Επικαιροποίηση των οδηγιών για τη θεραπεία του ΣΕΛ

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Πανεπιστημιακό Γενικό Νοσοκομείο «Αττικόν»

Χανιά, 10/11/2018

Οδηγίες EULAR για τον ΣΕΛ

EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics

G Bertsias,[1] J P A Ioannidis,[2] J Boletis,[3] S Bombardieri,[4] R Cervera,[5] C Dostal,[6] J Font,[5] I M Gilboe,[7] F Houssiau,[8] T Huizinga,[9] D Isenberg,[10] C G M Kallenberg,[11] M Khamashta,[12] J C Piette,[13] M Schneider,[14] J Smolen,[15] G Sturfelt,[16] A Tincani,[17] R van Vollenhoven,[18] C Gordon,[19] D T Boumpas[1]

- **2008**: Το πρώτο σετ **γενικών οδηγιών**

European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies

M Mosca,[1] C Tani,[1] M Aringer,[2] S Bombardieri,[1] D Boumpas,[3] R Brey,[4] R Cervera,[5] A Doria,[6] D Jayne,[7] M A Khamashta,[8] A Kuhn,[9] C Gordon,[10] M Petri,[11] O P Rekvig,[12] M Schneider,[13] Y Sherer,[14] Y Shoenfeld,[15] J S Smolen,[16] R Talarico,[1] A Tincani,[17] R F van Vollenhoven,[18] M M Ward,[19] V P Werth,[20] L Carmona[21]

- **2010**: **Παρακολούθηση** ΣΕΛ στην κλινική πράξη

EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs

G K Bertsias,[1] J P A Ioannidis,[2] M Aringer,[3] E Bollen,[4] S Bombardieri,[5] I N Bruce,[6] R Cervera,[7] M Dalakas,[8] A Doria,[9] J G Hanly,[10] T W J Huizinga,[11] D Isenberg,[12] C Kallenberg,[13] J C Piette,[14] M Schneider,[15] N Scolding,[16] J Smolen,[17] A Stara,[18] I Tassiulas,[19] M Tektonidou,[20] A Tincani,[21] M A van Buchem,[22] R van Vollenhoven,[23] M Ward,[24] C Gordon,[25] D T Boumpas[1]

- **2010**: **Νευροψυχιατρικός ΣΕΛ**

EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome

L Andreoli,[1,2] G K Bertsias,[3] N Agmon-Levin,[4,5] S Brown,[6] R Cervera,[7] N Costedoat-Chalumeau,[8,9] A Doria,[10] R Fischer-Betz,[11] F Forger,[12] M F Moraes-Fontes,[13] M Khamashta,[14,15] J King,[16] A Lojacono,[1,17] F Marchiori,[18] P L Meroni,[19] M Mosca,[20] M Motta,[21] M Ostensen,[22] C Pamfil,[23] L Raio,[24] M Schneider,[11] E Svenungsson,[25] M Tektonidou,[26] S Yavuz,[27] D Boumpas,[28,29] A Tincani[1,2]

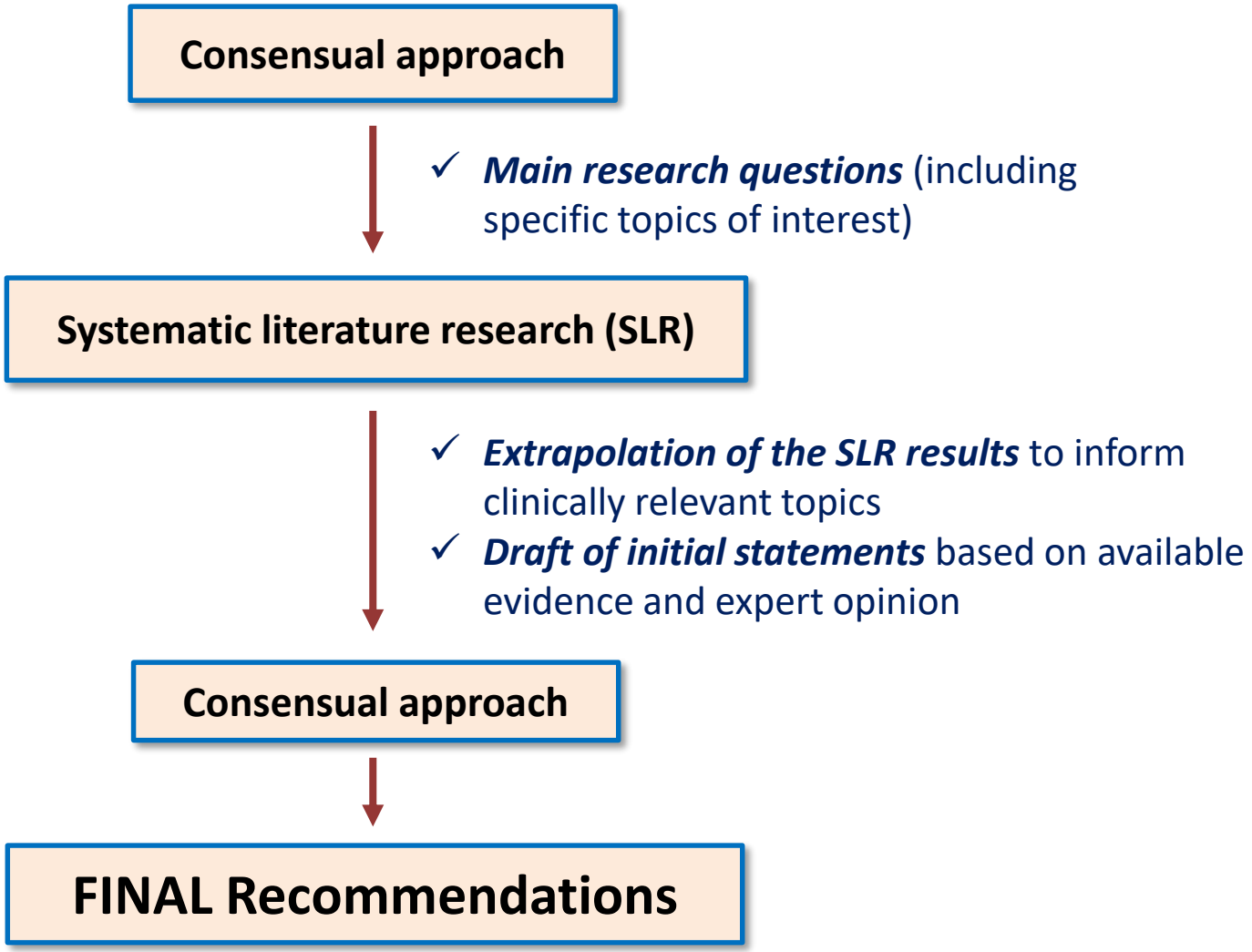
- **2012**: **Νεφρίτιδα ΣΕΛ**

Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis

George K Bertsias,[1] Maria Tektonidou,[2] Zahir Amoura,[3] Martin Aringer,[4] Ingeborg Bajema,[5] Jo H M Berden,[6] John Boletis,[7] Ricard Cervera,[8] Thomas Dörner,[9] Andrea Doria,[10] Franco Ferrario,[11] Jürgen Floege,[12] Frederic A Houssiau,[13] John P A Ioannidis,[14] David A Isenberg,[15] Cees G M Kallenberg,[16] Liz Lightstone,[17] Stephen D Marks,[18] Alberto Martini,[19] Gabriela Moroni,[20] Irmgard Neumann,[21] Manuel Praga,[22] Matthias Schneider,[23] Argyre Starra,[24] Vladimir Tesar,[25] Carlos Vasconcelos,[26] Ronald F van Vollenhoven,[27] Helena Zakharova,[28] Marion Haubitz,[29] Caroline Gordon,[30] David Jayne,[31] Dimitrios T Boumpas[1]

- **2017**: **Κύηση και γυναικεία υγεία στον ΣΕΛ**

EULAR standardized operating procedures



van der Heijde D, et al. *Ann Rheum Dis*. 2015; 74: 8-13

Questions for the literature review

What is the evidence for the benefits and harms of **glucocorticoids** in treating SLE?

