American College of Rheumatology
Empowering Rheumatology Professionals

Major Causes of Morbidity and Mortality in SLE

the lupus initiative
Eliminating Health Disparities in Lupus

WELCOME

Before we get started…

ABOUT THIS PROJECT

- The presentation is designed to be easily incorporated into medical school lectures on a variety of topics; they are tailor-made for the classroom setting, and easy to digest
- The PowerPoint presentation is designed for medical students M3 and M4

DRUGS AND DOSES

When prescribing medications, the physician is advised to check the product information sheet accompanying each drug to verify conditions of use and to identify any changes in drug dosage schedule of contra-indications.

USE OF PROFESSIONAL JUDGMENT

This activity, including all educational links, is intended to be used as a tool to assess the base knowledge of the learner.
The information presented relates to basic principles of diagnosis and therapy, and is meant in no way to substitute for an individual patient assessment based upon the healthcare provider's examination of the patient and consideration of laboratory data and other factors unique to the patient.

ACR DISCLOSURE STATEMENT

The American College of Rheumatology is an independent, professional organization that does not endorse specific procedures or products of any pharmaceutical/biotech concern.

SUPPORT

The project described is, in part, supported by the Centers for Disease Control and Prevention under Cooperative Agreement Number NU58 DP006138. Its contents are solely the responsibility of its developers/authors. Points of view or opinions do not, therefore, necessarily represent official views of the Centers for Disease Control and Prevention or the Department of Health and Human Services.

FACULTY REPORTED DISCLOSURES

[To be filled in]

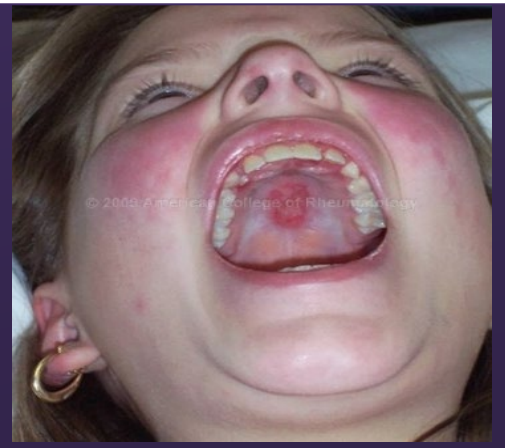
Learning Objectives

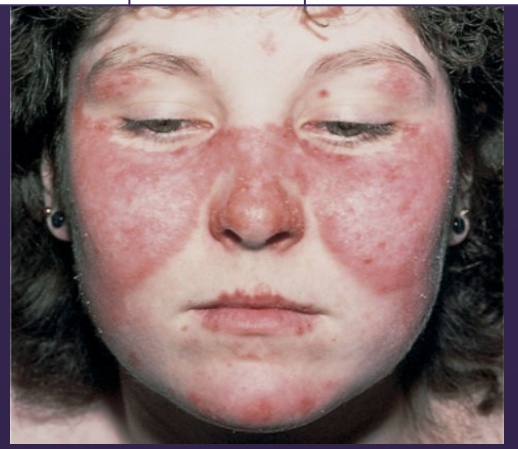
- Recognize the presentation, diagnostic workup, and initial management of common morbidities among patients with SLE, including neuropsychiatric manifestations, lupus nephritis, cardiovascular disease, skin and bone-related issues, malignancy, and hematologic abnormalities.
- Recognize the increased mortality rate among patients with SLE due to both their comorbidities and drug toxicities.
- Discuss ways to optimize SLE management to reduce morbidity and mortality.

Patient EM

- EM, an 18-year-old girl presents to the ED with altered mental status.
- Her parents say that she has been complaining of fatigue and facial rash for 6 months. In the past week, she became more and more confused, seeing things that weren't there, acting restless and combative.
- On exam, her temperature is 100 F, she has malar rash and several oral ulcers on the hard palate. She has disorganized thinking, lack of orientation, agitation, and delusions. EM is admitted.

Laboratory Test, Units	Result	Reference Range
Leukocyte count, cells/uL	3200	4000–11,000
Antinuclear antibodies	1:2560	1:40 or less
Anti-Smith antibody	Positive	Negative
Anti–double-stranded DNA antibodies, IU/mL	40	0–7
Complements, serum		
C3, mg/dL	77	100–233
C4, mg/dL	11	14–48





Patient EM - Does she have SLE?

- Classification criteria are NOT diagnostic criteria
  - Caveats for using the criteria:
  - Do not count a criterion if there is a more likely explanation than SLE.
  - Occurrence of a criterion on one occasion is sufficient.
  - SLE classification requires ≥ 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

Aringer, M, Costenbader, H, Daikh DI, et al. 2019 EULAR/ACR Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheumatol. 2019 Sep: 71(9): 1400-1412.

