus.

3.3. Retinoids (Acitretin) – finds application in subcutaneous skin lupus and in refractory skin lesions.

3.4. Mizoribine is a purine antagonist, with a mechanism similar to that of Azathioprine.

4. Plasmapheresis

It is used in thrombotic thrombocytopenic purpura, cryoglobulinemia, neuromyelitis optica, alveolar hemorrhage, lupus nephritis, severe vasculitis.

5. Total irradiation of the lymphatic system, lymphocytophoresis.

6. Non-steroidal anti-inflammatory drugs – are used as symptomatic therapy – for fever, headache, myalgia, arthralgia, arthritis and/or serositis.

7. Topical therapy

7.1. Topical corticosteroids

– non-fluorinated preparations – weaker effect, but can be used for a longer time

– fluorinated preparations – should be used for a period not exceeding two weeks, due to the risk of skin atrophy, telangiectasia.

7.2. Topical calcineurin inhibitors (Tacrolimus, Pimecrolimus).

IV. Antimalarials

1. Mechanism of action

– block T-like receptors (TLRs) 3, 7 and 9 by changing the pH or by a competitive principle of inhibition of TLRs;

– inhibit phospholipid A2, phospholipid C;

– stabilize lysosomal membranes;

– reduce estrogen production;

– inhibit the B-lymphocyte stimulator (BLyS, BAFF);

– antithrombotic effect, reduce serum blood sugar and cholesterol levels;

– UV protection.

Antimalarials have been shown to increase survival, prevent and/or reduce organ damage, partic-

ipate in maintaining remission, and reduce the frequency and severity of relapses.

Antimalarials have a protective effect against thrombosis, kidney damage and the development of infections.

2. Dosage regimen

- Hydroxychloroquine (Plaquenil®) – 5 mg/kg/day, may administer a higher dose of 7 mg/kg/day for a period not exceeding three months
- Chloroquine (Resochin®) – 500 mg daily for 1-2 months, then 250 mg daily
- Quinacrine – 25-100 mg/kg/daily

3. Antimalarials are used in cases of:

- skin lesions
- as an additive therapy for lupus nephritis
- antiphospholipid syndrome
- arthritis

4. Side effects

- rash
- gastrointestinal manifestations
- general malaise
- retinopathy of pigment (Chloroquine is more toxic than Hydroxychloroquine).

V. Intravenous immunoglobulins

Immunomodulatory effects of intravenous immunoglobulins (IVIG)

1. IVIG can be used as adjunctive therapy in cases of:

- Systemic lupus erythematosus
- Antiphospholipid syndrome with recurrent miscarriages

2. Mechanisms of action of IVIG in systemic lupus erythematosus (fig. 1):

- Idiotypic-anti-idiotypic interaction between anti-idiotypic antibodies in IgIV and antibodies directed against dsDNA, factor VII, in which anti-idiotypic networks are formed;
- The anti-idiotypic antibodies in IVIG activate the inhibitory FcγRIIB, which leads to an “off signal” on the B-cells and suppression of the production of autoantibodies.

The prophylactic dose of IVIG is 400 mg/kg, and the therapeutic dose from 800 mg/kg to 1gr – 2 gr/kg (in severe cases). Immunovenin intact is administered in the indicated dosage regimens in three applications per day. In antiphospholipid syndrome IVIG is administered at a dose of 400 mg/kg monthly from the time of pregnancy until 28-32 g.s.

Fig. 1. Mechanism of action of IVIG

Adverse drug reactions occurring with IVIG

Several drugs containing immunovenin for intravenous administration are present on the Bulgarian market – Immunovenin intact 5% IgG1, Privigen 100 mg/ml, Octagam 10%. One of the main differences between the different preparations is the content of IgA. The most widely used immunoglobulin preparation in everyday rheumatological practice is Immunovenin intact.