What is the evidence for the benefits and harms of **hydroxychloroquine** in treating SLE?

What is the evidence for the benefits and harms of **immunosuppressive/cytotoxic** agents in treating SLE?

What is the evidence for the benefits and harms of **calcineurin inhibitors** in treating SLE?

What is the evidence for the benefits and harms of **biologics** in treating SLE?

How should **skin involvement** in SLE be treated?

How should **renal involvement** in SLE be treated?

How should **neuropsychiatric involvement** in SLE be treated?

Management of **antiphospholipid syndrome** in SLE

How should SLE **flares** be treated?

How often and by which means should **disease activity and damage** be assessed in SLE?

What are the optimal **treatment targets** in SLE?

What is the **optimal duration** of immunosuppressive/biologic treatment in SLE?

How should **comorbidities** be managed in SLE?

Level and grading of evidence

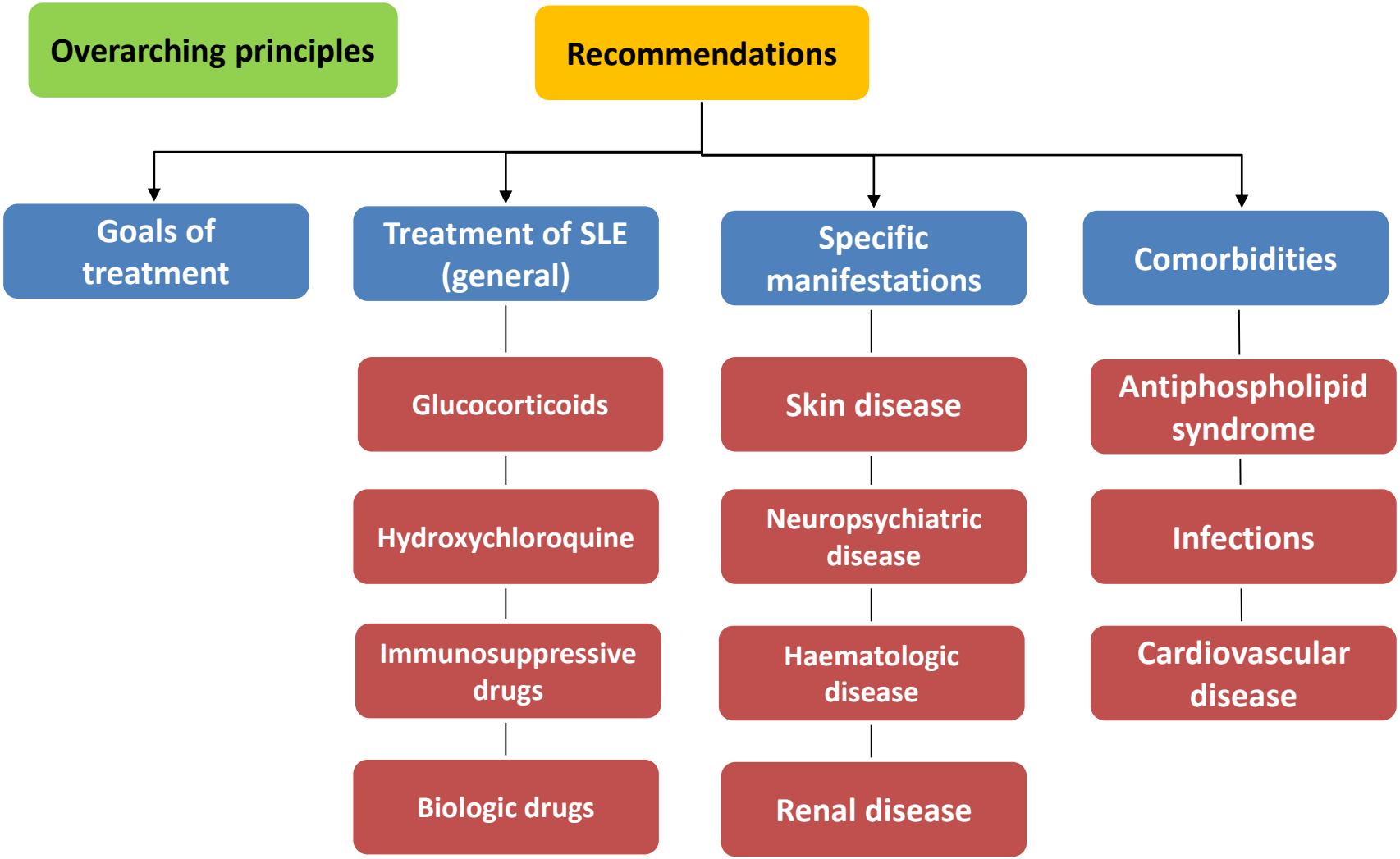
- **Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (LoE)**

LoE	Therapy/Prevention/Etiology/Harm	Risk factors/Prognosis
1a	Systematic reviews of RCTs	Systematic review of inception cohort studies
1b	Individual, high-quality RCT	Individual inception cohort study (high quality)
2a	Systematic reviews of cohort studies	Systematic review of retrospective cohort studies or data from RCTs
2b	Cohort study or low quality RCT	Retrospective cohort study or data from RCT
2c	"Outcomes" research studies	"Outcomes" research studies
3a	Systematic review of case-control studies	
3b	Case-control studies	
4	Case-series (and poor quality cohort and case-control studies)	Case-series (and poor quality prognostic cohort studies)
5	Expert opinion	Expert opinion

- **Grading of recommendations, assessment, development, and evaluations (GRADE)**

A	Consistent level 1 studies
B	Consistent level 2 or 3 studies; or extrapolations from level 1 studies
C	Level 4 studies; or extrapolations from level 2 or 3 studies
D	Level 5 evidence; or very inconsistent or inconclusive studies of any level

