



RhAPP

RHEUMATOLOGY ADVANCED
PRACTICE PROVIDERS

RHAPP NATIONAL CONFERENCE

SEPTEMBER 8-10, 2022



Lupus Fundamentals
Saturday, September 10, 2022 1:20 PM
Parallel Session 5
Jen McGill, PA-C, MPS

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Objectives

To provide an uncomplicated introduction to lupus and give the new provider tools to recognize, evaluate and treat their adult lupus patients

- Recognize that there are four distinct types of lupus
- Understand the tools used to diagnose systemic lupus erythematosus (SLE)
- Appreciate the basic pharmacologic interventions for SLE

Lupus



Defining Lupus

Lupus is a chronic autoimmune disease of unknown cause that can affect virtually any organ of the body. Immunologic abnormalities, especially the production of a number of antinuclear antibodies (ANA), are a prominent feature of the disease. It has a heterogeneous presentation with varied changing clinical presentations ranging from superficial impacting a single organ system, to severe multi-system disease.

History

The word lupus (**from the Latin word for wolf**) is attributed to the 13th century physician Rogerius, who used it to describe erosive facial lesions that were reminiscent of a wolf's bite. Early depictions were limited to cutaneous descriptions.



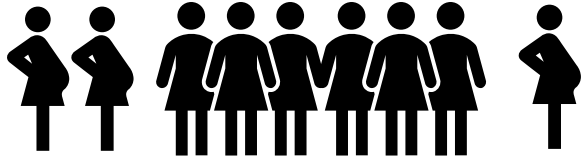
Who?



5 million people
worldwide with lupus



1.6 million
Americans



9:1



Who? Poor Prognostic Factors

- Male
- Poor Socioeconomic Status
- Very young or Very old age at diagnosis
- High disease activity
- African American
- Hypertension
- Renal Involvement
- Anti-Phospholipid Antibodies



Historical Treatments

Quinine Salicylates Steroids Antimalarials Cytotoxic Immunosuppressives Biologics.....

- 1894 Dr. J. F Payne successfully uses quinine
St. Thomas's Hospital London
- 1898 Salicylates +Quinine
- 1952 Dr. PS Hensch Corticosteroids
- Now: Cytotoxic/immunosuppressives, biologics,
and investigational therapeutics looking at
new pathways