In everyday rheumatological practice, intravenous immunoglobulins are used in the treatment of:

- Systemic lupus erythematosus with high immunological activity;
- Systemic lupus erythematosus, occurring with cerebrovasculitis, lupus nephritis, vasculitis and/or autoimmune hemolytic anemia, thrombocytopenia;
- Systemic lupus erythematosus with underlying antiphospholipid syndrome;
- Systemic lupus erythematosus with recurrent infections.

The most common side effects (Table 8) are fever, accompanied by chills, headache, arthritis, myalgia.

Table 8. The most common side effects

Fever with chills Dyspnea Nausea, vomiting Headache Tachycardia Back pain Chest pain and heaviness Myalgias Hypotension Rash
Manifestations on the part of the CNS Severe headache Aseptic meningitis
Renal manifestations Risk factors predisposing to the development of renal complications are: underlying renal failure, diabetic nephropathy, dehydration, sepsis, paraproteinemia, administration of nephrotoxic drugs. Azotemia Acute renal failure
Thromboembolic events Usually in the presence of additional risk factors associated with increased viscosity: cryoglobulinemia, hypergammaglobulinemia, and hypercholesterolemia. Thrombotic stroke Myocardial infarction Pulmonary thromboembolism
Anaphylaxis of anti-IgE antibodies against IgA It develops with repeated administration of IgIV
Side effects described in individual clinical cases Coagulopathy, Hemolysis, Cryoglobulinemia, Neutropenia, Uveitis, Non-infectious hepatitis, Rhythm disorders

Mechanism of Action	Sample target
T cells	CTLA4-Ig; CD40L mAbs; ICOS; increase in the number of CD4 + CD25 +, CD8 + CD28- cells
B cells	CD20+ mAbs; CD22+ mAbs; anti-BLyS; TACI-Ig; BAFF-RFc;
Complement	Anti-C5a
Cytokines	mAbs against sIL-6R, IL-6, IL-10, IL-17, IL-18
Congenital immune response	Anti-IFN α , anti-IFN γ ; blocking TLR7, TLR9
Blockade of cell surface receptors	Syk kinase inhibitors; Sirolimus
Toleragens	Nucleosome-related peptides; Sm Ag; 16/6 idotype;

Table 9. Immunosuppressants – indications for use * At this stage, the use of Rituximab and Abatacept in the various manifestations of SLE is not allowed in Bulgaria

Immunosuppressive therapy	Indications (excluding lupus nephritis and neurological manifestations of SLE)
Cyclophosphamide	- Systemic vasculitis, APS - Alveolitis - Haematological disorders – autoimmune hemolytic anemia, thrombocytopenia, thrombotic thrombocytopenic purpura - Optic neuritis
Azathioprine	- Severe skin manifestations - Arthritis - Autoimmune hemolytic anemia, thrombocytopenia - Lupoid hepatitis - Generalized active lupus
Mycophenolate mofetyl (MMF)	- Lupus pemphigoid, lichen-planus associated lupus - Alveolitis - Autoimmune hemolytic anemia, thrombocytopenia - Generalized active lupus, vasculitis
Methotrexate	- Arthritis - „Every lupus.“ - Generalized active lupus
Leflunomide	- Arthritis
Cyclosporine	- Arthritis - Oral ulcerations/Cutaneous lupus - Aplastic/Hypoplastic anemia
A ϕ pepeza	- Haematological disorders – thrombotic thrombocytopenic purpura, cryoglobulinemia - Alveolar hemorrhage
Belimumab (Benlysta®)	- Active lupus, despite standard therapy
Rituximab*	- Haematological disorders – autoimmune hemolytic anemia, thrombocytopenia - Arthritis, vasculitis, APS, severe Sjögren's syndrome
Abatacept*	- Arthritis

VI. Targeted therapy

1. Belimumab (Benlysta) – the only targeted therapy approved by the FDA and EMA for the treatment of patients with systemic lupus erythematosus.

1.1. Mechanism of action

– monoclonal antibody against soluble B lymphocyte stimulator (BLyS)

1.2. Dosage regimen – administered in a dose of 10 mg/kg, administered intravenously on 0-14-28 days, then once a month.

1.3. Belimumab is indicated as adjunctive therapy in patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity (positive anti-dsDNA and low complement values), despite standard therapy.