Structure of recommendations



Overarching principles

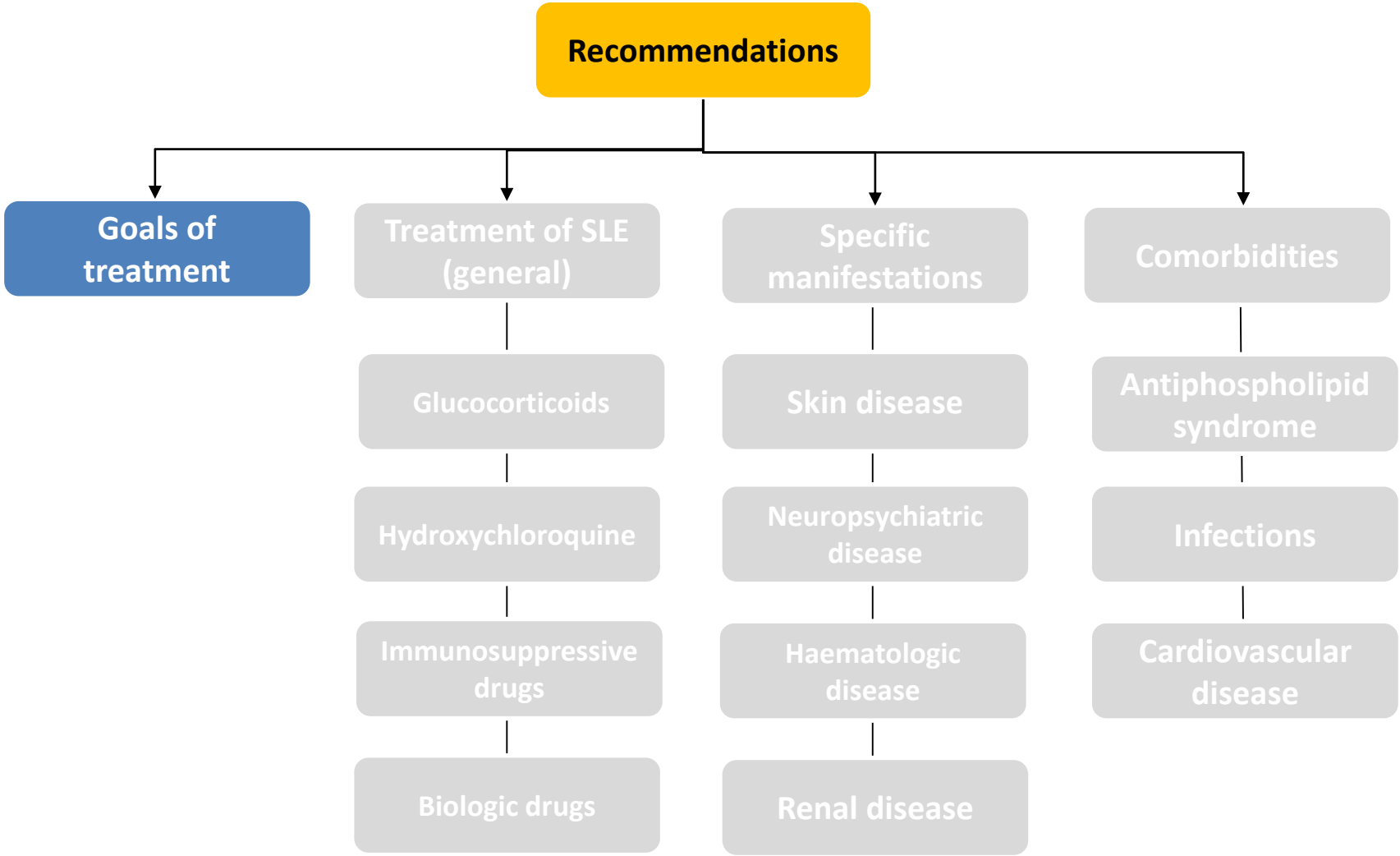
- SLE is a multisystem disease - occasionally limited to one or few organs - diagnosed on clinical grounds in the presence of characteristic serologic abnormalities.

- SLE care is multidisciplinary, based on a shared patient-physician decision, and should consider individual, medical and societal costs.

- Treatment of organ-/life-threatening SLE includes an initial period of high-intensity immunosuppressive therapy to control disease activity, followed by a longer period of less intensive therapy to consolidate response and prevent relapses.

- Treatment goals include long-term patient survival, prevention of organ damage and optimization of health-related quality of life.

Structure of recommendations

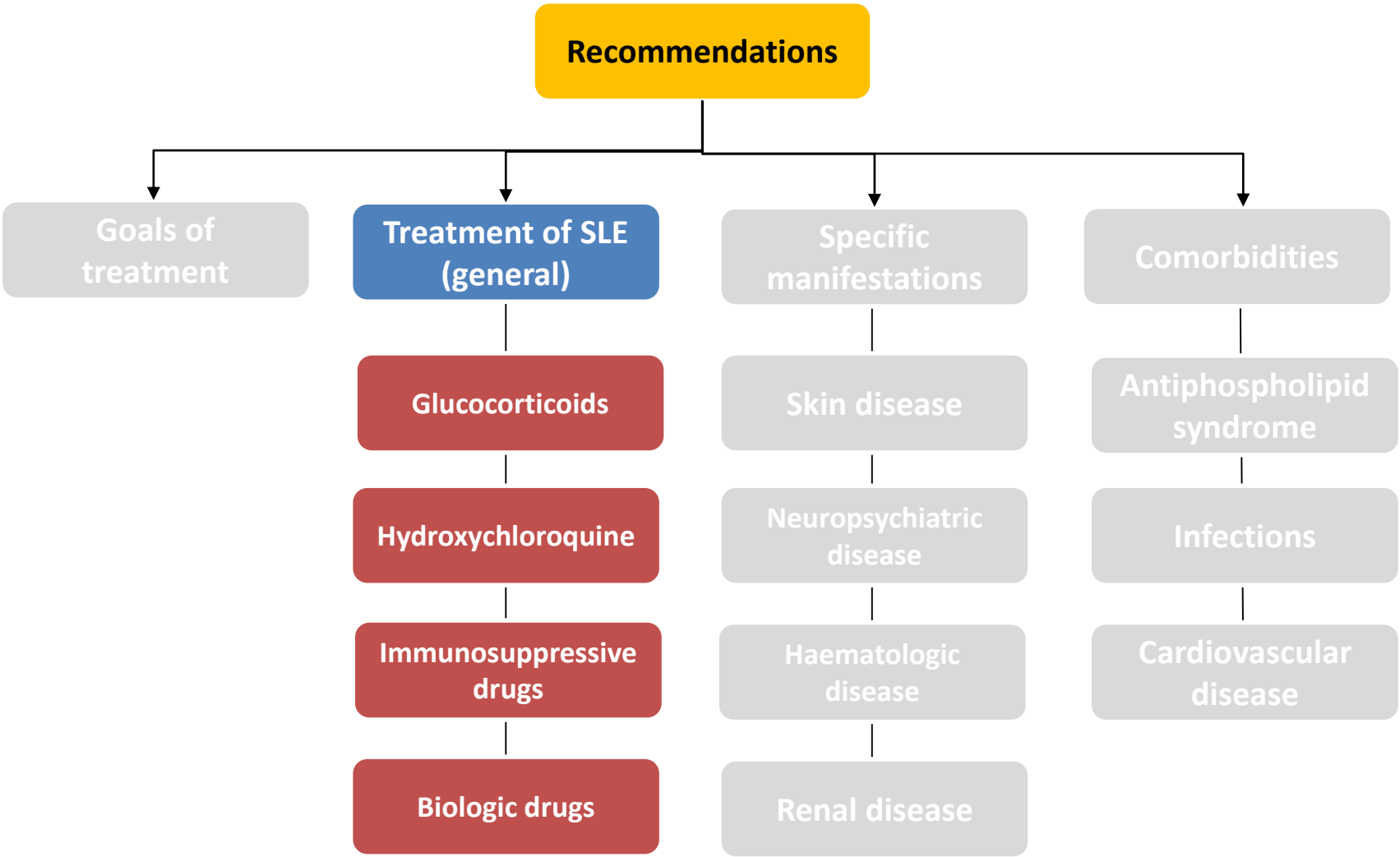


LoE	GoR
1a 1b	A
2a 2b 2c	B
3a 3b	C
4 5	D

1. Goals of treatment

Recommendation	LoE	GoR
1.1 Treatment in SLE should aim at remission or the lowest possible level of disease activity and prevention of flares in all organs, maintained with the lowest possible dose of glucocorticoids.	**2b**	**B**
1.2 Flares of SLE can be treated according to the severity of organ(s) involvement by adjusting ongoing therapies (glucocorticoids, immunomodulating agents) to higher doses, switching, or adding new therapies.	**2b**	**C**

