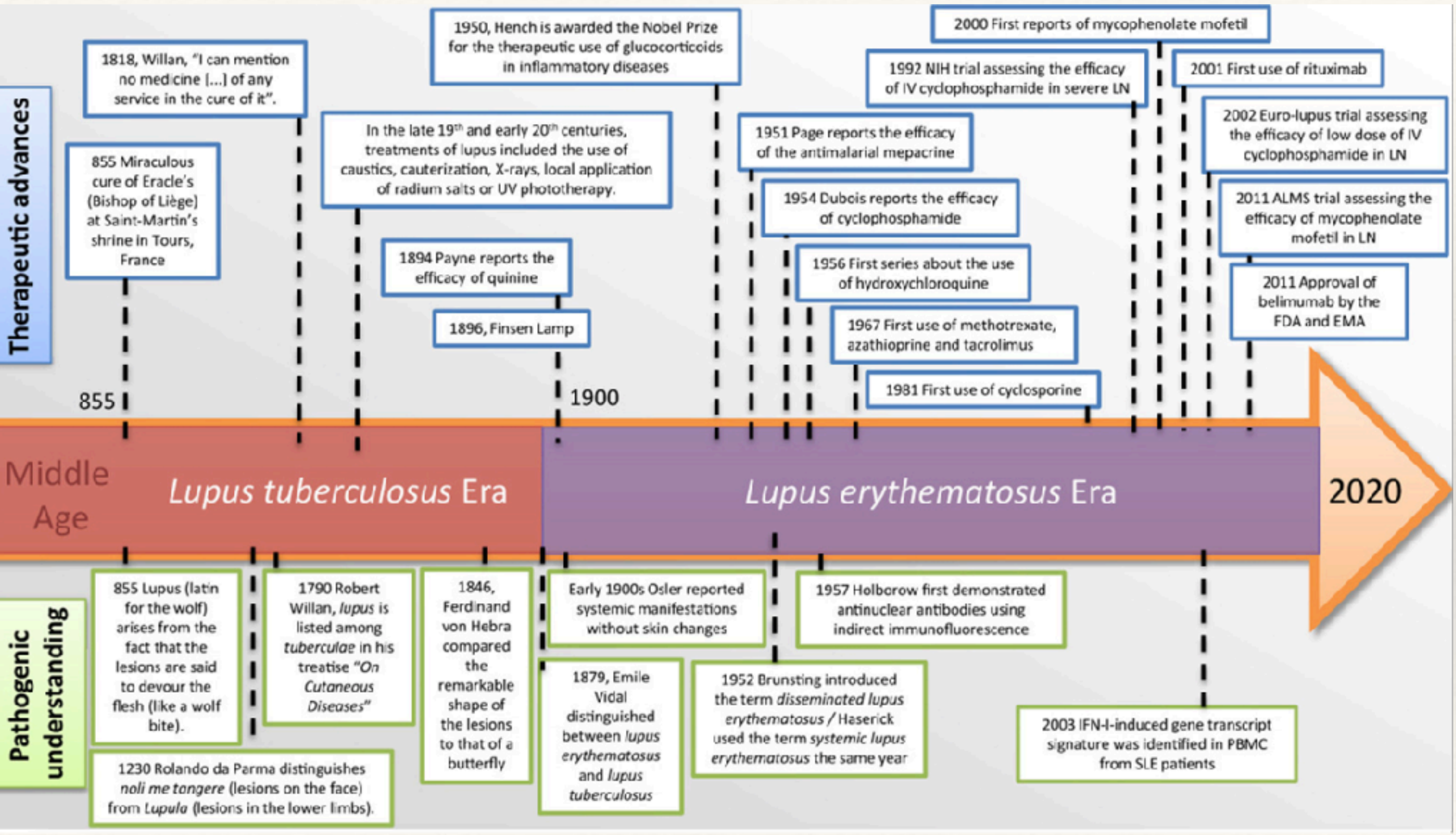
Old vs New in Systemic Lupus Erythematosus

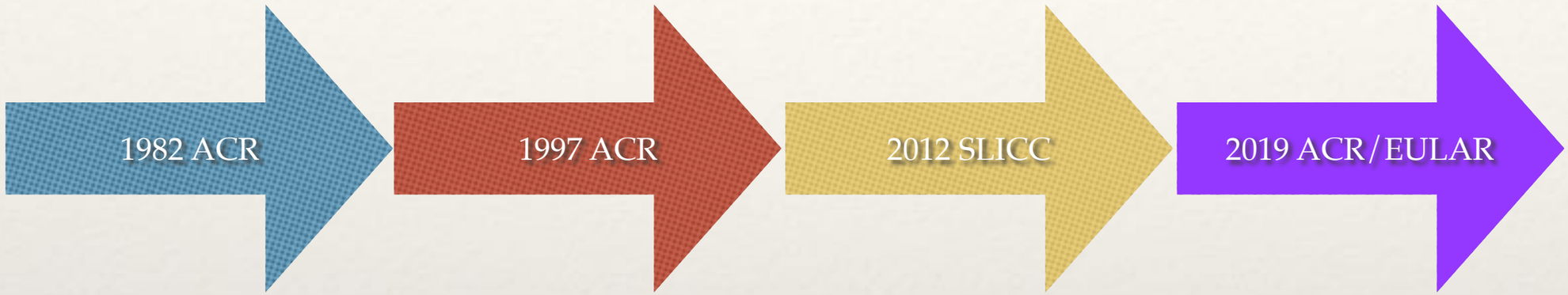
AP Yin Minn Soe
Department of Rheumatology
University of Medicine-1,
Yangon

Outlines

- History - 2018 MRS SLE guideline
- What is new after 2019
    - Classification Criteria- 2019 ACR/EULAR
    - Remission criteria- DORIS 2021
    - Disease activity Assessment-
        - SLE-DAS (2020)
        - Easy BILAG score (2022)
    - Treatment guidelines _2023 EULAR
    - T2U strategy (proposed strategy)


Therapeutic advances
855 Miraculous cure of Eracle's (Bishop of Liège) at Saint-Martin's shrine in Tours, France
1818, Willan, "I can mention no medicine [...] of any service in the cure of it".
In the late 19th and early 20th centuries, treatments of lupus included the use of caustics, cauterization, X-rays, local application of radium salts or UV phototherapy.
1894 Payne reports the efficacy of quinine
1896, Finsen Lamp
1950, Hench is awarded the Nobel Prize for the therapeutic use of glucocorticoids in inflammatory diseases
1951 Page reports the efficacy of the antimalarial mepacrine
1954 Dubois reports the efficacy of cyclophosphamide
1956 First series about the use of hydroxychloroquine
1967 First use of methotrexate, azathioprine and tacrolimus
1981 First use of cyclosporine
1992 NIH trial assessing the efficacy of IV cyclophosphamide in severe LN
2000 First reports of mycophenolate mofetil
2001 First use of rituximab
2002 Euro-lupus trial assessing the efficacy of low dose of IV cyclophosphamide in LN
2011 ALMS trial assessing the efficacy of mycophenolate mofetil in LN
2011 Approval of belimumab by the FDA and EMA
855
1900
2020
Middle Age
Lupus tuberculosus Era
Lupus erythematosus Era
Pathogenic understanding
855 Lupus (latin for the wolf) arises from the fact that the lesions are said to devour the flesh (like a wolf bite).
1230 Rolando da Parma distinguishes noli me tangere (lesions on the face) from Lupula (lesions in the lower limbs).
1790 Robert Willan, lupus is listed among tuberculae in his treatise "On Cutaneous Diseases"
1846, Ferdinand von Hebra compared the remarkable shape of the lesions to that of a butterfly
1879, Emile Vidal distinguished between lupus erythematosus and lupus tuberculosus
Early 1900s Osler reported systemic manifestations without skin changes
1952 Brunsting introduced the term disseminated lupus erythematosus / Haserick used the term systemic lupus erythematosus the same year
1957 Holborow first demonstrated antinuclear antibodies using indirect immunofluorescence
2003 IFN-I-induced gene transcript signature was identified in PBMC from SLE patients