2. Innovative targeted therapeutic strategies

Table. 9 summarizes the various immunosuppressive drugs and the respective indications for use.

VII. Application of the described drugs in connection with the various organ lesions in patients with SLE (Table 10).

Table 10. Medicines used in various organ lesions in SLE

Skin manifestations	
1. Acute cutaneous lupus erythematosus	moderate dose of CS for a short period of time antimalarial (HCQ, Chloroquine, Quinacrine)
2. Chronic cutaneous lupus erythematosus	- local therapy - sunscreens - antimalarial (HCQ, Chloroquine, Quinacrine)
3. Subacute cutaneous lupus erythematosus	- antimalarial (HCQ, Chloroquine, Quinacrine) - retinoids
4. Generalized cutaneous manifestations of lupus (oral ulceration, „butterfly“ rash, alopecia, urticaria)	- cyclosporine (especially for urticaria) - CS (non-fluorinated CS; fluorinated CS in short courses) - tacrolimus - topical therapy for oral ulcers - topical therapy for hair loss
Musculoskeletal manifestations	
The choice of therapy is determined by: - affected joint areas - duration - severity of the manifestations	- NSAIDs - CS - antimalarial - Methotrexate - Leflunomide - Azathioprine
Cardiopulmonary manifestations	
1. Serositis (pleurisy, pericarditis)	- NSAIDs - CS (high or moderate dose of CS) - antimalarial
2. Acute lupus pneumonitis Alveolar hemorrhage	- high dose CS, incl. pulse therapy - Cyclophosphamide - apheresis

3. Interstitial lung disease	- CS - immunosuppressive drug
4. PAH (pulmonary arterial hypertension)	see section PAH
5. Lupus myocarditis	- high dose of CS - NSAIDs - β -blocker, nitrates
6. Lupus endocarditis	- CS - antibacterial and anticoagulant therapy
Haematological manifestations	
1. Autoimmune hemolytic anemia	- high dose CS - immunosuppressive drugs - targeted therapy (Rituximab) *
2. Idiopathic thrombocytopenic purpura	- CS - immunosuppressive drug - IVIG - targeted therapy (Rituximab) * - splenectomy
3. Thrombotic thrombocytopenic purpura	- CS - apheresis - targeted therapy (Rituximab) *

* At this stage the use of Rituximab in the various manifestations of SLE is not allowed in the Republic of Bulgaria.

VIII. Regarding the treatment of renal and neurological manifestations in patients with lupus erythematosus, treatment recommendations have been developed.

Recommendations for the treatment of lupus nephritis

In 2012, the European League Against Rheumatism and the European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) published the main recommendations (guidelines) for the treatment of patients with lupus nephritis.

1. Indications for performing a puncture kidney biopsy (PBS)

Detection of proteinuria > 0.5 g/24 h, especially in combination with glomerular haematuria with/without cell cylinders, is an indication for PBB. In most cases, PBB is mandatory because clinical, laboratory, and immunological results cannot predict the histological type of renal involvement.

2. Pathomorphological assessment of renal biopsy

The changes were classified according to the criteria of the classification system of the International Society of Nephrology (ISN)/Renal Pathology Society (ISN/RPS) in 2004, assessing active and chronic glomerular and tubulointerstitial changes, as well as vascular changes associated with antiphospholipid antibodies/antiphospholipids.

3. Indications for initiation of treatment and purpose of immunosuppressive therapy in patients with lupus nephritis

The initiation of immunosuppressive treatment is determined by the result of a kidney biopsy. Immunosuppressive therapy is recommended for glomerulonephritis histological class IIIA or IIIA/C ($\pm$ V) and IVA or IVA/C ($\pm$ V), as well as for pure class V glomerulonephritis when protein loss exceeds 1.0 gr/24h despite administration of an optimal dose of ACE inhibitor.