Structure of recommendations



2. Treatment of SLE (general)

2.1 Glucocorticoids

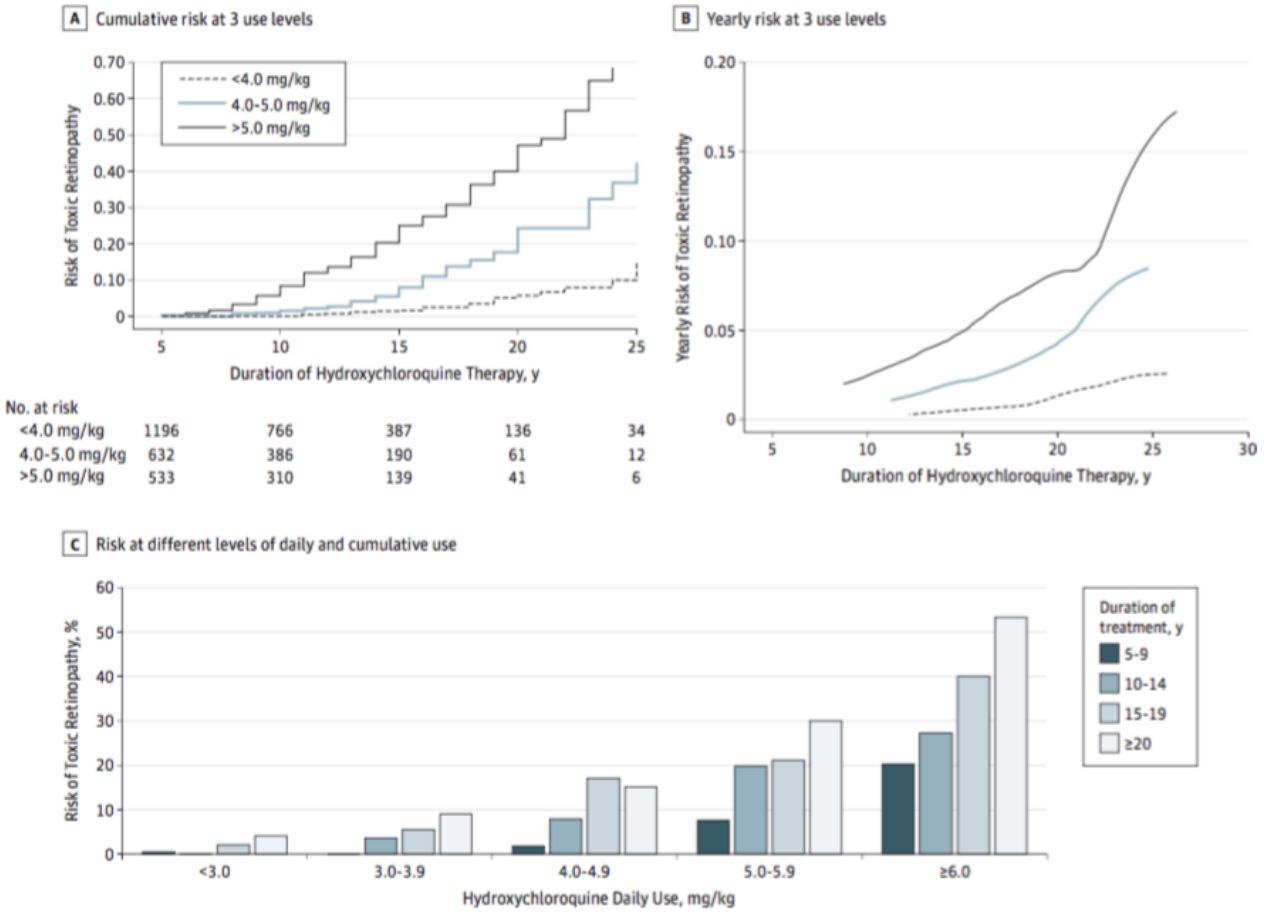
Recommendation	LoE	GoR
2.1.1 Glucocorticoids can be used at doses and route of administration that depend on the type and severity of organ involvement.	**2b**	**C**
2.1.2 Pulses of intravenous methylprednisolone (usually 500–1000 mg per day, for 1–3 days) provide immediate therapeutic effect and enable the use of lower starting dose of oral glucocorticoids.	**3b**	**C**
2.1.3 For chronic maintenance treatment, glucocorticoids should be minimized to less than 7.5 mg/day (prednisone equivalent) and, if possible, withdrawn.	**1b**	**B**
2.1.4 Prompt initiation of immunomodulatory agents can expedite the tapering/discontinuation of glucocorticoids.	**2b**	**B**

2. Treatment of SLE (general)

2.2 Hydroxychloroquine

Recommendation	LoE	GoR
2.2.1 HCQ is recommended for all patients with SLE, at a **dose not exceeding 5 mg/kg/real BW**.	**1b**	**A**
	3b	**C**
2.2.2 In the absence of risk factors for retinal toxicity, ophthalmologic screening (by visual fields examination and/or spectral domain-optical coherence tomography) should be performed at baseline, after 5 years, and yearly thereafter.	**2b**	**B**

Daily dose and duration of use most important for HCQ toxicity



1) > 5 mg/Kg: **OR 5.67**

2) > 10 years: **OR 3.22**

Note: "Bull's eye" on funduscopic examination is too late (advanced toxicity)! – Fundus examination no longer recommended as screening test

An older study using funduscopy (3995 RA+SLE pts) found retinal toxicity only in 0.65%

- Pts with CKD at increased risk: **OR 2.1 – 8.6** (2 studies)

2. Treatment of SLE (general)

2.3 Immunosuppressive therapies

Recommendation	LoE	GoR
2.3.1 In patients not responding to HCQ (alone or in combination with glucocorticoids) or patients unable to reduce glucocorticoids below doses acceptable for chronic use, addition of immunomodulating/immunosuppressive agents such as		
methotrexate	**1b**	**B**
azathioprine	**2b**	**B**
or **mycophenolate** should be considered.	**2a**	**B**
2.3.2 Immunomodulating/immunosuppressive agents can be included in the initial therapy in cases of organ-threatening disease.	**2b**	**C**
2.3.3 **Cyclophosphamide** can be used for severe organ- or life-threatening SLE as well as “rescue” therapy in patients not responding to other immunosuppressive agents.	**2b**	**C**

2. Treatment of SLE (general)

2.4 Biologics

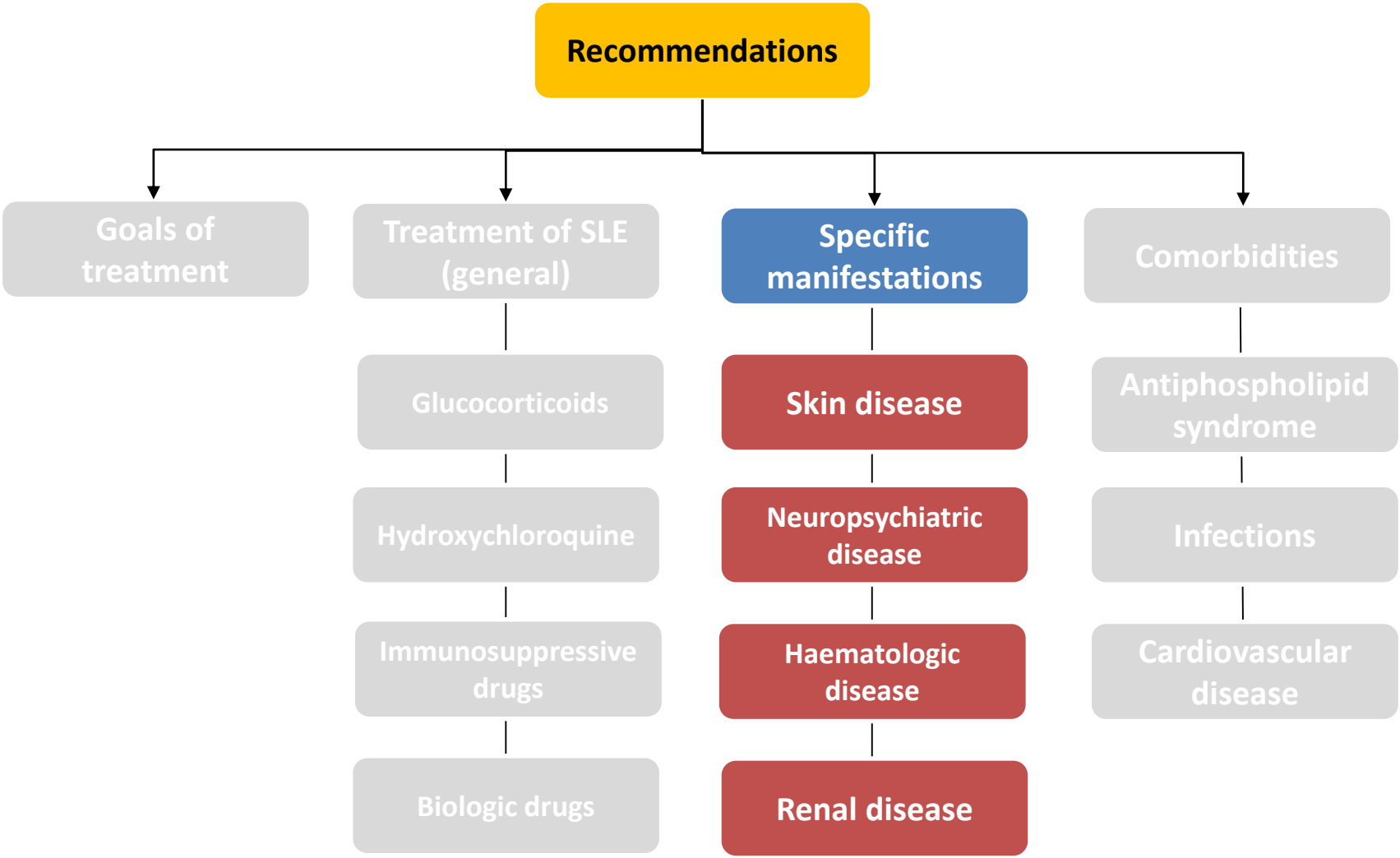
Recommendation	LoE	GoR
2.4.1 In patients with inadequate response to standard-of-care (combinations of hydroxychloroquine, glucocorticoids, other immunomodulating agents), defined as residual disease activity not allowing tapering of glucocorticoids and/or frequent relapses, add-on treatment with **belimumab** should be considered.	**1a**	**A**
2.4.2 In organ-threatening disease refractory or with intolerance/contra-indications to standard immunosuppressive agents, **rituximab** can be considered.	**2b**	**C**