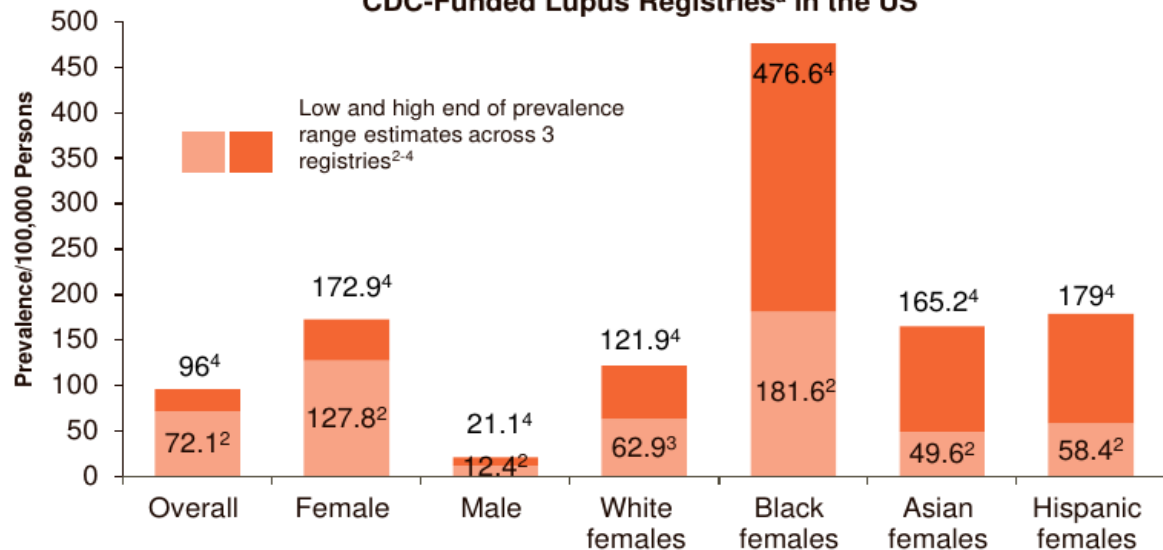


Belimumab
Anifrolumab
Voclosporin

SLE Patient Population

~240,000 to 320,000 adults in the US have SLE (calculated estimate)^{2,4,5b}

Estimated SLE Prevalence in US Adults:
CDC-Funded Lupus Registries^a in the US



Primarily affects **women (9:1)**⁶

Average **age of diagnosis** (adult-onset) is around **30 years of age**⁷

Symptoms for adult-onset SLE can present in **adolescence**⁸

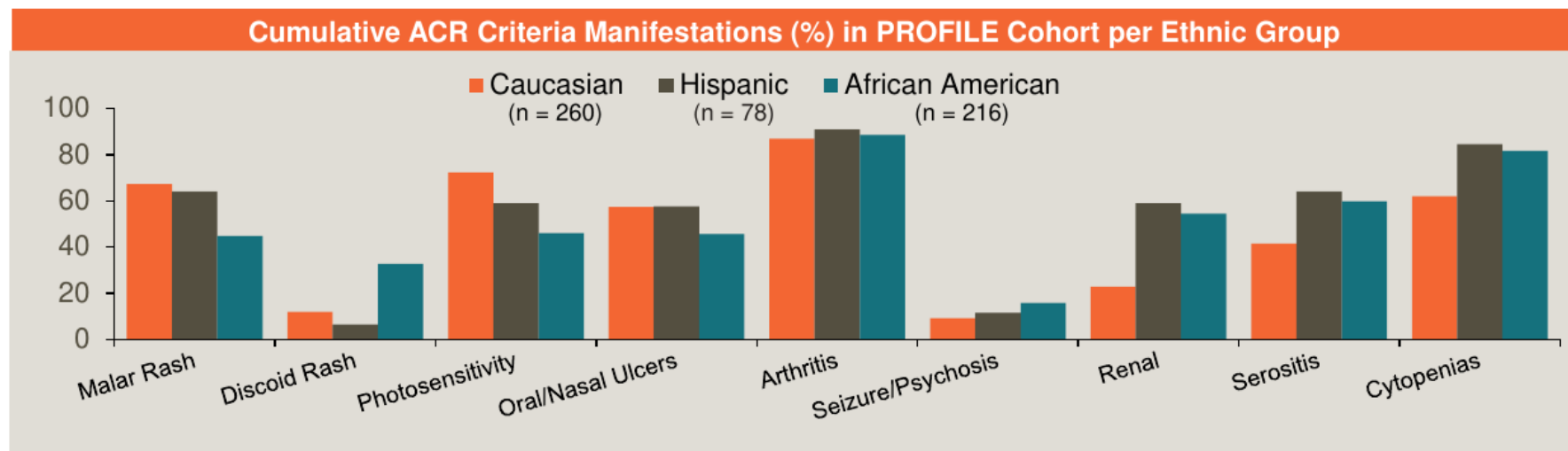
More common and severe among **women of ethnic minorities**⁹

^aData is based on American College of Rheumatology (ACR) criteria. ^bThe estimate for the US is derived from using the overall low and high end prevalence range estimates from registries¹⁻³, based on a US population of approximately 330 million in December 2019.⁵ CDC = Centers for Disease Control; SLE = Systemic Lupus Erythematosus.

1. American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. *Arthritis Rheum.* 1999;42(9):1785-1796.
2. Somers E, et al. *Arthritis Rheumatol.* 2014;66:369-378. 3. Lim S, et al. *Arthritis Rheumatol.* 2014;66:357-368. 4. Dall'Era M, et al. *Arthritis Rheumatol.* 2017;69(10):1996-2005. 5. US Census Bureau. <https://www.census.gov/popclock/>. Accessed December 25, 2019. 6. Zharkova O, et al. *Rheumatology.* 2017;56:i55-i66. 7. Merola JF, et al. *Lupus.* 2014;23(8):778-784. 8. Bertsias G, et al. *EULAR Textbook on Rheumatic Diseases.* Geneva, Switzerland: European League Against Rheumatism; 2012:476-505. 9. Pons-Estel GJ, et al. *Semin Arthritis Rheum.* 2010;39(4):257-268.

Clinical Manifestations Vary by Race

- Hispanic and African American patients tend to have more renal, hematologic, and serosal manifestations following diagnosis



Pooled cohort analysis (University of Alabama at Birmingham, AL; Johns Hopkins University, MD; University of Texas-Houston Health Science Center, TX; Northwestern University, IL) of 568 adults with SLE with a disease duration of < 10 years from diagnosis to enrollment. Mean ages were 38 - 42 years, with 86%, 92%, and 96% female in the Caucasian, African American, and Hispanic patient groups, respectively.