- Evolution of classification criteria



Suspicion of SLE		
ACR	SLICC	EULAR/ACR
any 4 of 11	Histology compatible with lupus nephritis and ANA or anti-dsDNA OR any 4 of 17 (at least one immunological)	ANA positive 10 points weighted items (highest in each domain counted only)

1982 1997 2012 2019

ACR 1982	ACR 1997	SLICC 2012	EULAR/ACR 2019	
			Mucocutaneous	
1. Malar rash		1. Acute cutaneous LE*	Acute cutaneous LE	6
		or SCLE	SCLE	4
2. Discoid rash		2. Chronic cutaneous LE†	Discoid LE	4
3. Photosensitivity				
4. Oral ulcers		3. Oral ulcers	Oral ulcers	2
		or nasal ulcers		
		4. Non-scarring alopecia	Non-scarring alopecia	2
5. Arthritis		5. Synovitis	Joint involvement	6
6. Serositis		6. Serositis	Serosal	
a) Pleuritis		Pleuritis	Effusion	5
b) Pericarditis		or pericarditis	Acute pericarditis	6
7. Renal disorder		7. Renal	Renal	
a) Persistent proteinuria		Proteinuria	Proteinuria	4
b) Cellular casts		or red cell casts		
		Histology compatible with lupus nephritis	ISN/RPS II/V	8
			ISN/RPS III/IV	10
8.Neurologic disorder		8. Neurologic	Neuropsychiatric	
a) Seizures		Seizures	Seizure	5
b) Psychosis		Psychosis	Psychosis	3
		Mononeuritis multiplex		
		Myelitis		
		Peripheral or cranial neuropathy		
		Acute confusional state	Delirium	2
9. Hematologic disorder			Hematologic	
a) Hemolytic anemia		9. Hemolytic anemia	Coombs+ hemolytic anemia	4
b) Leukopenia		10. Leukopenia	Leukopenia	3
c) Lymphopenia		or lymphopenia		
d) Thrombocytopenia		11. Thrombocytopenia	Thrombocytopenia	4
10. Immunologic disorder				
a) LE cell preparation				
			SLE-specific antibodies	
b) Anti-DNA	a) Anti-DNA	12. Anti-dsDNA	Anti-dsDNA	6
c) Anti-Sm	b) Anti-Sm	13. Anti-Sm	Anti-Sm	6
d) False-positive syphilis serology	c) Anti-phospholipid	14. Anti-phospholipid	Anti-phospholipid	2
		15. Low complements	Low complement	
			C3 or C4 low	3
			C3 and C4 low	4
		16. Coombs test without hemolytic anemia		
11. ANA	11. ANA	17. ANA	Entry criterion ANA	

❖ MRS SLE guideline (2018) Updated in 2020

I.Classification Criteria

Either Revised ACR 1987 criteria (1997 update) or SLICC 2012 criteria can be used to diagnose SLE.

2019 ACR/EULAR Classification Criteria

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

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
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
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 >0.5g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR	
Anti-β2GP1 antibodies OR	
Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody* OR	
Anti-Smith antibody	6

Total score:

↓

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

Criteria	Definition
Antinuclear antibodies (ANA)	ANA at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test at least once. Testing by immunofluorescence on HEp-2 cells or a solid-phase ANA screening immunoassay with at least equivalent performance is highly recommended

Criteria	Definition
Fever	Temperature >38.3°C

Criteria	Definition
Leukopenia	White blood cell count <4,000/mm3
Thrombocytopenia	Platelet count <100,000/mm3
❖ Autoimmune hemolysis	Evidence of hemolysis, such as reticulocytosis, low haptoglobin, elevated indirect bilirubin, elevated LDH, AND positive Coombs' (direct antiglobulin) test

Criteria	Definition
Delirium	Characterized by 1) change in consciousness or level of arousal with reduced ability to focus, 2) symptom development over hours to <2 days, 3) symptom fluctuation through- out the day, 4) either 4a) acute/subacute change in cognition (e.g., memory deficit or disorientation), or 4b) change in behavior, mood, or affect (e.g., restlessness, reversal of sleep/wake cycle)
Psychosis	Characterized by 1) delusions and/or hallucinations without insight and 2) 2) absence of delirium
Seizure	Primary generalized seizure or partial/focal seizure

Criteria	Definition
Non-scarring alopecia	Non-scarring alopecia observed by a clinician
Oral ulcers	Oral ulcers observed by a clinician
Subacute cutaneous ❖ OR discoid lupus	Subacute cutaneous lupus erythematosus observed by a clinician:Annular or papulosquamous (psoriasiform) cutaneous eruption, usually photodistributed OR Discoid lupus erythematosus observed by a clinician:† Erythematous-violaceous cutaneous lesions with secondary changes of atrophic scarring, dyspigmentation, often follicular hyperkeratosis/ plugging (scalp), leading to scarring alopecia on the scalp
Acute cutaneous lupus	Malar rash or generalized maculopapular rash observed by a clinician

Criteria	Definition
Pleural or pericardial effusion	Imaging evidence (such as ultrasound, x-ray, CT scan, MRI) of pleural or pericardial effusion, or both
Acute pericarditis	≥2 of 1) pericardial chest pain (typically sharp, worse with inspiration, improved by leaning forward), 2) pericardial rub, 3) EKG with new widespread ST elevation or PR depression, 4) new or worsened pericardial effusion on imaging (such as ultrasound, x-ray, CT scan, MRI)

Criteria	Definition
Joint involvement	EITHER 1) synovitis involving 2 or more joints characterized by swelling or effusion OR 2) tenderness in 2 or more joints and at least 30 minutes of morning stiffness

Criteria	Definition
Proteinuria >0.5 g/24 hours	Proteinuria >0.5 g/24 hours by 24-hour urine or equivalent spot urine protein-to- creatinine ratio
Class II or V lupus nephritis on renal biopsy according to ISN/RPS 2003 classification	Class II: Mesangial proliferative lupus nephritis Class V: Membranous lupus nephritis
Class III or IV lupus nephritis on renal biopsy according to ISN/RPS 2003 classification	Class III: Focal lupus nephritis: involving <50% of all glomeruli Class IV: Diffuse lupus nephritis: involving ≥50% of all glomeruli

Criteria	Definition
Positive antiphospholipid antibodies	Anticardiolipin antibodies (IgA, IgG, or IgM) at medium or high titer (>40 APL, GPL, or MPL, or >the 99th percentile) or positive anti-β2GPI antibodies (IgA, IgG, or IgM) or positive lupus anticoagulant
Anti-dsDNA antibodies OR anti-Sm antibodies	Anti-dsDNA antibodies in an immunoassay with demonstrated ≥90% specificity for SLE against relevant disease controls OR anti-Sm antibodies
Low C3 OR low C4	C3 OR C4 below the lower limit of normal
Low C3 AND low C4	Both C3 AND C4 below their lower limits of normal

The main structure of the EULAR/ACR 2019 classification criteria.

