Diagnosis and Management Challenges in SLE

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Definition

An autoimmune disease in which organs and cells undergo damage initially mediated by tissue binding autoABs and immune complexes.

- Chronic
- Variable phenotype and clinical manifestations
- Unpredictable flare

Prevalence

81-144per100000 in USA(highest in African-American)

F/M:5-15/1

Worldwide trend is increasing of both prevalence and incidence

Age: women in child bearing ages, but can develop at any age.

Later start in Men

PREDISPOSING FACTORS

GENES

High hazard ratios (≥6);

Deficiencies of C1q,C2,C4 (rare)
TREX1 mutations affecting DNA degradation (rare)

Affecting Ag presentation or persistence, e.g., phagocytosis of immune complexes

*HLA-DRB1 (*1501,*0301), DR3, DQA2*
CR2, FCGR2A/B

Enhance innate immunity, including production of IFNs

TNFAIP3, IRF5/TNPO3, IRF7/PHRF1, ITGAM, ICAMs

Alter adaptive immunity B and/or T cell signaling

BANK1, STAT4, MSHS, IZKF3, TCF7

GENES FOR LUPUS NEPHRITIS

HLA-DR3, STAT4, APOL1 (African Americans), *FCGR3A, ITGAM, IRF5, IRF7, TNFSF4 (Ox40L), DNAse1*