2. Treatment of SLE (general)

Drugs	Mild		Moderate		Severe		Target
	1st line	Refractory	1st line	Refractory	1st line	Refractory	
Hydroxychloroquine							**Remission** (SLEDAI = 0, no GC) *or* **Low disease activity** (SLEDAI ≤ 3-4, Pre ≤ 7.5 mg/d, stable IS doses)
Glucocorticoids	PO/IM	PO/IM	PO/IM	PO/IM	PO/IM	PO/IM	
Methotrexate							
Azathioprine							
Mycophenolate							
Cyclosporine A							
Cyclophosphamide							
Belimumab							
Rituximab							

Grade A
Grade B
Grade C
Grade D

Structure of recommendations

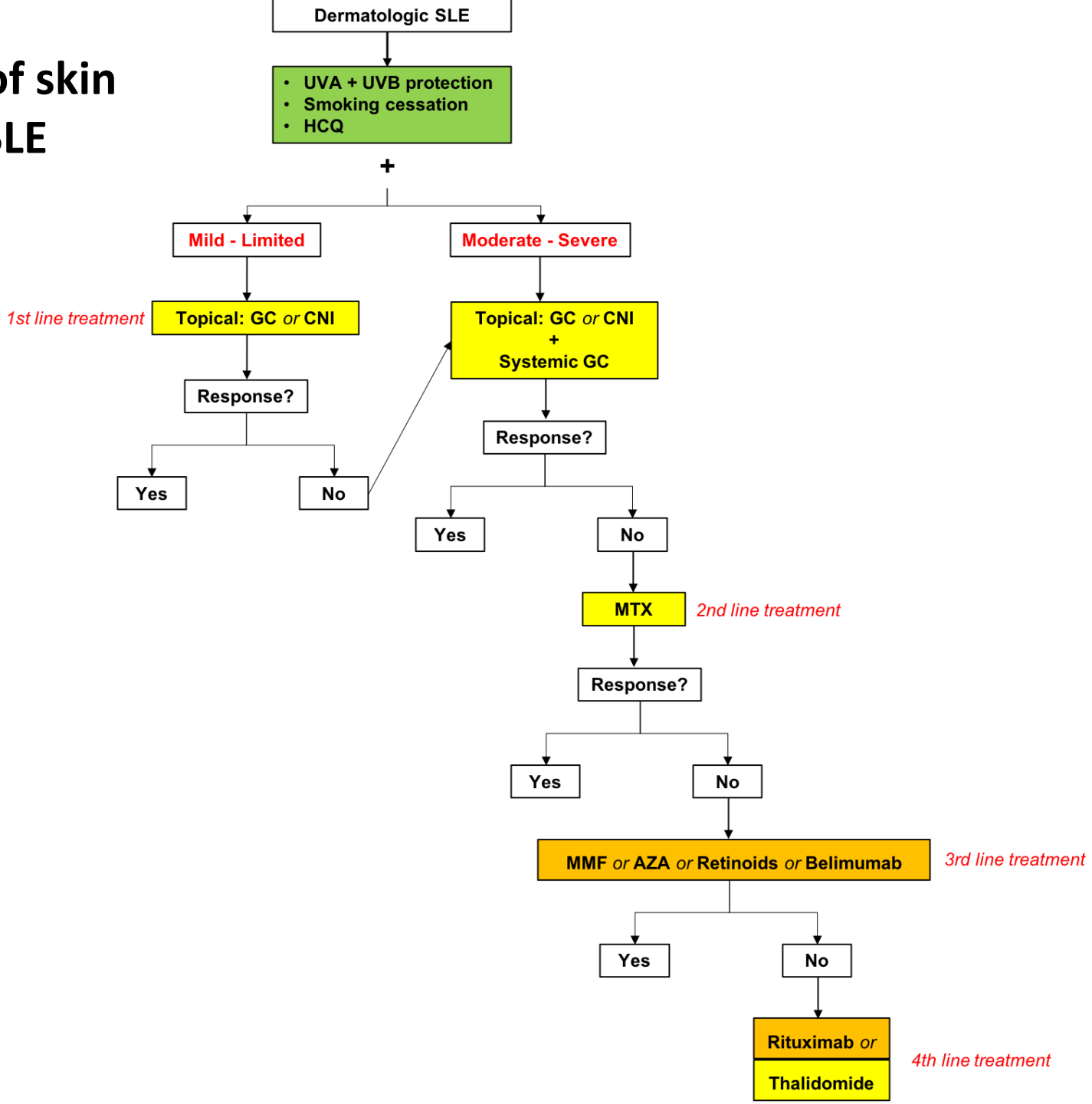


3. Specific manifestations

3.1 Skin disease

Recommendation	LoE	GoR
3.1.1 First-line treatment of skin disease in SLE includes		
topical agents (glucocorticoids, calcineurin inhibitors)	**2b**	**B**
antimalarials (HCQ, quinacrine)	**1a**	**A**
systemic glucocorticoids.	**4**	**C**
3.1.2 In non-responsive cases or cases requiring high-dose glucocorticoids,		
methotrexate,	**3a**	**B**
mycophenolate,	**4**	**C**
or **azathioprine** can be added.	**4**	**C**