Types of Lupus



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Types of Lupus

1. Cutaneous Lupus (CLE)
2. Neonatal Lupus (NLE)
3. Drug Induced Lupus (DIL)
4. Systemic Lupus Erythematosus (SLE)

Cutaneous Lupus

- Limited to the skin only
 - Discoid (chronic cutaneous) lupus
 - 10% progress to develop lupus in other organ systems
 - Sub cutaneous lupus
 - Ro/SSA antibodies for SCLE
 - Acute cutaneous

Skin Biopsy Immunofluorescent staining presence of immunoglobulin, complement, fibrinogen or immune complexes in tissue, in SLE (lupus band test)

1. Cutaneous Lupus



2. Neonatal Lupus



- Rare condition occurring with mother with a combination of SSA and/SSB antibodies
 - Ro 52ab ribonucleic protein as antigenic target
- Leads to impact fetus yielding baby with skin rash, liver problems, low blood counts or congenital heart block (bradycardic)

3. Drug Induced Lupus

Most Common: SSZ, Hydralazine, Isoniazid, Procainamide, Phenytoin

Laboratory findings: anti-histone ab, SSA

Timing: months to years (5% hydralazine, 20% procainamide)

Manifestations: fatigue, fever, myalgias, arthralgias, serositis

Treatment: Rx cessation

Medicines definitively associated with drug-induced lupus

Chlorpromazine	Methyldopa	Procainamide
Isoniazid	Minocycline	Quinidine
Hydralazine		

Medicines possibly associated with drug-induced lupus

Acebutolol	Phenylbutazone	Para-aminosalicylic
Acecaïnide	Phenytoin	Penicillamine
Nalidixic acid	Phenopyrazone	Penicillin
Adalimumab	Fluvastatin	Perazine
Allopurinol	Griseofulvin	Perphenazine
Aminoglutethimide	Guanoxan	Pyrazinamide
Amoprofan	Ibuprofen	Pyridoxine
Anthiomaline	Infliximab	Practolol
Atenolol	Interferon- α	Promethazine
Atorvastatin	Interferon- γ	Propafenone
Benoxaprofen	Interleukin-2	Propylthiouracil
Captopril	Labetalol	Propranolol
Carbamazepine	Leuprolide	Psoralen
Chlorprothixene	Levodopa	Quinidine
Chlorthalidone	Levomepromazine	Reserpine
Cimetidine	Lithium	Simvastatin
Cinnarazine	Lovastatin	Sulindac
Clonidine	Mephyton	Sulfadimethoxine
Danazol	Mesalazine	Sulfamethoxy-pyridazine
Diclofenac	Methimazole	Sulfasalazine
Diphenylhydantoin	Methysergide	Tetracyclines
Disopyramide	Methylthiouracil	Tetracin
Enalapril	Metoprolol	Thioamide
Spiro-nolactone	Metrizamide	Thioridazine
Streptomycin	Minoxidil	Timolol
Oestrogens	Nitrofurantoin	Tolazamide
Etanercept	Nomifensine	Tolmetin
Ethosuximide	Oxyphenisatin	Trimethadione
Ethylphenacetamide	Oxprenolol	



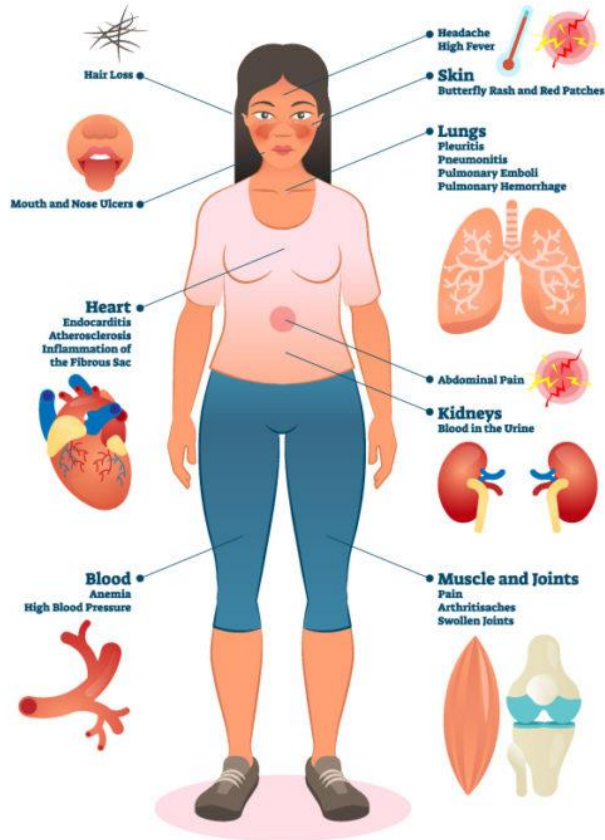
3. Drug Induced Lupus



4. Systemic Lupus Erythematosus

Heterogeneous inflammatory systemic autoimmune with innumerable clinical and laboratory manifestations resulting in anything from mild disease to severe life threatening illness