Obligatory entry criterion: ever positive ANA (≥1:80 or equivalent)			
≥10 points out of 10 domains (highest item of each domain counted only)			
1. Renal	Class III/IV LN 10	Class II/V LN 8	Proteinuria 4
2. Musculoskeletal	Joint involvement 6		
3. Serosal	Acute pericarditis 6	Effusion 5	
4. Mucocutaneous	ACLE 6	SCLE or discoid LE 4	Alopecia or oral ulcers 2
5. Neuropsychiatric	Seizure 5	Psychosis 3	Delirium 2
6. Hematological	Autoimmune Hemolysis 4	Thrombocytopenia 4	Leukopenia 3
7. Constitutional	Fever 2		
8. Specific antibodies	Anti-dsDNA 6	Anti-Sm 6	
9. Low complements	C3 and C4 low 4	C3 or C4 low 3	
10. APS antibodies	LAC 2	ACLA or anti-β2gpI 2	

Disease Activity Measurements

- Disease activity measurements in SLE are necessary for optimal patient care.
- They are central to clinical guidelines and treat-to-target approaches
- BILAG score (2004) ————Easy BILAG score
- SLEDAI score (2000)_____ SLE-DAS score
-

SLE-DAS = 0.366 + 3.132 x Arthritis + 0.454 x SJC + 4.408 x MucocutVasculitis + 3.138 x LocalRash + 3.887 x GeneralRash + 0.973 x Alopecia + 2.769 x MucosalUlcers + 0.754 x HypoC + 0.956 x IncreasedAnti-dsDNA – 17.584 x PProt + 3.811 x PProt x ln(Prot) + 26.105 x Thromb – 5.577 x Thromb x ln(PlatCount) + 6.118 x Leuk – 5.058 x Leuk x ln(LeukCount) + 18 x Neuropsych + 18 x SystemicVasc + 18 x CardioPulm + 9 x Myositis + 6 x Serositis + 9 x Hemolytic

SLE-DAS flare

Increase in SLE-DAS ≥ 1.72

Remission (no flare)	**Mild SLE flare**	**Moderate/severe SLE flare**
SLE-DAS ≤ 2.08	2.08 < SLE-DAS ≤ 7.64	SLE-DAS > 7.64

SLE-DAS

SLE Disease Activity Score Calculator

1. Neuropsychiatric involvement
2. Systemic vasculitis
3. **Mucocutaneous vasculitis**
4. Cardiac/Pulmonary involvement
5. Serositis
6. Proteinuria — Ratio mg/g or mg/24 h: 3000
7. Arthritis — 28 swollen joint count: 1 to 28
8. Myositis
9. Localized skin rash
10. Generalized skin rash
11. Alopecia
12. Mucosal ulcers
13. Hemolytic anemia
14. Thrombocytopenia — Platelet count(G/L): <100
15. Leukopenia — Leukocyte count(G/L): <3
16. Hypocomplementemia
17. Increased anti-dsDNA

Calculate

58.33

Original article

Easy-BILAG: a new tool for simplified recording of SLE disease activity using BILAG-2004 index

Lucy M. Carter [1], Caroline Gordon[2], Chee-Seng Yee[3], Ian Bruce [4], David Isenberg [5], Sarah Skeoch[6] and Edward M. Vital [1]

- Easy-BILAG is a high-accuracy, time-efficient tool for recording BILAG-2004 disease activity in SLE.
- It is the new recommended format for scoring BILAG-2004 index in clinical practice.
- Easy-BILAG and its training material is available free of charge for use in routine care at https://licensing.leeds.ac.uk/products/healthcare-questionnaires.

	ITEM	ABBREVIATED GLOSSARY	Not Present	Improving	Same	Worse	New	SCORE A - E
Mucocutaneous	Skin eruption - severe	Any lupus rash except panniculitis, bullous lesion and angio-oedema. Must involve >18% BSA	0	1	2	3	4	B
	Skin eruption - *mild*	As above but <18% BSA. If malar rash: observed by doctor and present at least 1/52	0	1	2	3	4	
	Mucosal ulceration - severe	Disabling (sig interfering with oral intake), extensive & deep. Observed by a physician.	0	1	2	3	4	
	Mucosal ulceration - *mild*	Localised and/or non-disabling ulceration	0	1	2	3	4	
	Alopecia - severe	Clinically detectable (diffuse or patchy) hair loss with scalp inflammation (redness over scalp)	0	1	2	3	4	
	Alopecia - *mild*	Diffuse or patchy hair loss without scalp inflammation (clinically undetectable /by history)	0	1	2	3	4	
	Digital infarct / nodular vasculitis	Localised single / multiple infarct(s) over digit(s) or tender erythematous nodule(s)	0	1	2	3	4	
	Periungual erythema / chilblains	Chilblains = localised inflammatory lesions (may ulcerate) precipitated by exposure to cold	0	1	2	3	4	
	Other features	Angio-oedema, panniculitis, cutaneous vasculitis, or splinter haemorrhages	No	YES → NEXT PAGE				
MSK	Arthritis - severe	Observed synovitis ≥2 joints + tenderness or ROM & ADL, on several days (corr) in past 4/52.	0	1	2	3	4	C
	Arthritis (moderate), tendonitis or tenosynovitis	≥1 joint (observed or history), some loss ROM, several days of past 4/52	0	1	2	3	4	
	Arthritis (mild), arthralgia or myalgia	Inflammatory pain over joints / muscle	0	1	2	3	4	
	Other features	Myositis	No	YES → NEXT PAGE				
CardioResp	Pleurisy / Pericarditis	Convincing history and/or physical findings. Do not score if unsure.	0	1	2	3	4	D
	Pleural effusion with dyspnoea	Supportive imaging required	0	1	2	3	4	
	Interstitial alveolitis/ pneumonitis	Supportive imaging required. Corrected Kco <70% 'normal or fall by > 20%.	0	1	2	3	4	
	Other features	Any other cardiac or respiratory problem due to active SLE.	No	YES → NEXT PAGE				
NeuroPsych	Mononeuropathy (single or multiplex)	Supportive electrophysiology required	0	1	2	3	4	E
	Polyneuropathy	Acute symmetrical distal sensory and/or motor deficit (supportive electrophysiology required)	0	1	2	3	4	
	Seizure disorder	Independent description of seizure by reliable witness	0	1	2	3	4	
	Other features	Any other CNS or PNS feature due to active SLE	No	YES → NEXT PAGE				

	ITEM	ABBREVIATED GLOSSARY	A	B	C	D	E	SCORE A - E
Haematology	Full blood count							C
		Hb WITHOUT evidence of haemolysis		<8.0	8.0-10.9	>10.9	Never	
		Hb WITH evidence of haemolysis	<8.0	8.0-9.9	>10		Never	
	Circle patient's values only if due to active *SLE*, i.e. exclude drug causes, iron deficiency	Total WCC (x10⁹/L)		<1.0	1-3.9	>3.9	Never	
		Neutrophils (x10⁹/L)		<0.5	0.5-1.9	>1.9	Never	
		Lymphocytes (x10⁹/L)			<1.0	>1.0	Never	
		Platelets (x10⁹/L)	<25	25-49	50-149	>149	Never	
	Other features	TTP or isolated Coombes	No	YES → NEXT PAGE				