Management of skin disease in SLE

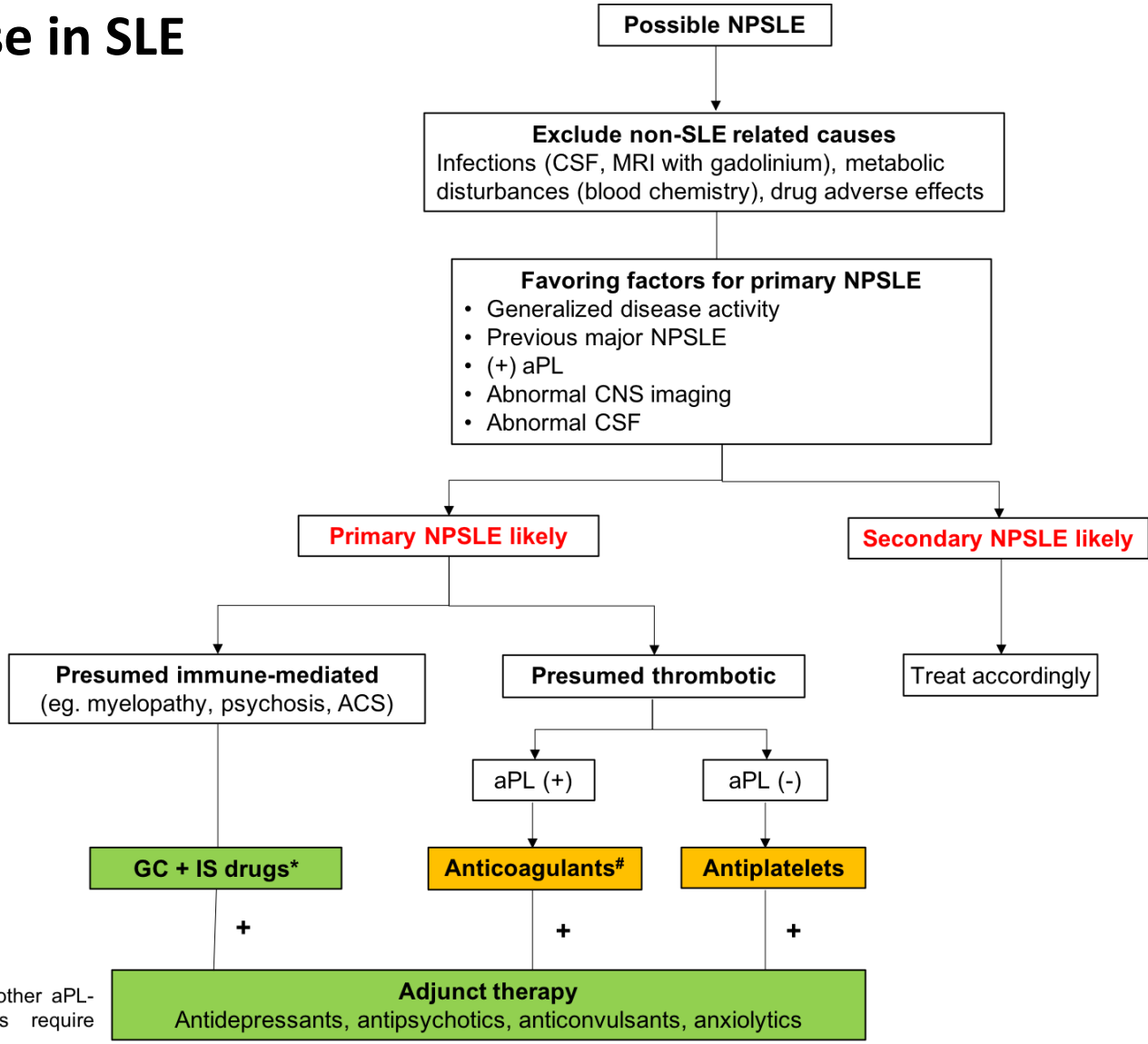


3. Specific manifestations

3.2 Neuropsychiatric disease

Recommendation	LoE	GoR
3.2.1 Attribution to SLE - as opposed to non-SLE - related neuropsychiatric manifestations, can be facilitated by neuroimaging, investigation of cerebrospinal fluid, consideration of risk factors [type and timing of the manifestation in relation to the onset of lupus, patient age, non-neurological lupus activity, presence of antiphospholipid antibodies (aPL)] and exclusion of confounding factors.	**2b**	**C**
3.2.2 Treatment of SLE-related neuropsychiatric disease includes **glucocorticoids/immunosuppressive agents** for manifestations considered to reflect an inflammatory process	**1b**	**A**
and **antiplatelet/anticoagulants** for atherothrombotic/aPL-related manifestations.	**2b**	**C**

Management of neuropsychiatric disease in SLE



* Preferred agents: **AZA** (for mild cases), **CYC, RTX**

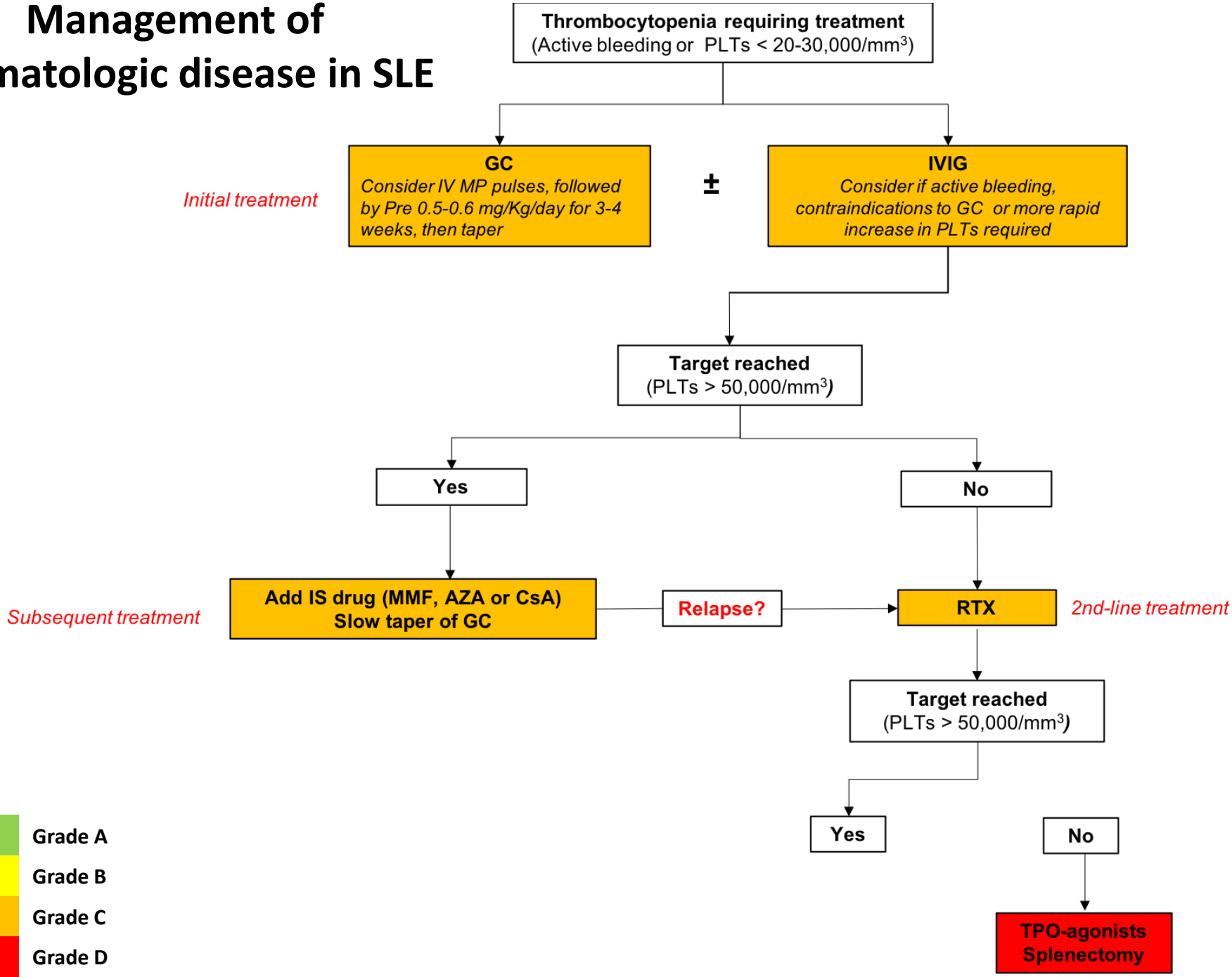
Anticoagulants are indicated mainly for aPL-related stroke; other aPL-associated manifestations, like chorea, may not always require anticoagulant therapy

3. Specific manifestations

3.3 Haematologic disease

Recommendation	LoE	GoR
3.3.1 **Acute treatment** of lupus thrombocytopenia includes high-dose glucocorticoids (including pulses of intravenous methylprednisolone) and/or intravenous immunoglobulin.	4	C
3.3.2 For maintenance of response, IS/GC-sparing agents such as **mycophenolate**, **azathioprine**,	2b	C
or **cyclosporine** can be used.	4	C
3.3.3 Refractory cases can be treated with **rituximab**	3a	C
or **cyclophosphamide**.	4	C