The main goal of treatment for lupus nephritis is to normalize renal function or at least to prevent its progressive loss. Treatment should aim to achieve complete remission with UPCR (Urine Protein to Creatinine Ratio) <50 mg/mmol and normal or close to normal renal function. Partial remission is defined as a reduction in protein loss of $\geq 50\%$ and normal or close to normal renal function, and partial remission should be achieved within approximately 6 months, but not later than 12 months after starting treatment.

4. Treatment of lupus nephritis

Induction therapy

4.1. In patients with glomerulonephritis histological class IIIA or IIIA/C ($\pm$ V) and IVA or IVA/C ($\pm$ V), the administration of Cyclophosphamide (CYC) intravenously, Mycophenolate mofetyl (MMF) and glucocorticoids is recommended as induction therapy due to their best ratio. toxicity. The dose of MMF is 3 g/day for six months or a low dose of CYC (total dose 3 g for three months).

4.2. In patients with poor prognostic factors (acute deterioration of renal function, pronounced cell hemispheres and/or fibrinoid necrosis), a higher dose of CYC ($0.75\text{--}1$ g/m²) was administered intravenously monthly for six consecutive months or 2-2.5 mg/kg/day administered orally.

4.3. Methylprednisolone (MP) is initially administered at a dose of 500-750 mg intravenously (pulse therapy) for 3 consecutive days, followed by oral glucocorticoids at a dose of 0.5 mg/kg/day for four weeks depending on the clinical response, after which the dose is reduced until the minimum required dose for disease control is reached (≤ 10 mg/day for 4-6 weeks). The goal of pulse glucocorticoid therapy is to increase efficacy as well as to reduce the cumulative corticosteroid dose.

4.4. In patients with class V lupus nephritis, it is recommended to start treatment with oral Prednisone 0.5 mg/kg/day together with MMF (2-3 gr/day for 6 months). Alternatively, CYC or calcineurin inhibitors (Ciclosporine, Tacrolimus) or Rituximab are recommended for non-responders.

4.5. Azathioprine (Aza) can be used as an alternative to MMF (MPA) or CYC at a dose of 2 mg/kg/day in individual patients with class III-IV lupus nephritis in the absence of poor prognostic factors or in the presence of contraindications for the use of MMF, CYC. The use of Aza is associated with a higher risk of recurrence.

NB! There are two regimens for intravenous CYC (a) Euro-Lupus regimen with low doses of CYC (500 mg i.v. once every 2 weeks to a total of 6 doses), followed by maintenance treatment with MMF or Aza orally. (b) The National Institutes of Health, where CYC is applied monthly for a period of 6 months, then every three months for the next two years. Dose reduction of CYC is required for creatinine clearance below 30 ml/min and for evidence of leukopenia.

Maintenance therapy for lupus nephritis

4.6. In patients who respond to induction therapy in order to consolidate the response to treatment and avoid new exacerbations, it is recommended to continue treatment with MMF 2 gr/day (or equivalent dose of MPA) or Aza 2 mg/kg/day for a period of time. not less than three years as stimulant therapy together with low doses of corticosteroid (5-7.5 mg/day). Continuation of treatment for more than three years should be individualized, with corticosteroid treatment discontinuing prior to immunosuppressive therapy.

4.7. Patients who have responded to initial treatment with MPA should remain on MPA unless pregnancy is expected. In this case, they must switch to Aza at least three months before conception.

4.8. Calcineurin inhibitors can be used in class V lupus nephritis.

In refractory lupus nephritis

4.9. In patients who do not respond to induction therapy, switching from MMF to CYC or from CYC to MMF is recommended at 6 months of treatment or in the presence of adverse reactions.

* Based on the results of some clinical trials, the need for Rituximab, calcineurin inhibitors (Cyclosporin A, Tacrolimus), intravenous immunoglobulin administered intravenously three times a day at a dose of 85 mg/kg/day, on average 255 mg/kg/day, plasma metabolism in rapidly progressing glomerulonephritis or immunoadsorption.