Gastrointestinal If active check next page	E	Ophthalmic If active check next page

Key	
	A
	B
	C
All	D (previous)
All	E (never)

Constitutional	
A	≥1200
B	≥ 200
C	≥ 10
D	0 previous
E	0 never

Renal	
A	≥1100
B	≥ 10
C	≥ 1
D	0 previous
E	0 never

For the following systems, circle all that apply and total the points to determine the domain score

	ITEM	ABBREVIATED GLOSSARY	No	Imp	Same	Worse	New	
Constitutional	Pyrexia	Documented Temp >37.5 (infection excluded)	0	10	1000	1000	1000	= 20 C
	Weight loss	Unintentional >5% loss in 1 month due to SLE	0	10	100	100	100	
	Lymphadenopathy or splenomegaly	Lymph node > 1cm diameter	0	10	100	100	100	
	Anorexia	Due to active SLE	0	10	100	100	100	

Renal								
Renal	Select all that apply:	Biopsy nephritis past 0 months?	(1000)	Active urinary sediment?	1000	Nephrotic syndrome?	100	= 2000 A
	Urinary PCR (mg/mmol); or equivalent	25-50 **or** >25 and improved by ≥25%	1	50-100 and unimproved	10	>100 and unimproved	(1000)	
	GFR (ml/min per 1.73m²);	<60 ml/min & <90% of previous	100	<30 ml/min & previously > 30			100	
	Serum creatinine:	>130 µmol/L & >130% of previous	100	>130 µmol/L & >115% previous			10	
	Blood pressure (mmHg):	Accelerated HTN (T to >170/110 within 1/12 with retinal changes)	100	BP >140/90 & T by 30 systolic or 15 diastolic			1	

Update the final domain scores with any items recorded on page two

No other items? BILAG COMPLETE

B

	ITEM	ABBREVIATED GLOSSARY	Nil	Imp	Same	Worse	New
Gastrointestinal	Lupus peritonitis	Serositis presenting as acute abdomen with rebound/guarding.	0	1	2	3	4
	Abdominal serositis or ascites	Not presenting as acute abdomen.	0	1	2	3	4
	Lupus enteritis / colitis	Vasculitis or inflammation of small or large bowel, with supportive imaging &/or biopsy.	0	1	2	3	4
	Malabsorption	Diarrhoea + abnormal D-xylose absorption / ↑faecal fat losses. Exclude Coeliac & gut vasculitis.	0	1	2	3	4
	Protein-losing enteropathy	See detailed glossary.	0	1	2	3	4
	Intestinal pseudo-obstruction	Subacute intestinal obstruction due to intestinal hypomotility.	0	1	2	3	4
	Lupus hepatitis	Raised transaminases, without AIH specific autoantibodies. Exclude drug- & viral hepatitis.	0	1	2	3	4
	Acute lupus cholecystitis	Exclude gallstones or infection.	0	1	2	3	4
	Acute lupus pancreatitis	Usually associated with multisystem involvement.	0	1	2	3	4
Ophthalmic	Orbital inflam / myositis / proptosis	Orbital inflammation + myositis / extra-ocular muscle swelling / proptosis. Imaging required.	0	1	2	3	4
	Keratitis - severe	Sight-threatening. Includes corneal melt and peripheral ulcerative keratitis.	0	1	2	3	4
	Keratitis - mild	Not sight-threatening.	0	1	2	3	4
	Anterior uveitis		0	1	2	3	4
	Post. uveitis/retinal vasculitis - severe	Sight-threatening and/or retinal vasculitis not due to vaso-occlusive disease.	0	1	2	3	4
	Post. uveitis/retinal vasculitis - *mild*	Not sight-threatening. Not due to vaso-occlusive disease.	0	1	2	3	4
	Episcleritis		0	1	2	3	4
	Scleritis - severe	Necrotising anterior scleritis. And &/or post scleritis requiring systemic therapy.	0	1	2	3	4
	Scleritis - mild	Anterior/posterior scleritis not requiring systemic steroids.	0	1	2	3	4
	Retinal / choroidal vaso-occlusive disease	See detailed glossary table.	0	1	2	3	4
	Isolated cottonwool spots	Also known as cytoid bodies.	0	1	2	3	4
	Optic neuritis	Exclude anterior ischaemic optic neuropathy.	0	1	2	3	4
	Anterior ischaemic optic neuropathy	Visual loss with pale swollen optic disc due to occlusion of posterior ciliary arteries.	0	1	2	3	4

OTHER PAGE 1 FEATURES: Record here and update the score for that domain on page one:

Mucocutan	Angio-oedema - severe	Urticaria variant in subcut, submucosal &deep dermal tissues. Potentially life-threatening.	0	1	2	3	4
	Angio-oedema - mild	As above but not life-threatening.	0	1	2	3	4
	Panniculitis/ bullous lupus - severe	See detailed glossary table.	0	1	2	3	4
	Panniculitis/ bullous lupus - mild	Affects <9% BSA & does not fulfil any criteria for severe panniculitis.	0	1	2	3	4
	Major cutaneous vasculitis/thrombosis	Cutaneous vasculitis/thrombosis → extensive gangrene /ulceration / skin infarction.	0	1	2	3	4
	Splinter haemorrhages		0	1	2	3	4
MSK	Myositis - severe	Significantly ↑ muscle enzymes with significant muscle weakness.	0	1	2	3	4
	Myositis - *mild*	Significantly ↑muscle enzymes + myalgia but no significant muscle weakness.	0	1	2	3	4
Cardiorespiratory	Myocarditis - mild	↑ cardiac enzymes &/or ECG changes. No heart failure/arrhythmia/valve dysfunction.	0	1	2	3	4
	Myo /Endocarditis + cardiac failure	See detailed glossary table.	0	1	2	3	4
	Arrhythmias	Due to myocarditis / non-infective inflammation. ECG evidence required.	0	1	2	3	4
	New valvular dysfunction	Due to myocarditis / non-infective inflammation. Supportive imaging required.	0	1	2	3	4
	Cardiac tamponade	Supportive imaging required.	0	1	2	3	4
	Pulmonary haemorrhage/vasculitis	With haemoptysis &/or dyspnoea &/or pulmonary HTN. Imaging &/or histology required.	0	1	2	3	4
	Shrinking lung syndrome	Acute ↓ lung volumes (< 70% predicted) + normal corrected Kco. Diaphragmatic dysfunction.	0	1	2	3	4
	Aortitis	+/- dissection with supportive imaging, claudication, bruits or BP discrepancy >10 mmHg.	0	1	2	3	4
	Coronary vasculitis	Imaging evidence of non-atheromatous coronary narrowing/ obstruction /aneurysm.	0	1	2	3	4
Neuropsychiatric	Aseptic meningitis	See detailed glossary table.	0	1	2	3	4
	Cerebral vasculitis	With features of vasculitis in another system. Supportive imaging &/or biopsy required.	0	1	2	3	4
	Demyelinating syndrome	Discrete white matter lesion + neurological deficit. Ideally ≥1 prior recorded event. Exclude MS.	0	1	2	3	4
	Myelopathy	Acute onset, rapidly evolving paraparesis, quadriparesis and/or sensory level. Exclude SOL.	0	1	2	3	4
	Acute confusional state	See detailed glossary table.	0	1	2	3	4
	Psychosis	Delusions &/or hallucinations. Excludes primary psychotic disorder, drugs or during delirium.	0	1	2	3	4
	Acute inflammatory demyelinating polyradiculoneuropathy	See detailed glossary table.	0	1	2	3	4
	Cranial neuropathy	Exclude optic neuropathy which is classified under ophthalmic system.	0	1	2	3	4
	Plexopathy	Supportive electrophysiology study required.	0	1	2	3	4
	Cognitive dysfunction	Sufficient to impair ADLs. Includes attention, memory, language, visuospatial, psychomotor.	0	1	2	3	4
	Status epilepticus	A seizure or seizures lasting >30 minutes without full recovery to baseline.	0	1	2	3	4
	Cerebrovascular disease	Not vasculitis. See detailed glossary table.	0	1	2	3	4
	Movement disorder	Exclude drug-induced.	0	1	2	3	4
	Autonomic disorder	See detailed glossary table.	0	1	2	3	4
	Cerebellar ataxia	Cerebellar ataxia in isolation of other CNS features. Usually subacute presentation.	0	1	2	3	4
	Severe lupus headache	Unremitting, Disabling, unresponsive to narcotics, >3 days. Exclude SOL and CNS infection.	0	1	2	3	4
	Headache from intracranial hypertension	Exclude cerebral sinus thrombosis.	0	1	2	3	4
Haem	TTP	Micro-angiopathic haemolytic anaemia + thrombocytopenia. Other causes excluded.	0	1	2	3	4
	Coombes positive (isolated)	Without evidence of haemolysis.	Negative			Positive	