Management of haematologic disease in SLE



3. Specific manifestations

3.4 Renal disease

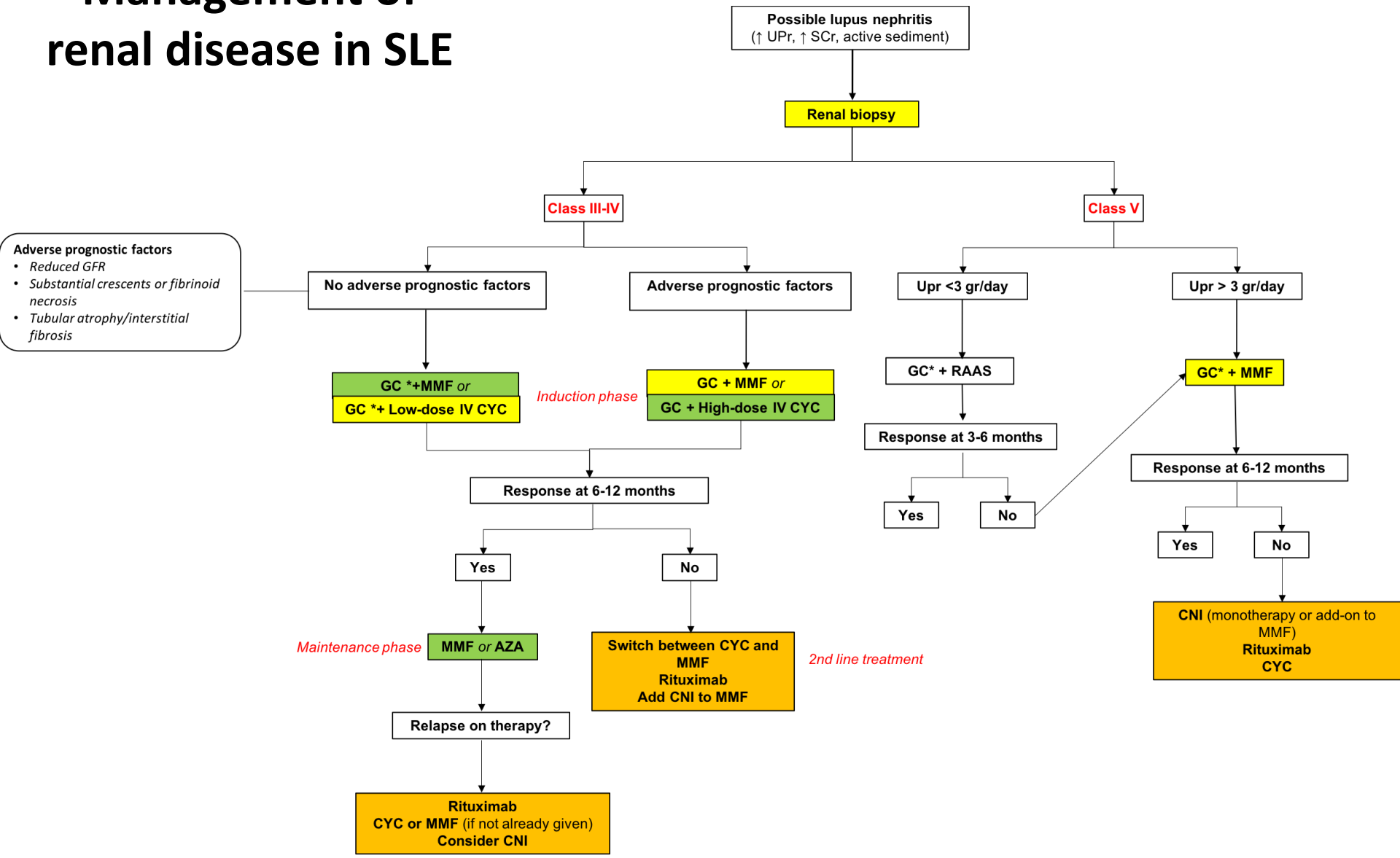
Recommendation	LoE	GoR
3.4.1 Early recognition of signs of renal involvement and - when present - performance of a diagnostic renal biopsy are essential to ensure optimal outcomes.	**2b**	**B**
3.4.2 Mycophenolate	**1a**	**A**
or **low-dose IV cyclophosphamide** are recommended as initial (induction) treatment, as they have the best efficacy/toxicity ratio.	**2a**	**B**
3.4.3 In patients at high risk for renal failure (reduced glomerular filtration rate, histologic presence of crescents or fibrinoid necrosis, or tubular atrophy/interstitial fibrosis], **mycophenolate**	**2b**	**B**
or **high-dose IV cyclophosphamide** can be used.	**1b**	**A**
3.4.4 For maintenance therapy, **mycophenolate** or **azathioprine** should be used.	**1a**	**A**