2019 ACR/EULAR Classification Criteria

Entry Criterion: positive ANA ≥ 1:80

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia *	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies*** *	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure *	5	Anti-Smith antibody	6 *
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		

* indicates criteria that patient EM meets, she gets 22 points

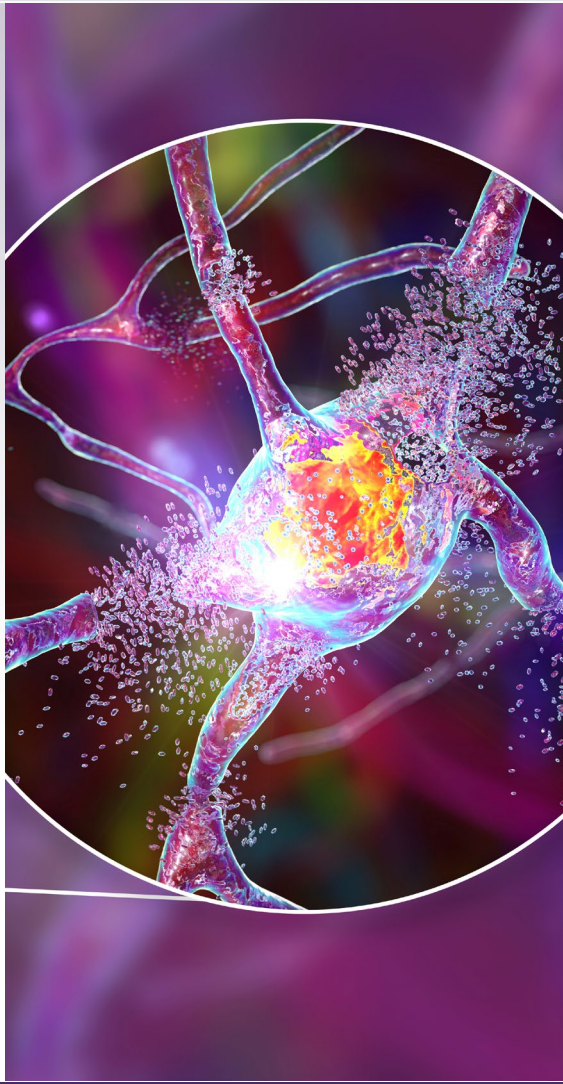
Patient EM - Diagnosis and Treatment Plan

- Exclude other causes of confusion (e.g., infectious, metabolic, drug-induced, vascular
- Neuroimaging and cerebral spinal fluid studies to help to determine the cause
- Measure antiphospholipid antibodies, which can, in some patients, alter the management plan
- With diagnosis of SLE and neuropsychiatric lupus, EM is treated with hydroxychloroquine and corticosteroids

Sacks JJ, Helmick CG, Langmaid G, Sniezek JE. MMWR Morb Mortal Wkly Rep. 2002;51(17):371-374.
Hanly JG et al. Arthritis Rheumatol. 2019;71(2):281. Epub 2019 Jan 18.

Neuropsychiatric Lupus (NPSLE)

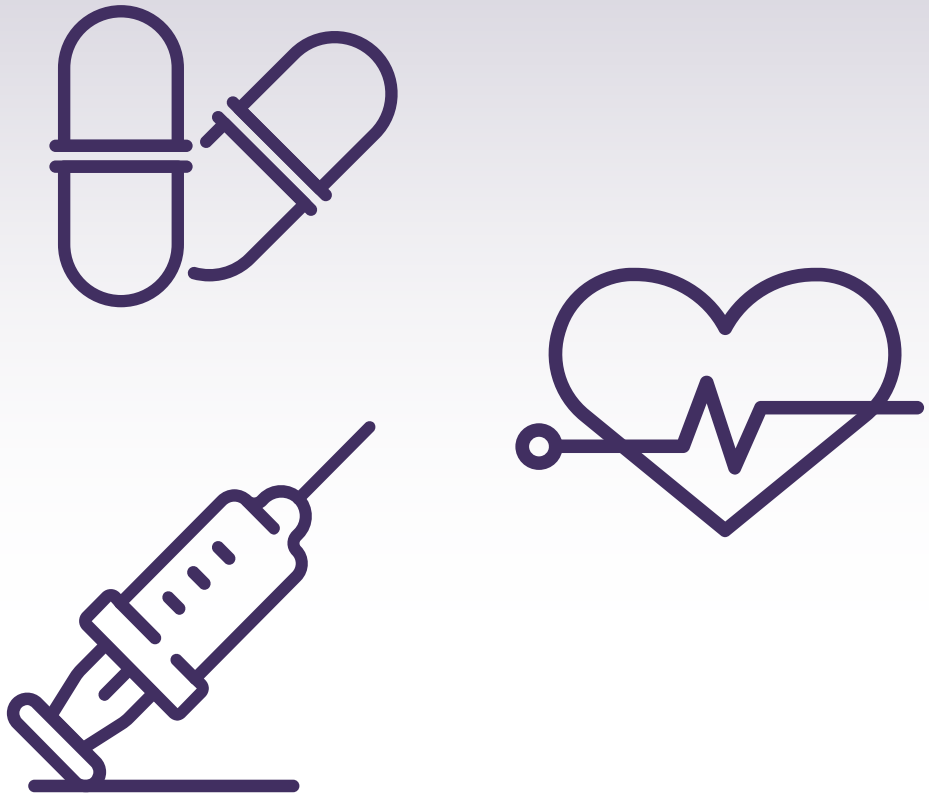
- Cumulative incidence is ~30%–40%
- 19 case definitions of neuropsychiatric manifestations involving central and peripheral nervous systems
- NPSLE may occur during periods of disease quiescence in other organs
- Usually, an early manifestation of SLE
- In early disease, ~20% of patients already have atrophy on brain MRI, and ~10% have focal lesions
- Not all neuropsychiatric manifestations in SLE patients are directly attributable to SLE. Two thirds may be due to other causes