Objective. BILAG-2004 index is a comprehensive disease activity instrument for SLE but administrative burden and potential frequency of errors limits its use in routine practice. We aimed to develop a tool for more accurate, time-efficient scoring of BILAG-2004 index with full fidelity to the existing instrument.

Methods. Frequency of BILAG-2004 items was collated from a BILAG-biologics registry (BILAG-BR) dataset. Easy-BILAG prototypes were developed to address known issues affecting speed and accuracy. After expert verification, accuracy and usability of the finalized Easy-BILAG was validated against standard format BILAG-2004 in a workbook exercise of 10 case vignettes. Thirty-three professionals ranging in expertise from 14 UK centres completed the validation exercise.

Results. Easy-BILAG incorporates all items present in ≥5% BILAG-BR records, plus full constitutional and renal domains into a rapid single page assessment. An embedded glossary and colour-coding assists domain scoring. A second page captures rarer manifestations when needed. In the validation exercise, Easy-BILAG yielded higher median scoring accuracy (96.7%) than standard BILAG-2004 documentation (87.8%, $P = 0.001$), with better inter-rater agreement. Easy-BILAG was completed faster (59.5 min) than the standard format (80.0 min, $P = 0.04$) for 10 cases. An advantage in accuracy was observed with Easy-BILAG use among general hospital rheumatologists (91.3 *vs* 75.0, $P = 0.02$), leading to equivalent accuracy as tertiary centre rheumatologists. Clinicians rated Easy-BILAG as intuitive, convenient, and well adapted for routine practice.

Conclusion. Easy-BILAG facilitates more rapid and accurate scoring of BILAG-2004 across all clinical settings, which could improve patient care and biologics prescribing. Easy-BILAG should be adopted wherever BILAG-2004 assessment is required.

Rheumatology key messages

- Easy-BILAG is a high-accuracy, time-efficient tool for recording BILAG-2004 disease activity in SLE.
- It is the new recommended format for scoring BILAG-2004 index in clinical practice.
- Easy-BILAG and its training material is available free of charge for use in routine care at https://licensing.leeds.ac.uk/products/healthcare-questionnaires.

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Management of SLE

A. SLE requires multidisciplinary, individualised management with patient education and shared decision-making, taking into consideration the costs to patient and society.

B. SLE disease activity should be assessed at each clinic visit (the frequency depending on physician's discretion), with evaluation of organ damage (at least annually), using validated instruments.

C. Non-pharmacological interventions, including sun protection, smoking cessation, healthy, balanced diet, regular exercise and measures to promote bone health are important to improve long-term outcomes.

D. Pharmacological interventions are directed by patient characteristics, type and severity of organ involvement, treatment- related harms, comorbidities, risk for progressive organ damage and patient preferences.

E. Early SLE diagnosis (including serological assessment), regular screening for organ involvement (especially nephritis), prompt initiation of treatment aiming at remission (or low disease activity if this is not possible), and strict adherence to treatment are essential to prevent flares and organ damage, improve prognosis and enhance quality of life.

❖ MRS SLE guideline (2018) Updated in 2020

Treatment of non-organ threatening lupus i.e. mild to moderate disease activity

Mild disease actvity

- Prednisolone- 20mg/day for 1-2 weeks and taper gradually
- And HCQ-200mg/day
- And/or Methotrexate-7.5-15mg/week
- And/or NSAIDS (for few days to weeks only)

Moderate disease activity

Prednisolone 0.5 mg/day for 2-4 weeks and taper gradually

(If necessary Pulse IVI Methylprednisolone 250 mg for 1-2days can be given)

And HCQ 6.5 mg/kg/day

And AZA 1.5 -2.0mg/kg/day or MTX 10- 20 mg/week or MMF 1-2g/day or leflunomide 20 mg/day or ciclosporin 2.0mg/kg/day

Severe disease activity – Intensive therapy

MMF 2-3gm a day for 6 months*

PLUS

GC IV pulse x 3 days then prednisone 1 mg/kg per day tapered after 4 weeks to lowest effective dose

OR

CYC
600mg (>40kg BW)
500mg (≤40kg BW)
PLUS
GC IV pulse x 3 days then prednisone 1 mg/kg per day tapered after 4 weeks to lowest effective dose

6 mos

Improved

MMF 1-2 gm/day
OR
AZA 1-2mg/kg/day
Or
Leflunamide 20mg/d
Or
3 monthly CYC
+/- low-dose daily GC

Improved

MMF 1-2 gm/day
OR
AZA 1-2mg/kg/day
Or
Leflunamide 20mg/d
Or
3 monthly CYC
+/- low-dose daily GC

Not Improved

CYC
+
Pulse GC then
Daily GC

Improved

MMF 1-2 gm/day
OR
AZA 1-2mg/kg/day
Or
Leflunamide 20mg/d
Or
3 monthly CYC
+/- low-dose daily GC

Not Improved

Rituximab
Or
Multi-targeted Rx
Or
Single dose
RTX+Leflunamide

6 mos

Not Improved

MMF 2-3gm daily
for 6 months
+
Pulse GC then
Daily GC

Improved

MMF 1-2 gm/day
OR
AZA 1-2mg/kg/day
Or
Leflunamide 20mg/d
Or
3 monthly CYC
+/- low-dose daily GC

Not Improved

Rituximab
Or
Multi-targeted Rx
Or
Single dose
RTX+Leflunamide

EULAR recommendations for the management of systemic lupus erythematosus: 2023 update