Common Symptoms of Lupus



- Sicca
- Fevers
- Hair loss
- Rashes
- Joint pain
- Joint Swelling
- Chest pain
- Headaches
- Sun sensitivity
- Digital color changes
- Anemia
- Mucosal ulcers

Easy Mnemonic for Systemic Lupus Criteria

Diagnostic criteria in SLE

S • Serositis [pleuritis, pericarditis]

O • Oral ulcers

A • Arthritis

P • Photosensitivity

M
Malar rash

B • Blood [all are low - anemia, leukopenia, thrombocytopenia]

R • Renal [protein]

A • ANA

I • Immunologic [DS DNA, etc.]

N • Neurologic [psych, seizures]

D
Discoid rash

2019 EULAR/ACR Classification Criteria for SLE

Entry criteria: ANA at a titer of $\geq 1:80$ (ever)	Clinical domains & criteria	Weight	Immunology domains & criteria	Weight
↓	Constitutional Fever	2	Antiphospholipid antibodies Anti-cardiolipin antibodies OR Anti- $\beta 2$ GP1 antibodies OR Lupus anticoagulant	2
	Hematologic Leukopenia Thrombocytopenia Autoimmune hemolysis	3 4 4	Complement proteins Low C3 OR low C4 Low C3 AND low C4	3 4
↓	Neuropsychiatric Delirium Psychosis Seizure	2 3 5	SLE-specific antibodies Anti-dsDNA antibody ^a OR Anti-Smith antibody	6
	Mucocutaneous Non-scarring alopecia Oral ulcers Subacute cutaneous OR discoid lupus Acute cutaneous lupus	2 2 4 6		
↓	Serosal Pleural or pericardial effusion Acute pericarditis	5 6		
	Musculoskeletal Joint involvement	6		
↓	Renal Proteinuria > 0.5 g/24h Renal biopsy Class II or V LN Renal biopsy Class III or IV LN	4 8 10		

Additive Criteria

- Do not add criterion if another likely cause
- Can have only 1 occurrence
- SLE classification requires at least 1 clinical criteria and score of ≥ 10
- Criteria do not have to occur simultaneously
- Within each domain, only count highest score toward total score

^aIn an assay with 90% specificity against relevant disease controls.

CASE STUDY #1

24-year-old Caucasian female with fatigue, fevers, weight loss, photosensitivity, painless mouth sores, and puffy painful fingers.

Should she be screened for lupus?

What is your clinical suspicion? Low? High?

Now what?



Case Study #1: Labs

- ANA with titer (>sensitivity but lowest specificity--)
- dsDNA (>specificity)
- anti-Smith (>specificity)
- APL Screen (LAC, anti B2 glycoprotein, anti-cardiolipin)
- Urine (protein-to-creatinine ratio)
- CBC
- CMP
- ESR
- CRP

Case #1

Results: +ANA 1:1280 homogeneous pattern CRP 2.0 ,
ESR 32, +ds DNA 18.0 , +anti smith ab , urine wnl

>4/11 ACR Criteria met:

Immunologic Criteria= +ANA, +dsDNA, +anti smith ab

Clinical Criteria= photosensitivity, oral ulcers, arthralgias

Start treatment: Hydroxychloroquine 5 mg/kg w/ baseline
eye exam +/- prednisone bridge, follow up <3 months