5. Concomitant treatment for lupus nephritis

5.1. In relation to the effects of ACE inhibitors or angiotensin-eceptor blockers on intraglomerular pressure they are shown in all patients with lupus nephritis (except pregnant women) with proteinuria ≥ 0.5 gr/24 h (UPCR > 50 mg/mmol) or hypertension.

5.2. The use of statins is recommended for persistent dyslipidemia (recommended target LDL-cholesterol levels 2.58 mmol/l).

5.3. Treatment with is recommended for all patients with lupus nephritis Hydroxychloroquine (6.5 mg/kg/day or 400 mg/24 h) in order to improve the outcome by reaching remission faster.

5.4. The use of aspirin in patients with antiphospholipid syndrome, calcium and vitamin D supplementation, immunization with killed vaccines reduce the complications of chronic kidney disease

5.5. In patients with nephrotic syndrome with serum albumin < 20 g/l the presence of antiphospholipid antibodies should be considered the use of anticoagulant therapy. The anticoagulant treatment is carried out with Heparin intravenously in a daily dose usually up to 30 000 IU divided into three infusions of 10 000 IU. In order to titrate the patient's tolerance to Heparin, in the first days are infused 3 5000 IU times with aPPT control, after which the dose is gradually increased increases from 3 to 7500 IU to 3 times to 10 000 IU.

6. Follow-up of patients with lupus nephritis

6.1. Patients with active lupus nephritis should be monitored periodically, monitoring includes body weight, arterial pressure, serum creatinine, eGFR, serum albumin, proteinuria, microscopic examination of urine sediment, serum levels of C3, C4, anti-ds DNA antibodies, complete blood count. Intermittently should antiphospholipid antibodies and lipid profile are monitored.

6.2. The change in serum creatinine (eGFR), hemoglobin, proteinuria and blood pressure have a predictive value on survival in patients with lupus nephritis.

6.3. After diagnosis, patients with lupus nephritis should follow up every 2-4 weeks for the first 2-4 months. Monitoring of renal and extrarenal activity of the disease should be performed throughout the patient's life, at least once every 3-6 months.

6.4. Repeated kidney biopsy is performed in certain cases:

- in case of deterioration of renal function or cases refractory to immunosuppressive therapy (no decrease in protein loss below 50%, persistent proteinuria after the first year and/or worsening of eGFR)
- in case of recurrence of lupus nephritis to detect change (activity and chronicity indices) and/or
- progression of the histological class

Repeated renal biopsy provides additional prognostic information.

7. Treatment of end-stage renal disease in lupus nephritis

7.1. In patients with lupus nephritis, all methods of renal replacement therapy may be used, but an

increased risk of infections and vascular thrombosis is possible.

7.2. Systemic lupus erythematosus should not be active during kidney transplantation. Transplantation should be performed when there is no evidence of lupus activity or the activity is lower for at least 3-6 months. Antiphospholipid antibodies must be tested as they are associated with an increased risk of vascular events in the transplanted kidney.

8. Anti-phospholipid-associated nephropathy in patients with systemic lupus erythematosus

Hydroxychloroquine as well as antiplatelet and/or anticoagulant therapy should be used in patients with systemic lupus erythematosus and anti-phospholipid-associated nephropathy.

9. Pregnancy and lupus nephritis

9.1. Pregnancy can be planned in stable patients with inactive lupus and UPCr <50 mg/mmol for the previous 6 months, with a GFR of > 50 ml/min. Medicines that can be used during pregnancy are: Hydroxychloroquine, low dose Prednisone, Azathioprine and/or calcineurin inhibitor. The intensity of treatment should not be reduced in anticipation of pregnancy. Acetylsalicylic acid should be used during pregnancy to reduce the risk of developing preeclampsia. Pregnant women with lupus nephritis should be monitored every 4 weeks by both a rheumatologist and an obstetrician-gynecologist.

9.2. The onset of lupus nephritis during pregnancy should be treated with drugs for which a safe profile has been established during pregnancy, and the choice of therapy is determined by the severity of the manifestations.