Antonis Fanouriakis ,[1] Myrto Kostopoulou ,[1] Jeanette Andersen,[2] Martin Aringer ,[3] Laurent Arnaud ,[4] Sang-Cheol Bae ,[5] John Boletis,[6] Ian N Bruce,[7] Ricard Cervera,[8] Andrea Doria ,[9] Thomas Dörner ,[10] Richard A Furie ,[11] Dafna D Gladman ,[12] Frederic A Houssiau ,[13] Luís Sousa Inês ,[14] David Jayne ,[15] Marios Kouloumas,[16] László Kovács,[17] Chi Chiu Mok ,[18] Eric F Morand ,[19] Gabriella Moroni,[20] Marta Mosca,[21] Johanna Mucke ,[22] Chetan B Mukhtyar ,[23] György Nagy ,[24,25,26] Sandra Navarra,[27] Ioannis Parodis ,[28,29,30] José M Pego-Reigosa,[31] Michelle Petri ,[32] Bernardo A Pons-Estel,[33] Matthias Schneider,[22] Josef S Smolen,[34] Elisabet Svenungsson ,[28,29] Yoshiya Tanaka ,[35] Maria G Tektonidou ,[36] YK Onno Teng ,[37] Angela Tincani ,[38] Edward M Vital ,[39] Ronald F van Vollenhoven ,[40] Chris Wincup ,[41] George Bertsias ,[42] Dimitrios T Boumpas [1,43,44]

	Level of agreement	
	Mean (SD)	% with score ≥8
Overarching principles		
A. SLE requires multidisciplinary, individualised management with patient education and shared decision-making, taking into consideration the costs to patient and society.	9.88 (0.40)	100
B. SLE disease activity should be assessed at each clinic visit (the frequency depending on physician's discretion), with evaluation of organ damage (at least annually), using validated instruments.	9.74 (0.63)	100
C. Non-pharmacological interventions, including sun protection, smoking cessation, healthy, balanced diet, regular exercise and measures to promote bone health are important to improve long-term outcomes	9.90 (0.37)	100
D. Pharmacological interventions are directed by patient characteristics, type and severity of organ involvement, treatment-related harms, comorbidities, risk for progressive organ damage, and patient preferences.	10 (0)	100
E. Early SLE diagnosis (including serological assessment), regular screening for organ involvement (especially nephritis), prompt initiation of treatment aiming at remission (or lovv disease activity if remission is not possible) and strict adherence to treatment are essential to prevent flares and organ damage, improve prognosis and enhance quality of life.	9.81 (0.51)	100
Recommendation/statement		
1. Hydroxychloroquine is recommended for all patients (**1b/A**), unless contraindicated, at a target dose of 5 mg/kg real body weight/day (**2b/B**) but individualised based on risk for flare (**2b/B**) and retinal toxicity.	9.21 (1.35)	90.4
2. Glucocorticoids, if needed, are dosed based on the type and severity of organ involvement (**2b/C**), and should be reduced to maintenance dose of ≤5 mg/day (prednisone equivalent) (**2a/B**) and, when possible, withdrawn; in patients with moderate-to-severe disease, pulses of intravenous methylprednisolone (125–1000 mg/day, for 1–3 days) (**3b/C**) can be considered.	9.57 (0.77)	97.6
3. In patients not responding to hydroxychloroquine (alone or in combination with glucocorticoids) or patients unable to reduce glucocorticoids below doses acceptable for chronic use, addition of immunomodulating/immunosuppressive agents (eg, methotrexate (**1b/B**), azathioprine (**2b/C**) or mycophenolate (**2a/B**)) and/or biological agents (eg, belimumab (**1a/A**) or anifrolumab (**1a/A**)) should be considered.	9.32 (0.91)	95.2
4. In patients with organ-threatening or life-threatening disease, intravenous cyclophosphamide (**2b/C**) should be considered; in refractory cases, rituximab (**2b/C**) may be considered.	9.38 (0.99)	95.2
5. Treatment of active skin disease should include topical agents (glucocorticoids, calcineurin inhibitors) (**2b/B**), antimalarials (hydroxychloroquine, chloroquine) (**1a/A**), and/or systemic glucocorticoids (**4/C**) as needed, with methotrexate (**1b/B**), mycophenolate (**4/C**), anifrolumab (**1a/A**), or belimumab (**1a/B**) considered as second-line therapy.	9.35 (1.06)	95.2
6. In active neuropsychiatric disease attributed to SLE, glucocorticoids and immunosuppressive agents for inflammatory manifestations (**1b/A**) and antiplatelet agents/anticoagulants for atherothrombotic/aPL-related manifestations (**2b/C**) should be considered.	9.68 (0.81)	97.6
7. For acute treatment of severe autoimmune thrombocytopenia, high-dose glucocorticoids (including pulses of intravenous methylprednisolone) (**4/C**), with or without intravenous immunoglobulin G (**4/C**), and/or rituximab (**2b/B**), and/or high-dose intravenous cyclophosphamide (**4/C**), followed by maintenance therapy with rituximab (**2b/B**), azathioprine (**2b/C**), mycophenolate (**2b/C**), or cyclosporine (**4/C**) should be considered.	9.48 (0.86)	97.6
8. Patients with active proliferative lupus nephritis should receive low-dose (EuroLupus) intravenous cyclophosphamide (**1a/A**) or mycophenolate (**1a/A**) and glucocorticoids (pulses of intravenous methylprednisolone followed by lower oral doses); combination therapy with belimumab (either with cyclophosphamide or mycophenolate (**1b/A**)) or calcineurin inhibitors (especially voclosporin or tacrolimus, combined with mycophenolate, **1b/A**) should be considered.	9.36 (1.06)	92.8
9. Following renal response, treatment of lupus nephritis should continue for at least 3 years (**2b/B**); patients initially treated with mycophenolate alone or in combination with belimumab or a calcineurin inhibitor should remain on these drugs (**1a/A**), whereas azathioprine or mycophenolate should replace cyclophosphamide for those initially treated with cyclophosphamide alone (**1a/A**) or in combination with belimumab (**1a/A**).	9.56 (0.81)	95.2
10. In patients at high-risk for renal failure (defined as reduced GFR, histological presence of cellular crescents or fibrinoid necrosis, or severe interstitial inflammation), high-dose (NIH regimen) intravenous cyclophosphamide (**1a/A**) in combination with pulse intravenous methylprednisolone, can be considered.	9.57 (0.86)	95.2
11. In patients with SLE achieving sustained remission, gradual tapering of treatment should be considered, with withdrawal of glucocorticoids first (**2a/B**).	9.89 (0.38)	100
12. SLE associated with thrombotic antiphospholipid syndrome (APS) should be managed with long-term vitamin K antagonists after the first arterial or unprovoked venous thrombotic event (**1b/B**); low dose aspirin (75–100 mg/day) should be considered in patients with SLE without APS but with high-risk aPL profile (**2a/B**).	9.57 (0.83)	97.6
13. Immunisations for the prevention of infections (herpes zoster virus, human papillomavirus, influenza, COVID-19 and pneumococcus), management of bone health, nephroprotection and cardiovascular risk, and screening for malignancies, should be performed (**5/D**).	9.85 (0.36)	100

Treatment of Non-Renal Systemic Lupus Erythematosus

General measures

Sun protection
Exercise
No smoking
Balanced diet
Vaccinations
Normal body weight
Blood pressure, lipid, glucose control