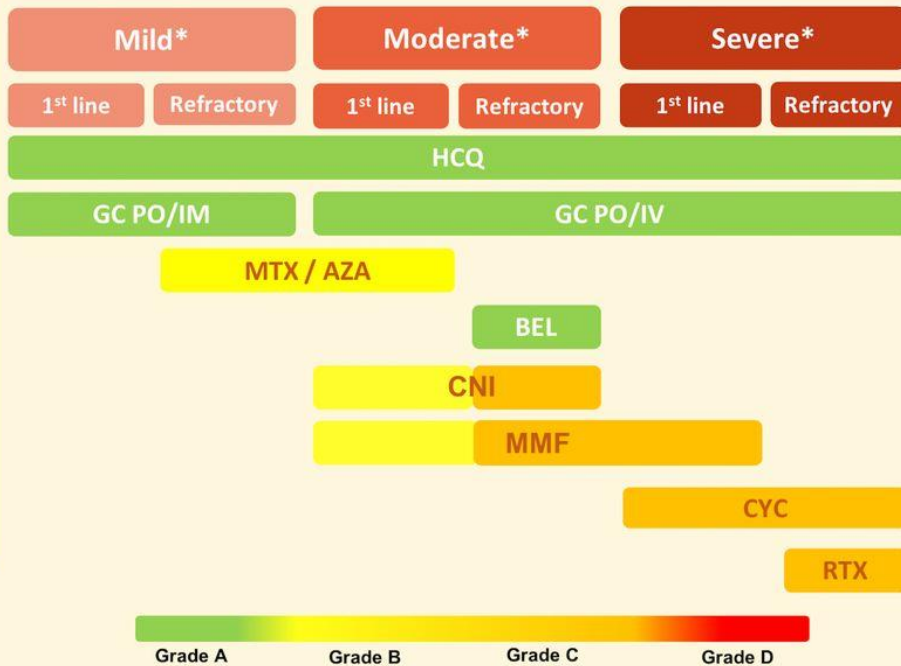
Case #1: Treatment

Treatment of non-renal Systemic Lupus Erythematosus

Adjunct:

Sun protection
Vaccinations
Exercise
No smoking
Body weight
Blood pressure
Lipids
Glucose

Antiplatelets
anti-coagulants
(in aPL- positive patients)



Target

Remission

SLEDAI = 0
HCQ
No GC

or

Low disease activity

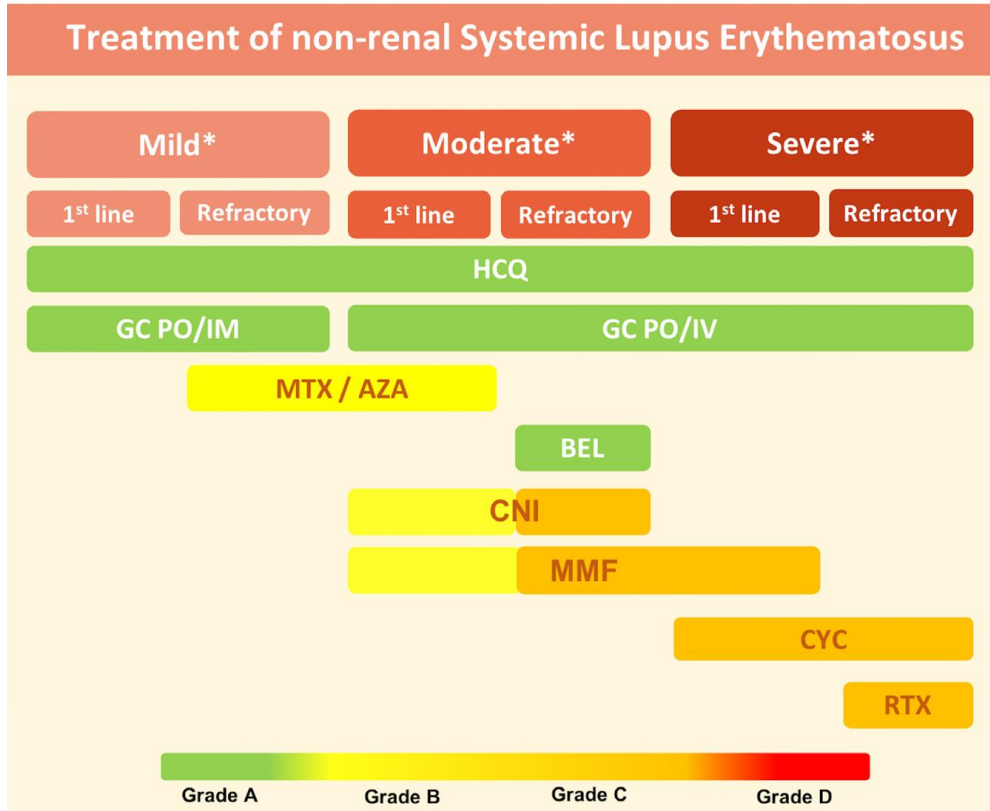
SLEDAI \leq 4
HCQ
Pre \leq 7.5 mg/d
Immunosuppressives
(in stable doses and well-tolerated)