EULAR recommendations for the treatment of neuropsychiatric systemic lupus erythematosus (NPSLE)c (NPSLE)

1. Neuropsychiatric systemic lupus erythematosus (NPSLE)

Neuropsychiatric manifestations may precede, develop in parallel, or follow the diagnosis of systemic lupus erythematosus. In 50-60% of patients neuropsychiatric manifestations develop in the first year after diagnosis of SLE, and in 40-50% of patients active disease is observed.

2. Frequency of neuropsychiatric manifestations

Common (5-15%) neuropsychiatric manifestations include cerebrovascular accidents, seizures; relatively common (1-5%) – cognitive impairment, depression, episode of acute confusion; rare (< 1%) – psychosis, myelitis, chorea, cranial nerve damage and aseptic meningitis.

3. Risk factors associated with the development of NPSLE

The identified risk factors for the development of neurolupus are disease activity, precursor neuropsychiatric manifestations (cognitive impairment, seizures), positive antiphospholipid antibodies (especially in cerebrovascular accidents, seizures, chorea).

4. Diagnostic algorithm

In patients with SLE with new onset/symptoms suggestive of neurolupus, the initial diagnostic algorithm is similar to that used in patients with neurological manifestations without systemic lupus erythematosus.

Depending on the neuropsychiatric manifestations, diagnostic tests include: lumbar puncture followed by examination of the cerebrospinal fluid (exclusion of CNS infection), EEG, neuropsychological tests to assess cognitive function, neuroimaging (MRI) to assess the structure and function of the brain.

The magnetic resonance imaging protocol included brain and spinal cord imaging with MR sequences of T1/T2, FLAIR, DWI, and contrast-enhanced T1 images.

5. Treatment

Therapy indicated for the treatment of neuropsychiatric manifestations in SLE (acute period of confusion, aseptic meningitis, myelitis, damage to the cranial and peripheral nerves, psychosis) includes glucocorticoids and immunosuppressive drugs. Treatment should be initiated after the exclusion of causes unrelated to systemic lupus erythematosus, leading to the development of various neurological and mental manifestations.

Antiplatelet/anticoagulant therapy should be used when neuropsychiatric manifestations are associated with positive antiphospholipid antibodies, especially in thrombotic cerebrovascular events.

Additive therapeutic behavior in lupus-related neuropsychiatric manifestations includes symptomatic agents (anticonvulsants, antiplatelet agents), treatment of infections, hypertension, metabolic disorders (complications exacerbating systemic lupus erythematosus).

6. Specific neuropsychiatric manifestations

Cerebrovascular accidents

Atherosclerotic/thrombotic/embolic cerebrovascular accidents (strokes, transient ischemic attacks (TIAs)) are common in patients with SLE. Hemorrhagic strokes and strokes in the course of cerebrovasculitis are less common, which determines the less frequent use of immunosuppressive therapy. If

hemorrhage is suspected, MRI (DWI sequences) is required.

Therapeutic behavior includes:

- a. In indications for thrombolysis; surgical intervention
- b. Starting Aspirin
- c. Secondary prophylaxis, which includes control of cardiovascular risk factors, administration of antiplatelet/anticoagulant therapy, in case of indicated carotid endarterectomy
- d. Methylprednisolone, Cyclophosphamide pulse therapy is indicated for SLE activity
- e. Anticoagulant therapy should be used for a long time in patients with a history of stroke and who meet the criteria for antiphospholipid syndrome for secondary prevention and to reduce the risk of recurrent stroke.

Cognitive disorders

Mild or moderate cognitive impairment is characteristic of patients with SLE, while severe cognitive impairment is relatively rare, between 3-5% of patients. Cognitive impairment should be confirmed by neuropsychological tests performed in collaboration with a clinical neuropsychologist.

Indications for MRI in cognitive impairment include:

- a. Age under 60 years
- b. Rapid, unexplained deterioration in cognitive function
- c. Concomitant, other neurological manifestations
- d. Exacerbation/development of cognitive impairment with immunosuppressive and/or anticoagulant/antiplatelet therapy.