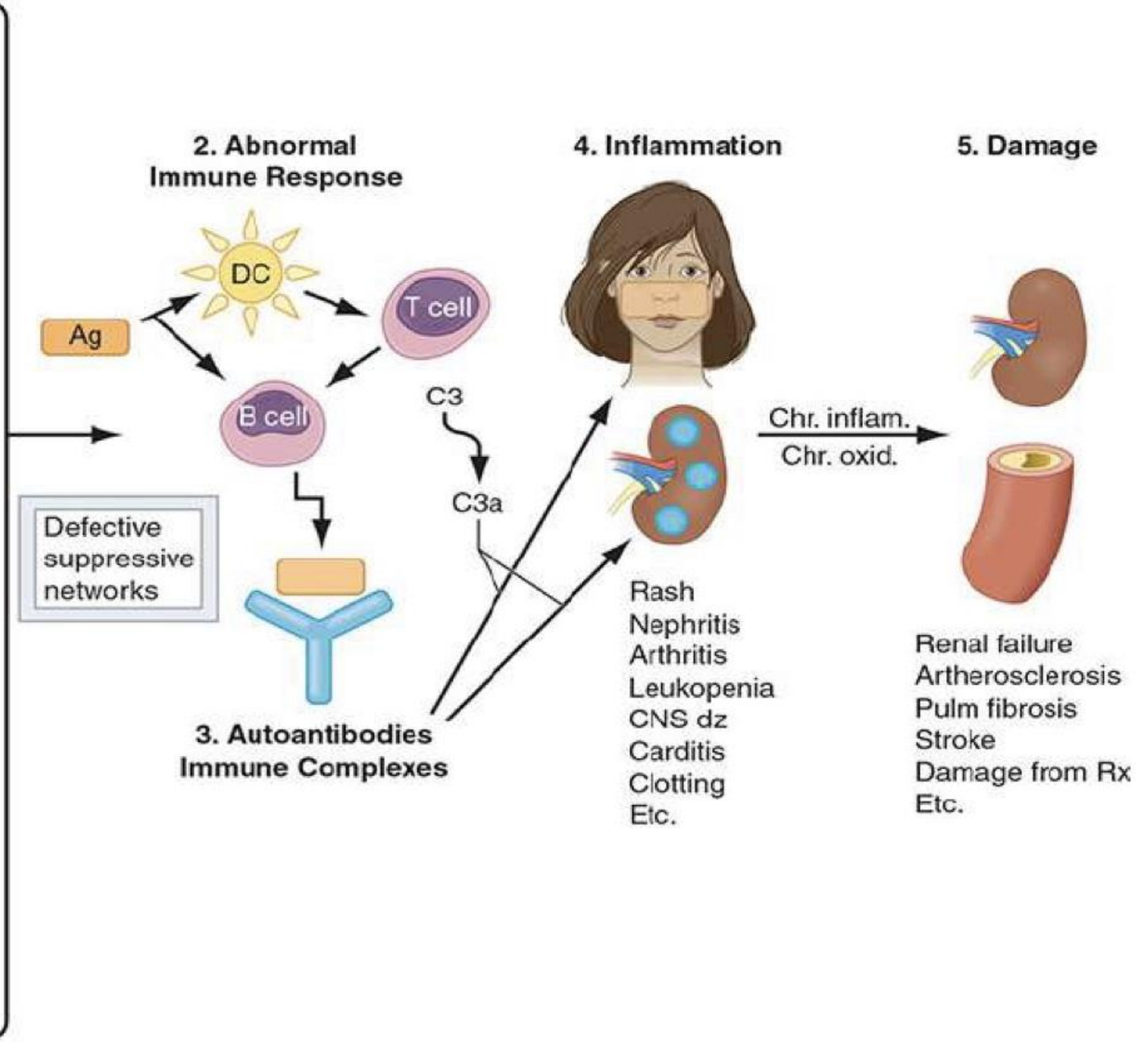
ENVIRONMENT/MICROENVIRONMENT

Ultraviolet light, smoking, crystalline silica, ?EBV infection, femaleness

EPIGENETICS

Hypomethylation of DNA: In CD4+T, B and monocytes
Some affect IFN production
Histone modifications: Some increase expression of predisposing genes and/or IFN production
MicroRNA affecting gene expression

Mir-21, -146A, -155, -569, -30A, Let-7a



MANIFESTATION	PREVALENCE, %
Systemic: Fatigue, malaise, fever, anorexia, weight loss	95
Musculoskeletal	95
Arthralgias/myalgias	95
Polyarthritis	60
Hand deformities	10
Myopathy/myositis	25/5
Ischemic necrosis of bone	15
Cutaneous	80
Photosensitivity	70
Malar rash	50
Oral ulcers	40
Alopecia	40
Discoid rash	20
Vasculitis rash	20
Other (e.g., urticaria, subacute cutaneous lupus)	15
Hematologic	85
Anemia (chronic disease)	70
Leukopenia (<4000/μL)	65
Lymphopenia (<1500/μL)	50
Thrombocytopenia (<100,000/μL)	15
Lymphadenopathy	15
Splenomegaly	15
Hemolytic anemia	10
Neurologic	60
Cognitive disorder	50
Mood disorder	40
Depression	25
Headache	25
Seizures	20
Mono-, polyneuropathy	15
Stroke, TIA	10
Acute confusional state or movement disorder	2–5
Aseptic meningitis, myelopathy	<1
Cardiopulmonary	60
Pleurisy, pericarditis, effusions	30–50

Myocarditis, endocarditis	10
Lupus pneumonitis	10
Coronary artery disease	10
Interstitial fibrosis	5
Pulmonary hypertension, ARDS, hemorrhage	<5
Shrinking lung syndrome	<5
Renal	30–50
Proteinuria ≥500 mg/24 h, cellular casts	30–60
Nephrotic syndrome	25
End-stage renal disease	5–10
Gastrointestinal	40
Nonspecific (nausea, mild pain, diarrhea)	30
Abnormal liver enzymes	40
Vasculitis	5
Thrombosis	15
Venous	10
Arterial	5
Ocular	15
Sicca syndrome	15
Conjunctivitis, episcleritis	10
Vasculitis	5

TABLE 356-4 2019 EULAR/ACR Classification Criteria for Systemic Lupus Erythematosus (SLE)

Positive ANA (titer at least 1:80) is obligatory entry criterion, followed by additive weighted criteria in 7 clinical and 3 immunologic domains. Accumulating ≥ 10 points classifies as SLE.

All manifestations must be attributable to SLE.

	CLINICAL CRITERIA		
DOMAIN	**CRITERIA**	**% OF PATIENTS WITH FEATURE[a]**	**WEIGHT**
Constitutional, 80%	Fever	50	2
Hematologic, 50%	Leukopenia	30	3
	Thrombocytopenia	20	4
	Autoimmune hemolytic anemia	10	4
Neuropsychiatric, 75%	Delirium	5	2
	Psychosis	7	3
	Seizure	11	5
Mucocutaneous, 80%	Nonscarring alopecia	15	2
	Oral ulcers	45	2
	Subcutaneous or discoid lupus	30	4
	Acute cutaneous lupus	70	6
Serosal, 50%	Pleural or pericardial effusion	50	5
	Acute pericarditis	35	6
Musculoskeletal, 95%	Joint involvement	90	6
Renal, 50%	Proteinuria >0.5 g/24 h	50	4
	Renal biopsy class II or V LN	25% of LN	8
	Renal biopsy class III or IV LN	60% of LN	10
	IMMUNOLOGIC CRITERIA		
DOMAIN	**CRITERIA**	**% OF PATIENTS WITH FEATURE[a]**	**WEIGHT**
Antiphospholipids	+ Anticardiolipin, anti–β_2-glycoprotein, or lupus anticoagulant (LAC)	40	2
Complements	Low C3 *or* C4	35	3
	Low C3 *and* C4	30	4
SLE-specific antibodies	Anti-dsDNA or anti-Smith antibodies	40	6