3. Specific manifestations

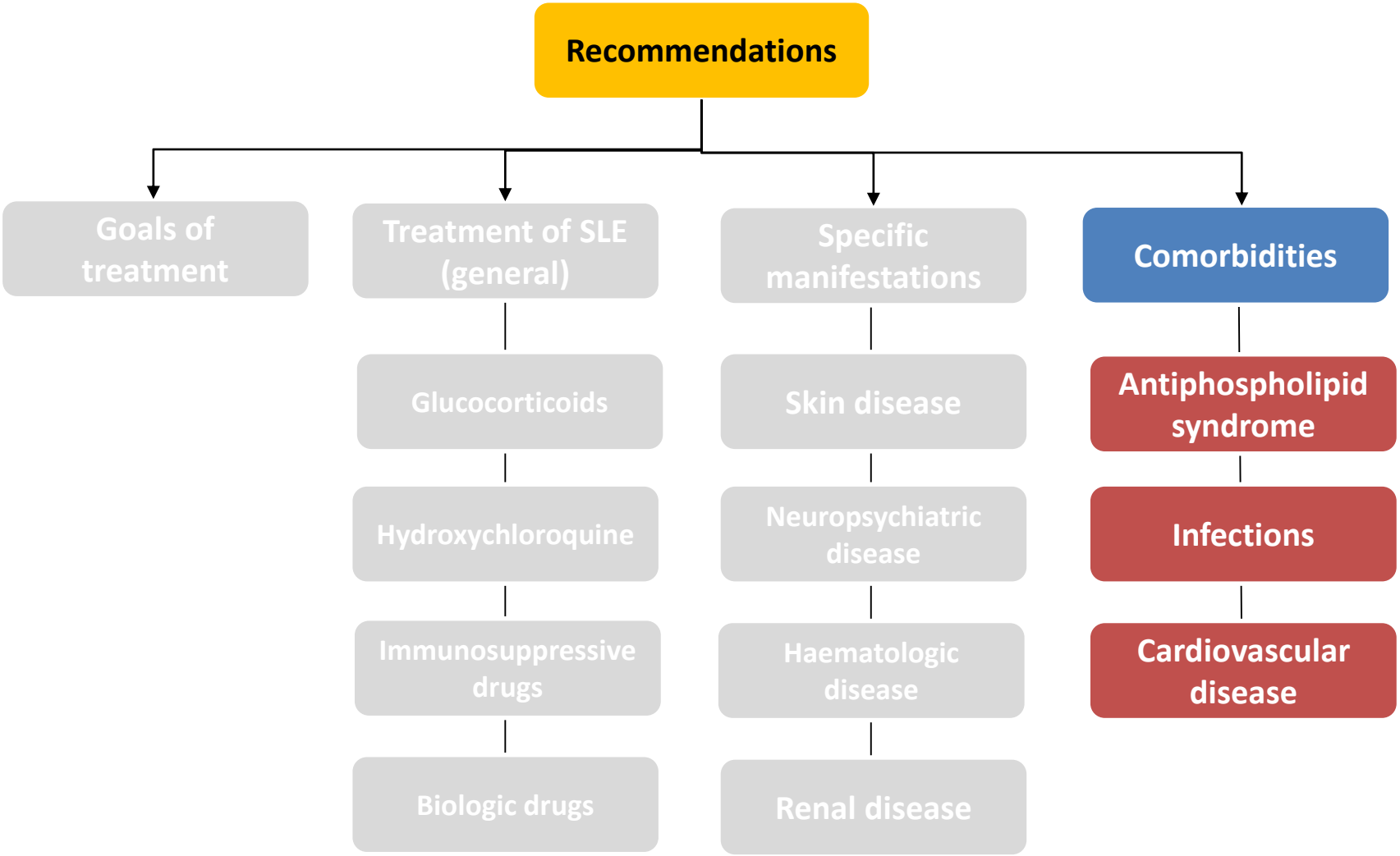
3.4 Renal disease

Recommendation	LoE	GoR
3.4.5 In cases with stable/improved renal function but **incomplete renal response** (persistent proteinuria >1 g/24h after at least one year of immunosuppressive treatment), **repeat biopsy** can distinguish chronic from active kidney lesions.	4	C
3.4.6 Mycophenolate may be combined with low dose of a **calcineurin inhibitor** in *severe nephrotic syndrome*	2b	C
or *incomplete renal response*,	4	C
in the absence of uncontrolled hypertension, high chronicity index at kidney biopsy, and/or reduced GFR.		

Management of renal disease in SLE



Structure of recommendations



4. Comorbidities

4.1 Antiphospholipid antibodies and antiphospholipid syndrome

Recommendation	LoE	GoR
4.1.1 All SLE patients **should be screened** at diagnosis for aPL.	**1a**	**A**
4.1.2 SLE patients with **high-risk aPL profile** (persistently positive medium/high titres or multiple positivity) may receive primary prophylaxis with **antiplatelet agents**, especially if other atherosclerotic/thrombophilic factors are present, after balancing the bleeding hazard.	**2a**	**C**
4.1.3 For secondary prevention (thrombosis, pregnancy complication/loss), the therapeutic approach should be the same as for primary anti-phospholipid syndrome.	**1b**	**B**

4. Comorbidities

4.2 Infectious diseases

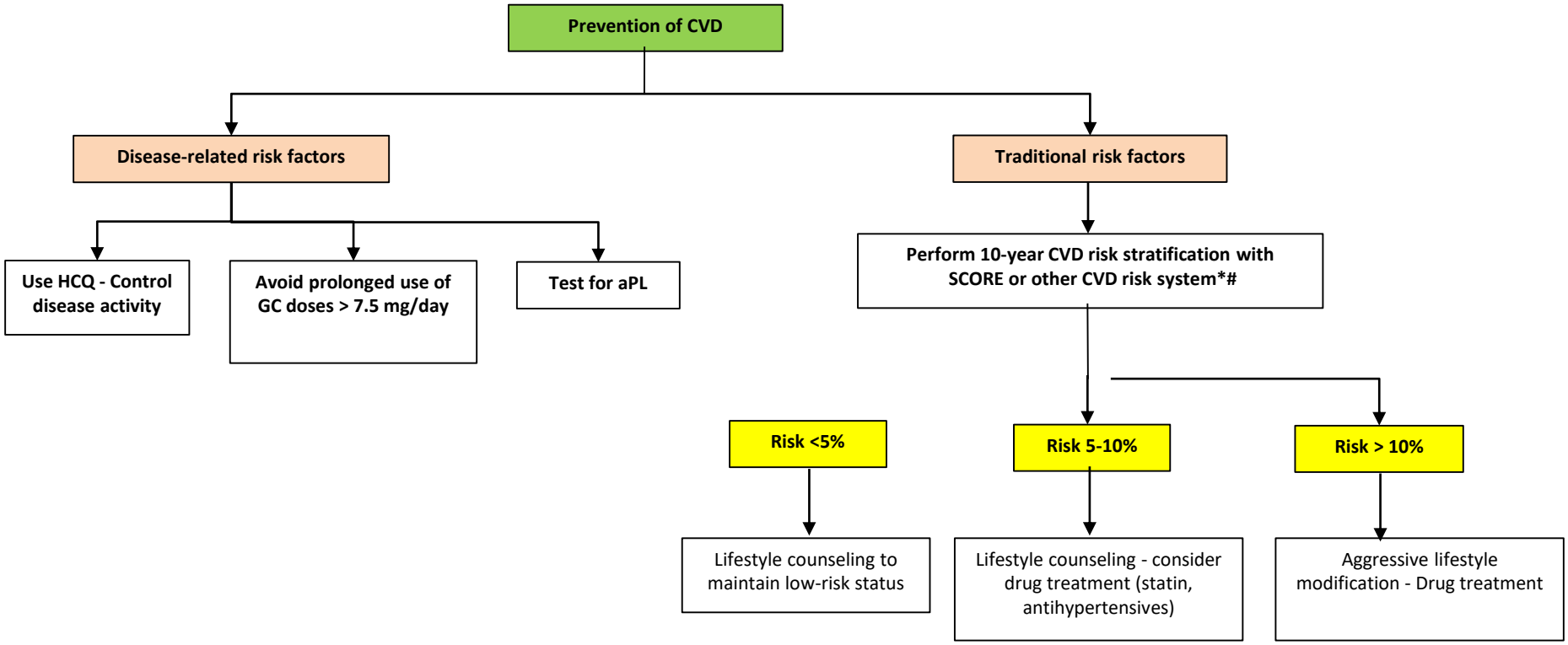
Recommendation	LoE	GoR
4.2.1 SLE patients should be assessed for **general and disease-related risk factors** for infections such advanced age/frailty (**–/D**), comorbidities (**–/D**), renal involvement (**2b/B**), immunosuppressive/biologic therapy (**1b-2b/B-C**) and high-dose glucocorticoids (**1a/A**).		
4.2.2 General preventative measures (including immunizations) and early recognition and treatment of infection/sepsis are recommended (**–/D)**.	**-**	**D**

4. Comorbidities

4.3 Cardiovascular disease

Recommendation	LoE	GoR
4.3.1 Patients with SLE should undergo regular assessment for **traditional (1b/B-C)** and **disease-related risk factors** for cardiovascular disease, including persistently active disease **(1b/B)**, increased disease duration **(1b/A)**, medium/high titres of aPL **(1b/A)**, renal involvement **(1b/B)** (especially, persistent proteinuria and/or GFR <60 ml/min) and chronic use of glucocorticoids **(1b/B)**.		
4.3.2 Based on their individual cardiovascular risk profile, SLE patients may be candidates for prevention with **low-dose aspirin**	**2b**	**D**
and/or **lipid-lowering agents**.	**2b**	**D**

Primary prevention of cardiovascular disease in SLE



* Systematic Coronary Risk Evaluation (SCORE): https://www.escardio.org/Education/Practice-Tools/CVD-prevention-toolbox/SCORE-Risk-Charts

Because many lupus patients are young women, calculation of relative risk (or "risk age") is preferred over absolute risk

Βασικά σημεία – Αλλαγές σε σχέση με παλαιότερες οδηγίες

- HCQ: Όχι πάνω από 5 mg/Kg – Όχι monitoring μόνο με βυθοσκόπηση!
- Κορτικοειδή: Σκεφτείτε ώσεις μεθυλπρεδνιζολόνης, αντί να δώσετε PO 1 mg/Kg ως αρχική δόση
- Belimumab: Ανθεκτικός, μετρίως σοβαρός,, εξωνεφρικός ΣΕΛ
- Rituximab: Ανθεκτικός, σοβαρός ΣΕΛ (νεφρικός/εξωνεφρικός)
- Organ-specific recommendations
- CNIs και νεφρίτιδα: Όχι ακόμη ως 1^{η} γραμμής θεραπεία σε υπερπλαστική νεφρίτιδα

Ευχαριστίες

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