Mild: constitutional symptoms/ mild arthritis/ rash \leq 9% BSA/PLTs $50-100 \times 10^3/\text{mm}^3$; SLEDAI \leq 6; BILAG C or \leq 1 BILAG B manifestation

Moderate: RA-like arthritis/ rash 9-18% BSA/cutaneous vasculitis \leq 18% BSA; PLTs $20-50 \times 10^3/\text{mm}^3$ /serositis; SLEDAI 7-12; \geq 2 BILAG B manifestations

Severe: major organ threatening disease (nephritis, cerebritis, myelitis, pneumonitis, mesenteric vasculitis; thrombocytopenia with platelets $<20 \times 10^3/\text{mm}^3$; TTP-like disease or acute hemophagocytic syndrome; SLEDAI $>$ 12; \geq 1 BILAG A manifestations

Case #1: Starting Treatments



Case Study #2

- 37 yr Hispanic Female presents with +ANA, body aches, burning skin, hair loss, dry mouth, digital color changes, poor temperature regulation, difficulty with memory and concentration, and headaches
- What does your exam look like?
Is there joint swelling, history of clots, pleurisy, photosensitivity?

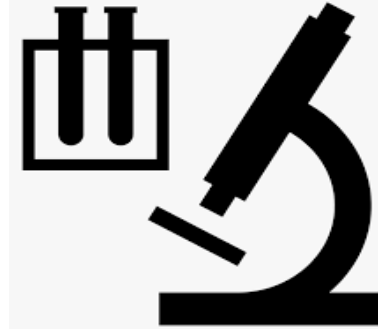


Case Study #2

Low index of suspicion---→Surveillance

Otherwise do labs:

- ANA
- *Type Titer*
- Complements
- *C3, C4, Ch50*
- dsDNA
- CBC/CMP
- Anti Smith ab
- ESR/CRP
- SSA/SSB
- UA w/micro
- Anti Phospholipids
- *APL, LAC, $\alpha+\beta$ glycop*
- RNP
- CK
- SCL70



Case Study #3

28 year old African American Male who presents with fatigue, fevers (101.8F), myalgias, headaches, elevated BP, and urine changes (pink)

Should he be screened for lupus?

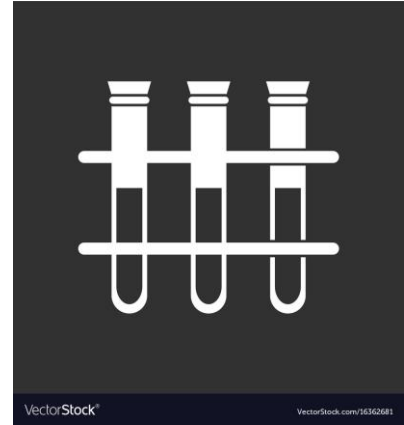
What is your clinical suspicion? Low? High?

Now what?



Case Study #3: Labs

- ANA with titer (>sensitivity but lowest specificity--)
- dsDNA (>specificity)
- anti-Smith (>specificity)
- APL Screen (LAC, anti B2 glycoprotein, anti-cardiolipin)
- Urine (protein-to-creatinine ratio)
- CBC
- CMP
- ESR
- CRP



Case #3

Lab Results: serum creatinine rose to 1.6 mg/dl: UA showed 3+ blood and 3+ protein, and the urinary sediment revealed several red blood cell casts.

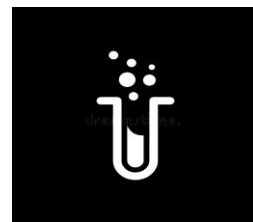


The ACR lupus classification criteria define LN by proteinuria >0.5 g/day or a **urinary protein/creatinine ratio (UPCR) of >0.5 or urinary protein greater than 3+ by dipstick analysis or urinary cellular casts of more than five cells per high-power field** (*in the absence of urinary tract infection*)

Start prednisone, discuss initial tx of mycophenolate or cyclophosphamide– calcineurin inhibitor (Voclosporin or tacrolimus) or belimumab refer to nephrology