Therapeutic behavior includes:

- a. Psycho-educational groups
- b. Therapy with corticosteroids and immunosuppressants to control SLE activity
- c. Cognitive impairment associated with positive antiphospholipid antibodies necessitated the use of anticoagulant therapy.

Treatment of lupus- and non-lupus-related conditions prevents further deterioration of cognition.

Seizures

Single seizures are characteristic of patients with SLE and are associated with general disease activity.

The diagnostic methods used (MRI, EEG) aim to exclude structural brain changes, inflammatory processes and metabolic disorders.

Therapeutic behavior includes:

Antiepileptic therapy – not recommended in patients with a single seizure, in whom no lesion

is detected by magnetic resonance imaging, which is associated with the epiphenomenon, as well as those without an epileptogenic focus. Long-term antiepileptic therapy is used in patients with recurrent seizures

When epileptic seizures are in the course of active lupus pulse therapy with Methylprednisolone and an immunosuppressant is indicated

In most patients without lupus activity, immunosuppressive therapy is not indicated for the prevention of recurrent seizures or for the control of refractory epileptic phenomena.

Anticoagulant therapy is indicated in patients with antiphospholipid syndrome.

Chorea

Therapeutic behavior

a. Symptomatic therapy with dopamine antagonists,

b. Glucocorticoids, immunosuppressive drugs and/or anticoagulant therapy should be used in severe cases with marked lupus activity with/without thrombotic events.

Acute period of confusion

A lumbar puncture should be performed, followed by cerebrospinal fluid and MRI scans to rule out causes other than SLE, especially infections.

In severe cases, therapy with corticosteroids and immunosuppressive drugs is recommended.

Depression and psychosis

Depression in SLE is relatively uncommon, psychosis is rare, and steroid-induced psychosis may occur. Steroid-induced psychosis has been reported in approximately 10% of SLE patients treated with a corticosteroid at a dose higher than 1 mg/kg.

No association has been established between certain serological markers or characteristic magnetic resonance imaging images and depressive states.

Therapeutic behavior includes:

a. Antidepressants and/or antipsychotics

b. Corticosteroid and immunosuppressive therapy should be used in SLE-related psychoses, especially in established lupus activity. Recommended immunosuppressive therapy includes pulses with Cyclophosphamide followed by administration of Azathioprine.

c. Rituximab is used in refractory clinical cases.

Myelopathy

The term myelopathy includes transverse myelitis as well as ischemic/thrombotic myelopathy.

The diagnostic approach includes MRI of the brain and spinal cord, lumbar puncture with examination of cerebrospinal fluid.

Therapeutic behavior includes:

a. Pulse therapy with Methylprednisolone alone or in combination with the immunosuppressant Cyclophosphamide.

b. Plasmapheresis in severe clinical cases

c. Anticoagulant therapy in myelopathy associated with positive antiphospholipid antibodies.

Optic neuritis

Usually in patients with SLE, optic neuritis is bilateral.

Diagnostic behavior includes a complete ophthalmological examination – fundoscopy, fluoroangiography, MRI, visual evoked potentials.

Optic neuritis should be differentiated from ischemic optic neuropathy, and ischemic optic neuropathy is usually unilateral and characteristic of patients with positive antiphospholipid antibodies.

Therapeutic behavior includes:

a. Pulse therapy with Methylprednisolone and Cyclophosphamide.

b. Anticoagulant therapy for positive antiphospholipid antibodies.

Peripheral neuropathy

Peripheral nervous system damage includes polyneuropathy, mononeuropathy, acute inflammatory demyelinating polyradiculoneuropathy, myasthenia gravis, plexopathy. Peripheral neuropathy often occurs with other neuropsychiatric manifestations, and the diagnostic approach includes electro-neuromyography, lumbar puncture with subsequent examination of cerebrospinal fluid (acute inflammatory demyelinating polyradiculoneuropathy), in rare cases peripheral nerve biopsy.

Therapeutic behavior includes:

a. Use of glucocorticoids and immunosuppressants

b. In severe clinical cases, intravenous immunoglobulins, plasmapheresis, Rituximab are used

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