Acetylsalicylic acid, VKA
(in aPL+/APS)

Assess adherence to treatment

Mild*		Moderate*		Severe*	
1st line	2nd line	1st line	2nd line	1st line	2nd line

HCQ (all patients unless contraindicated)

GC PO/IV (if needed, short-term use to control active disease; taper to ≤5 mg/day as quickly as possible and discontinue, if possible)

MTX					
AZA					
MMF		MMF			
BEL†					
ANI †					
		CNI	CNI		
				CYC	
				RTX	RTX

Grade A — Grade B — Grade C — Grade D

Target

Remission
Clinical SLEDAI=0
HCQ
GC ≤ 5 mg/day

or

Low disease activity
SLEDAI ≤4
HCQ
GC ≤ 5 mg/day

Immunosuppressive or biological agents at stable, tolerated dose

Treatment of Lupus Nephritis

	Initial	Subsequent
Adjunct treatment for kidney protection# *ACEi/ARBs* *Consider SGLT2i (if decreased eGFR)* *VKA, heparin (if concomitant APS nephropathy)*	**HCQ (all patients unless contraindicated)**	
	GC PO/IV (consider pulse IV MP, then 0.3-0.5 mg/kg/day depending on severity; taper to ≤ 5 mg/day as quickly as possible)	
	MMF	
	Low-dose CYC	**AZA/MMF**
	MMF/low-dose CYC + BEL§	**MMF/AZA + BEL§**
	MMF + CNI (esp. VOC, TAC)^	**Any of the above–mentioned unless contraindicated^**
	High-dose CYC *,¶	
Assess adherence to treatment	**RTX †**	

Targets

3 months
≥25% reduction in UPr

6 months
≥50% reduction in UPr to <3 gr/day

12 to 24 months
UPr <0.5-0.7 gr/day

(all with eGFR within 10% from baseline)

Grade A — Grade B — Grade C — Grade D

LUPUS SCIENCE & MEDICINE™

2021 DORIS definition of remission in SLE: final recommendations from an international task force

Box 1 The 2021 DORIS definition of remission in SLE

- Clinical SLEDAI=0.
- Physician Global Assessment <0.5 (0–3).
  - Irrespective of serology.
  - The patient may be on antimalarials, low-dose glucocorticoids (prednisolone ≤5 mg/day), and/or stable immunosuppressives including biologics.

van Vollenhoven RF, *et al*. *Lupus Science & Medicine* 2021;**8**:e000538. doi:10.1136/lupus-2021-000538

ABSTRACT

Objective To achieve consensus on a definition of remission in SLE (DORIS).

Background Remission is the stated goal for both patient and caregiver, but consensus on a definition of remission has been lacking. Previously, an international task force consisting of patient representatives and medical specialists published a framework for such a definition, without reaching a final recommendation.

Methods Several systematic literature reviews were performed and specific research questions examined in suitably chosen data sets. The findings were discussed, reformulated as recommendations and voted on.

Results Based on data from the literature and several SLE-specific data sets, a set of recommendations was endorsed. Ultimately, the DORIS Task Force recommended a single definition of remission in SLE, based on clinical systemic lupus erythematosus disease activitiy index (SLEDAI)=0, Evaluator's Global Assessment <0.5 (0–3), prednisolone 5 mg/day or less, and stable antimalarials, immunosuppressives, and biologics.

Conclusion The 2021 DORIS definition of remission in SLE is recommended for use in clinical care, education, and research including clinical trials and observational studies.

Weaning of maintenance immunosuppressive therapy in lupus nephritis (WIN-Lupus): results of a multicentre randomised controlled trial

Noemie Jourde-Chiche ,[2,1] Nathalie Costedoat-Chalumeau ,[4,3] Karine Baumstarck,[5] Anderson Loundou,[5] Laurence Bouillet,[6] Stéphane Burtey,[1,2] Valérie Caudwell,[7] Laurent Chiche,[8] Lionel Couzi,[9] Laurent Daniel,[1,10] Christophe Deligny,[11] Bertrand Dussol,[2,12] Stanislas Faguer ,[13] Pierre Gobert,[14] Guillaume Gondran,[15] Antoine Huart,[13] Aurélie Hummel,[16] Emilie Kalbacher,[17] Adexandre Karras,[18,19] Marc Lambert,[20] Véronique Le Guern,[21] Ludivine Lebourg,[22] Sandrine Loubière,[23] Hélène Maillard-Lefebvre,[24] François Maurier,[25] Micheline Pha,[26] Viviane Queyrel,[27] Philippe Remy,[28] Françoise Sarrot-Reynauld,[29] David Verhelst,[14] Eric Hachulla ,[30] Zahir Amoura,[31] Eric Daugas ,[32,33] for the WIN-Lupus study group

Jourde-Chiche N, *et al*. *Ann Rheum Dis* 2022;**81**:1420–1427. doi:10.1136/annrheumdis-2022-222435

The WIN-Lupus trial tested whether IST discontinuation after 2–3 years was non-inferior to IST continuation for two more years in proliferative LN.

Methods

- multicentre RCT
- Patients receiving maintenance IST with azathioprine or mycophenolate mofetil for 2–3 years, and hydroxychloroquine, were randomised (1:1) into two groups: (1) IST continuation and (2) IST discontinuation.
- The primary endpoint was the relapse rate of proliferative LN at 24 months.
- Main secondary endpoints were the rate of severe SLE flares, survival without renal relapse or severe flare, adverse events.

Results

Between2011and2016, 96patients(outof200 planned) were randomised in WIN-Lupus: IST continuation group (n=48), IST discontinuation group (n=48).

Relapse of proliferative LN occurred in 5/40 (12.5%) patients with IST continuation and in 12/44 (27.3%) patients with IST discontinuation (difference 14.8% (95% CI −1.9 to 31.5)).

Non-inferiority was not demonstrated for relapse rate; time to relapse did not differ between the groups.

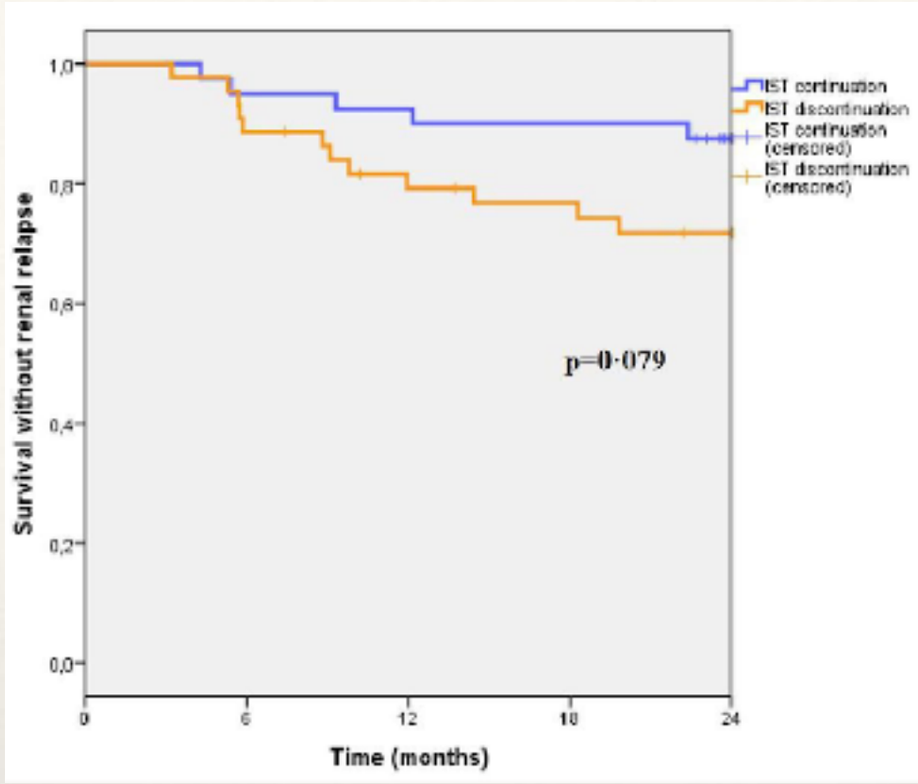
Severe SLE flares (renal or extrarenal) were less frequent in patients with IST continuation (5/40 vs 14/44 patients; p=0.035).