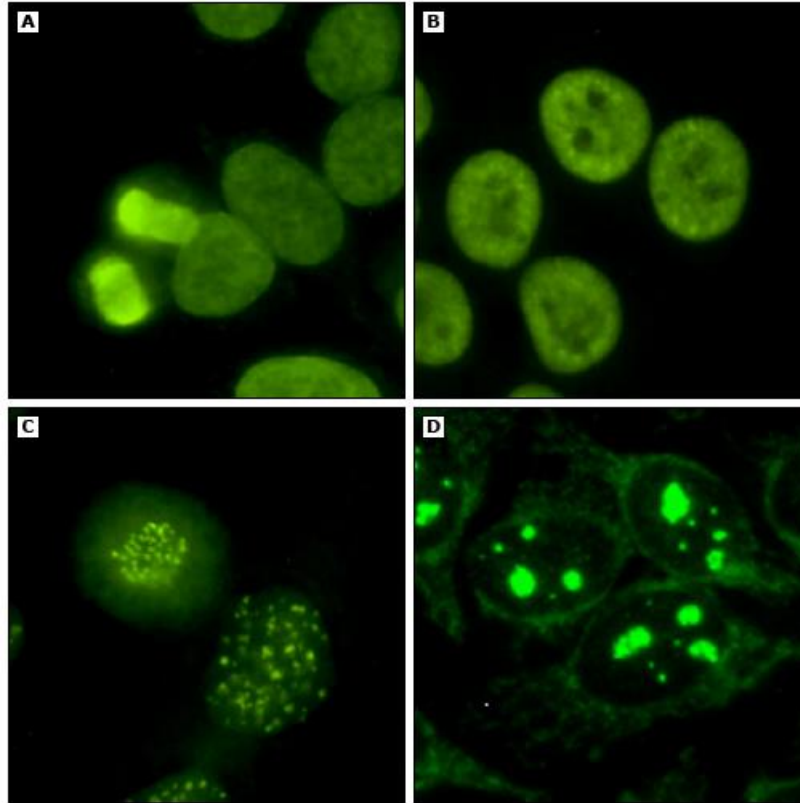
Labs

Test	Description
ANA	Screening test; sensitivity 95%; not diagnostic without clinical features
Anti-dsDNA	High specificity; sensitivity only 70%; level is variable based on disease activity
Anti-Sm	Most specific antibody for SLE; only 30-40% sensitivity
Anti-SSA (Ro) or Anti-SSB (La)	Present in 15% of patients with SLE and other connective-tissue diseases such as <u>Sjögren syndrome</u> ; associated with <u>neonatal lupus</u>
Anti-ribosomal P	Uncommon antibodies that may correlate with risk for CNS disease, including increased hazards of psychosis in a large inception cohort, although the exact role in clinical diagnosis is debated ^[108]
Anti-RNP	Included with anti-Sm, SSA, and SSB in the ENA profile; may indicate mixed connective-tissue disease with overlap SLE, <u>scleroderma</u> , and myositis
Anticardiolipin	IgG/IgM variants measured with ELISA are among the antiphospholipid antibodies used to screen for antiphospholipid antibody syndrome and pertinent in SLE diagnosis
Lupus anticoagulant	Multiple tests (eg, direct Russell viper venom test) to screen for inhibitors in the clotting cascade in antiphospholipid antibody syndrome
Direct Coombs test	Coombs test–positive anemia to denote antibodies on RBCs
Anti-histone	Drug-induced lupus ANA antibodies are often of this type (eg, with procainamide or hydralazine; p-ANCA–positive in minocycline-induced drug-induced lupus)



ANA = antinuclear antibody; CNS = central nervous system; ds-DNA = double-stranded DNA;
 ELISA = enzyme-linked immunoassay; ENA = extractable nuclear antigen; Ig = immunoglobulin;
 p-ANCA = perinuclear antineutrophil cytoplasmic antibody; RBCs = red blood cells; RNP = ribonucleic protein;
 SLE = systemic lupus erythematosus; Sm = Smith; SSA = Sjögren syndrome A; SSB = Sjögren syndrome B.

ANA Staining Significance



A. Homogeneous

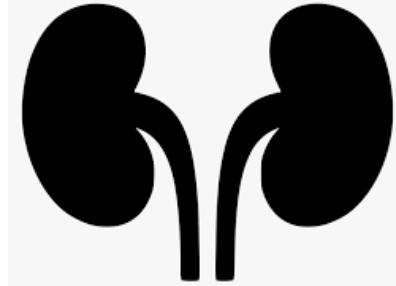
B. Speckled

C. Centromere

D. Nucleolar

Summary

- **Recognize that there are four distinct types of lupus**
 - *Cutaneous, Drug Induced, Neonatal and Systemic*
- **Understand the tools used to diagnose systemic lupus erythematosus (SLE)**
 - **Common Symptoms (MDSOAPBRAIN), ACR Criteria, Labs, Profiles, Prognostic Factors**
- **Appreciate the basic pharmacologic interventions for SLE**
 - **PLQ, MTX, AZA, CNI, BEL, MMF, CYC**