CLINICAL MANIFESTATIONS	IMMUNOLOGIC MANIFESTATIONS
Skin	ANA > reference negative value
Acute, subacute cutaneous LE (photosensitive, malar, maculopapular, bullous)	Anti-dsDNA > reference, if by ELISA 2× reference
Chronic cutaneous LE (discoid lupus, panniculitis, lichen planus–like, hypertrophic verrucous, chillblains)	Anti-Sm
Oral or nasal ulcers	Antiphospholipid (any of lupus anticoagulant, false-positive RPR, anticardiolipin, anti–β_2-glycoprotein 1)
Nonscarring alopecia	Low serum complement (C3, C4, or CH50)
Synovitis involving ≥2 joints	Positive direct Coombs test
Serositis (pleurisy, pericarditis)	
Renal	
Prot/Cr ≥0.5	
RBC casts	
Biopsy[a]	
Neurologic	
Seizures, psychosis, mononeuritis, myelitis, peripheral or cranial neuropathies, acute confusional state	
Hemolytic anemia	
Leukopenia (<4000/μL) or lymphopenia (<1000/μL)	
Thrombocytopenia (<100,000/μL)	

Where Do We Stand?

Despite significant improvements in:

- Understanding of the pathophysiology
- Diagnosis
- Management(from a1-year survival of less than 50% before the discovery of glucocorticoids to over 90% at 10 years)

patients with SLE still have significant mortality and carry a risk of progressive organ damage accrual and reduced health-related quality of life


MAIN CHALLENGES IN SLE
Holistic approach
Biomarkers
- find new
T2T
Treat-to-Target
- target validation
Dissecting SLE
- omics
Early Diagnosis
- window of time
Comorbidities
- preventing
Drugs
- developing new
- optimizing old
Managing Pregnancy
- from planning
- to delivery
Minimizing GCs
- related damage
- cumulative dose
Disease activity
- new approaches
- new tools

Diagnosis Delay

Insidious onset

Clinically evident disease developing over years

Variable manifestations

Mimicker conditions

SLE in men ,Childhood and Late Onset lupus can have different course and manifestations

There are classification criteria's vs. diagnostic criteria

Median delay in SLE diagnosis is approximately 2 years

Does Earlier Diagnosis Of SLE Matter?

Patient with less than 6 months' delay may experience lower flare and hospitalization

In Patients with major organ disease delay in prompt diagnosis has been linked to adverse outcome.

Failure to achieve low disease activity in the first 6 months after diagnosis has been associated with early damage accrual.

In patients with early diagnosis, quality of life can be improved over a period of 2 years.

Promoting Early Diagnosis

A clear identification of ” window of opportunity”

Early diagnosis (<6 months)

New tools for SLE classification and diagnosis

7-22% of early SLE are not correctly classified using EULAR/ACR2019 and SLICC2012criteria individually.

Promoting Early Diagnosis

Important Role Of General Practitioner:

SLE patients consult with GP during the 5 year prior to diagnosis

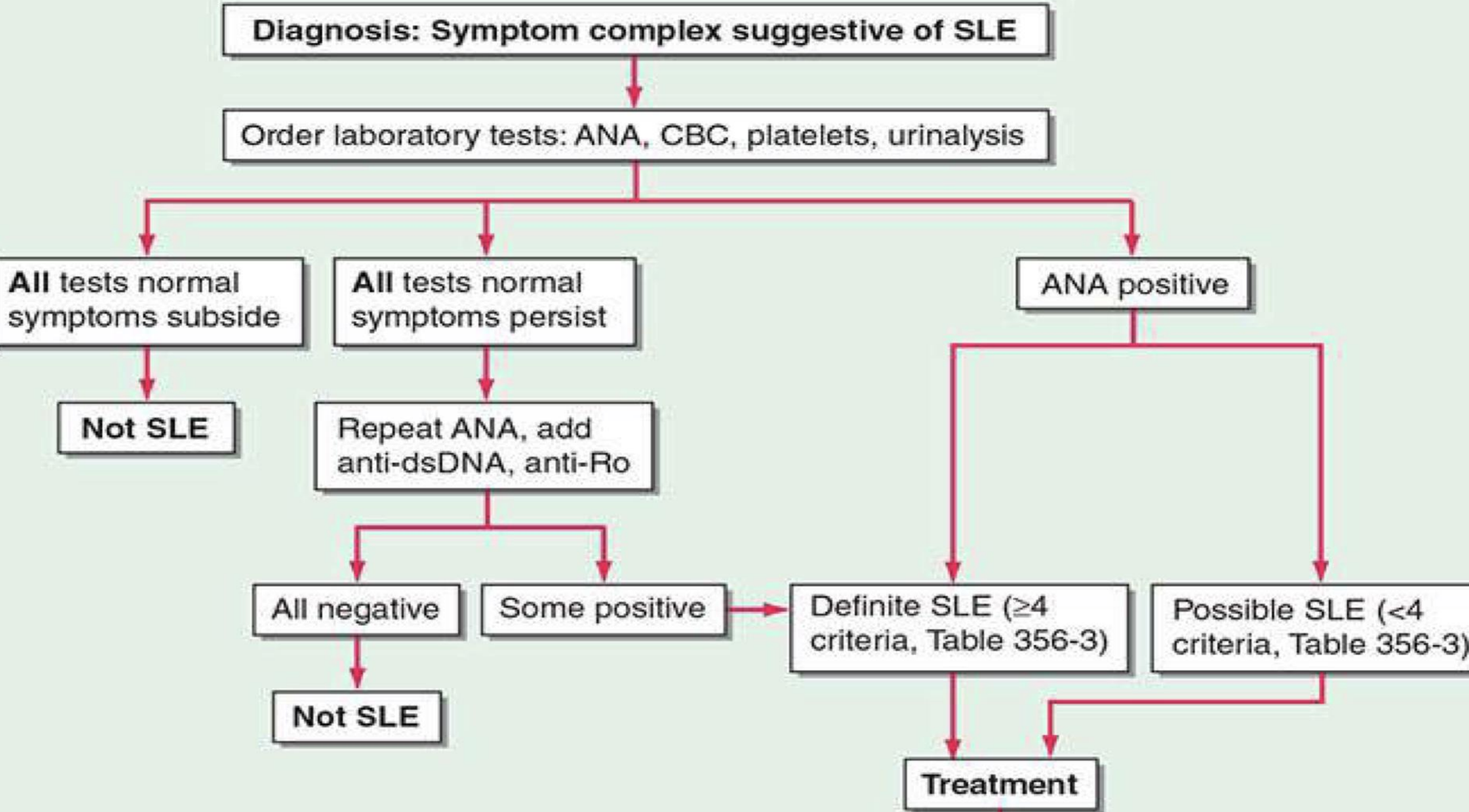
Pre –lupus and UCTD entity would be of value to be recognized with GP

Differential Diagnosis and overlap syndromes should be considered

Recognizing warning sign to refer to Rheumatologist

ANA Test Interpretation:

- Highly sensitive
- Low Diagnostic Specificity
- Titer and Pattern
  - Although most patients with SLE have positive ANA test results, most patients with positive ANA do not have SLE


Diagnosis: Symptom complex suggestive of SLE
Order laboratory tests: ANA, CBC, platelets, urinalysis
All tests normal symptoms subside
All tests normal symptoms persist
ANA positive
Not SLE
Repeat ANA, add anti-dsDNA, anti-Ro
All negative
Some positive
Definite SLE (≥4 criteria, Table 356-3)
Possible SLE (<4 criteria, Table 356-3)
Not SLE
Treatment

Major Challenges of SLE Management

Major Challenges of SLE Management

Treat to Target(T2T):

Targeting Disease Remission(or Low Disease Activity) and Reduction or Withdrawn of GCs to prevent of flares and damage reduction

Recently the LLDAS has been validated as a SLE treatment end point

Lupus Low Disease Activity & Clinical Remission

- There was no clear definition of them
- Importance of durable absence or residual of disease activity measured using validated tools(SLEDAI,PGA)
- Stable treatment with antimalarial and/or immunosuppressant's and a low dose of GCs(prednisone≤5 in CR and ≤7.5 in LLDAS)
- New tools for SLE activity assay

Major Challenges of SLE Management

Assessing SLE Disease Activity

physical evaluation

efficacy and response to medications

patient personal feeling

Tools for SLE activity assess:

(SLEDAI),(BILAG),(ECLAM)and (PGA)

Biomarkers like as ANTI DsDNA and C3,C4

Considering New Ways to Assess Disease Activty

Major Challenges of SLE Managemet

Preventing Comorbidities

- Cardiovascular disease is the leading cause of mortality
  - Need of validated tools for Cv risk estimation
  - Wide spread use of HCQ recommended

- Infections are higher risk factor than disease activity for mortality
- GCs /immunosuppressive /lupus nephritis are most important infection risk factor in lupus

Major Challenges of SLE Management