Adverse events did not differ between the groups.

Conclusions

Non-inferiority of maintenance IST discontinuation after 2–3 years was not demonstrated for renal relapse.

IST discontinuation was associated with a higher risk of severe SLE flares.



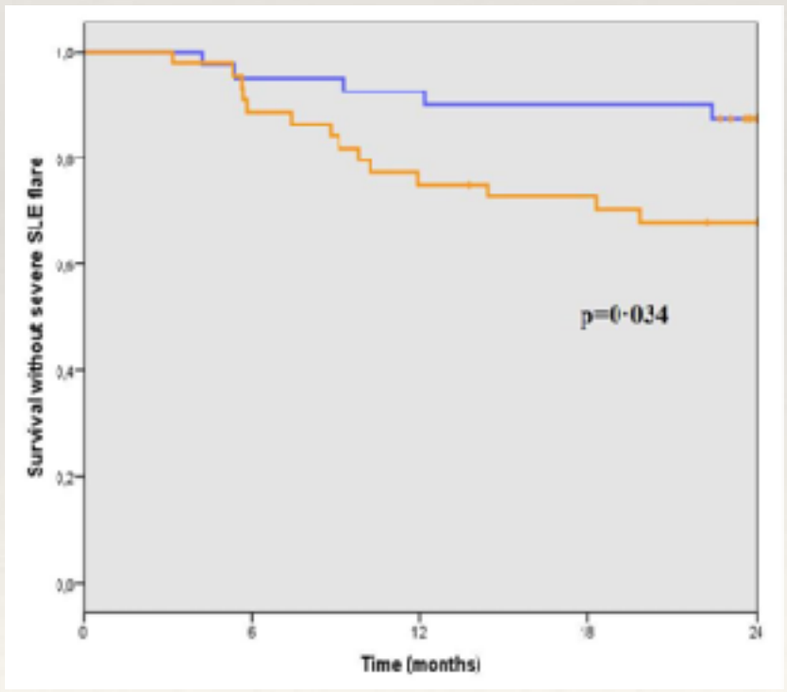


Table 2 Adverse events

	IST continuation (N=48)	IST discontinuation (N=48)	All patients (N=96)
Death	0	0	0
Renal adverse everts	14	18	32
Serum creatinine +20%	14	16	30
Serum creatinine +50%	0	2	2
End-stage kidney disease	0	0	0
Infections	19	14	33
Severe	1	3	4
Appendicitis	0	1	1
Malaria	0	1	1
Zoster	1	1	2
Other	18	11	29
Lower urinary tract	6	4	10
Upper respiratory tract	4	4	8
Ear, nose, and throat	2	1	3
Erysipelas	1	1	2
Dermatomycosis	2	0	2
Cervical human papillomavirus	2	1	3
Warts	1	0	1
Haematological	41	48	89
Myelodysplastic syndrome	1	0	1
Hypereosinophilia	1	0	1
Haematoma	0	1	1
Anaemia with Hb <10 g/dL	5	2	7
Anaemia with Hb <8 g/dL	1	0	1
Leucopenia <4 G/L	16	17	33
Leucopenia <3 G/L	0	4	4
Neutropenia <1.5 G/L	3	7	10
Neutropenia <1 G/L	0	1	1
Lymphopenia <1 G/L	12	16	28
Lymphopenia <0.5 G/L	1	0	1
Thrombopenia <100 G/L	1	0	1
Other	3	6	9
Cataract	1	1	2
Alopecia	0	2	2
Rash unrelated to SLE	1	0	1
New-onset hypertension	1	0	1
Obstructive sleep apnoea	0	1	1
Unexplained chest pain	0	1	1
Unexplained transient dyspnoea	0	1	1

	IST continuation (N=48)	IST discontinuation (N=48)	All patients (N=96)
Death	0	0	0
Renal adverse events	14	18	32
Serum creatinine +20%	14	16	30
Serum creatinine +50%	0	2	2
End-stage kidney disease	0	0	0
Haematological	41	48	89
Myelodysplastic syndrome	1	0	1
Hypereosinophilia	1	0	1
Haematoma	0	1	1
Anaemia with Hb <10 g/dL	5	2	7
Anaemia with Hb <8 g/dL	1	0	1
Leucopenia <4 G/L	16	17	33
Leucopenia <3 G/L	0	4	4
Neutropenia <1.5 G/L	3	7	10
Neutropenia <1 G/L	0	1	1
Lymphopenia <1 G/L	12	16	28
Lymphopenia <0.5 G/L	1	0	1
Thrombopenia <100 G/L	1	0	1

Proposed algorithm to discuss treatment de-escalation.

Lupus Nephritis Activity

1. Treatment ≥ 3 years — No
   ↓ YES
2. Stable kidney function — No
   ↓ YES
3. UPCR < 0,5-0,7 g/g (or chronic lesions only on biopsy) — No
   ↓ YES
4. Quiescent extra-renal SLE — No
   ↓ YES
5. No pregnancy planned soon
   ↓ YES

Previous LN relapse(s) ?

Risk factors for relapse? (C3, APS)

Repeat KB? (histological remission?)

Compliance to treatment — POOR

GOOD

Treatment-related adverse events
- Infection
- Malignancy

YES

THINK TO UNTREAT (T2U)
Treatment de-escalation

1. **Corticosteroids**
   - Weaning down to 0 mg/j
   - Low dose (2.5-7.5 mg/day) maintained if needed for extra-renal activity
2. **Mycophenolate / Azathioprine**
   - Progressive tapering after 3 years until weaning
3. **Hydroxychloroquine**
   - Maintained long-term, with monitoring of retinal toxicity

Proposed tapering

	MMF (mg/day)	AZA (mg/day)
D0	2000	150
M3	1500	100
M6	1000	75
M9	500	50
M12	0	0

Reference

- 2018 MRS SLE guideline
- 2019 EULAR/ACR classification criteria for SLE
- EULAR recommendations for the management of systemic lupus erythematosus: 2023 update
- Easy-BILAG: a new tool for simplified recording of SLE disease activity using BILAG-2004 index
- The SLE-DAS provides an accurate and feasible flare tool in the clinical setting: a validation study
- Weaning of maintenance immunosuppressive therapy in lupus nephritis (WIN-Lupus): results of a multicentre randomised controlled trial

“Type a quote here.”

–Johnny Appleseed