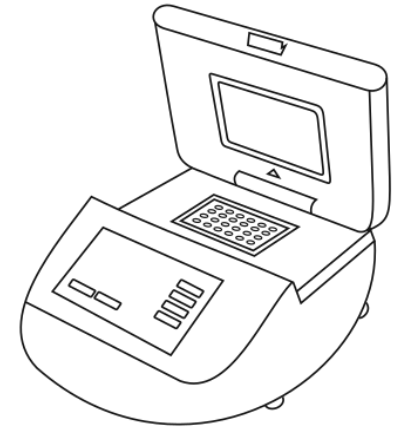
2019 EULAR/ACR Classification Criteria for SLE

Entry criteria: ANA at a titer of $\geq 1:80$ (ever)	Clinical domains & criteria	Weight	Immunology domains & criteria	Weight
If negative: do not classify as SLE If positive: apply additive criteria	Constitutional Fever	2	Antiphospholipid antibodies Anti-cardiolipin antibodies OR Anti- $\beta 2$ GP1 antibodies OR Lupus anticoagulant	2
	Hematologic Leukopenia Thrombocytopenia Autoimmune hemolysis	3 4 4	Complement proteins Low C3 OR low C4 Low C3 AND low C4	3 4
Additive Criteria	Neuropsychiatric Delirium Psychosis Seizure	2 3 5	SLE-specific antibodies Anti-dsDNA antibody ^a OR Anti-Smith antibody	6
	Mucocutaneous Non-scarring alopecia Oral ulcers Subacute cutaneous OR discoid lupus Acute cutaneous lupus	2 2 4 6		
<ul style="list-style-type: none"> • Do not add criterion if another likely cause • Can have only 1 occurrence • SLE classification requires at least 1 clinical criteria and score of ≥ 10 • Criteria do not have to occur simultaneously • Within each domain, only count highest score toward total score 	Serosal Pleural or pericardial effusion Acute pericarditis	5 6		
	Musculoskeletal Joint involvement	6		
	Renal Proteinuria > 0.5 g/24h Renal biopsy Class II or V LN Renal biopsy Class III or IV LN	4 8 10		

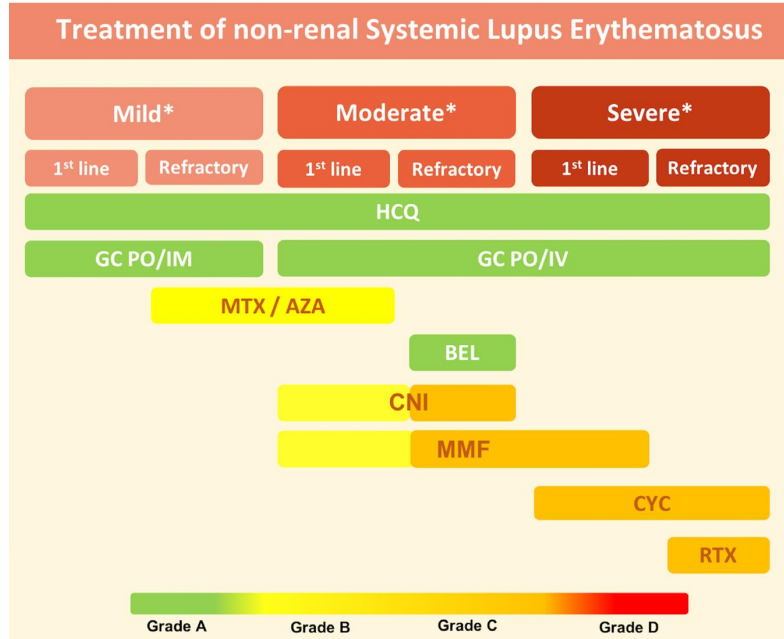
^aIn an assay with 90% specificity against relevant disease controls.

Labs

ANA	<i>Type Titer</i>	Complements	<i>C3, C4, Ch50</i>
dsDNA		CBC/CMP	
Anti Smith ab		ESR/CRP	
SSA/SSB		UA w/micro	
Anti Phospholipids	<i>APL, LAC, α+β glycop</i>	RNP	
CK		SCL70	



Treatments



HCQ: Hydroxychloroquine

GC: Corticosteroid

MTX: Methotrexate

AZA: Azathioprine

CNI: Calcineurin

BEL: Belimumab

MMF: Mycophenolate

CYC: Cyclophosphamide

RTX: Rituximab





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