Muscal E, Brey R. Neurol Clin. 2010;28(1):61-73. Sanna G, Bertolaccini ML, Cuadrado MJ, et al. J Rheumatol. 2003;30(5):985-992. Hanly, JG. Arthritis Rheumatol. 2019 Jan;71(1):33-42

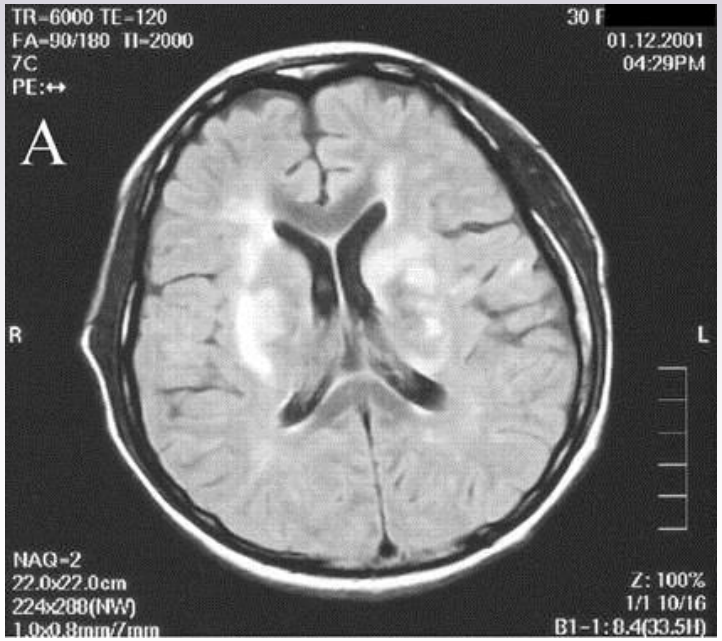
Rule Out Causes Other than SLE for Neuropsychiatric Symptoms

- Infections
- Medications and toxins
  - Prescription medications
  - Illicit drugs
  - Dietary supplements
  - Alternative and complementary therapies
  - Cardiovascular
  - Hypertension
  - Ischemic or hemorrhagic stroke
- Other



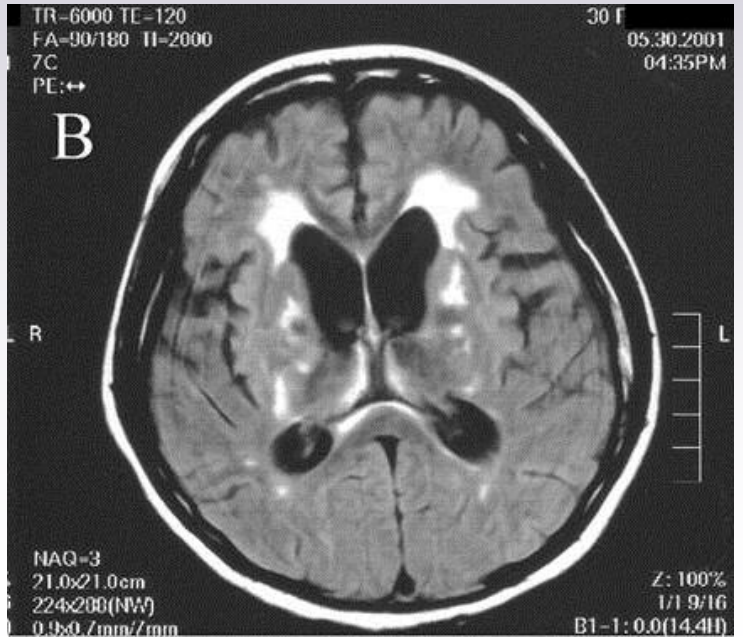
CT or MRI Findings of NPSLE

Atrophy (most common) | Vascular abnormalities



A. The initial MRI scan with fluid- attenuated inversion-recovery reveals multiple high-intensity areas in the deep white matter.

Demyelination | Inflammation

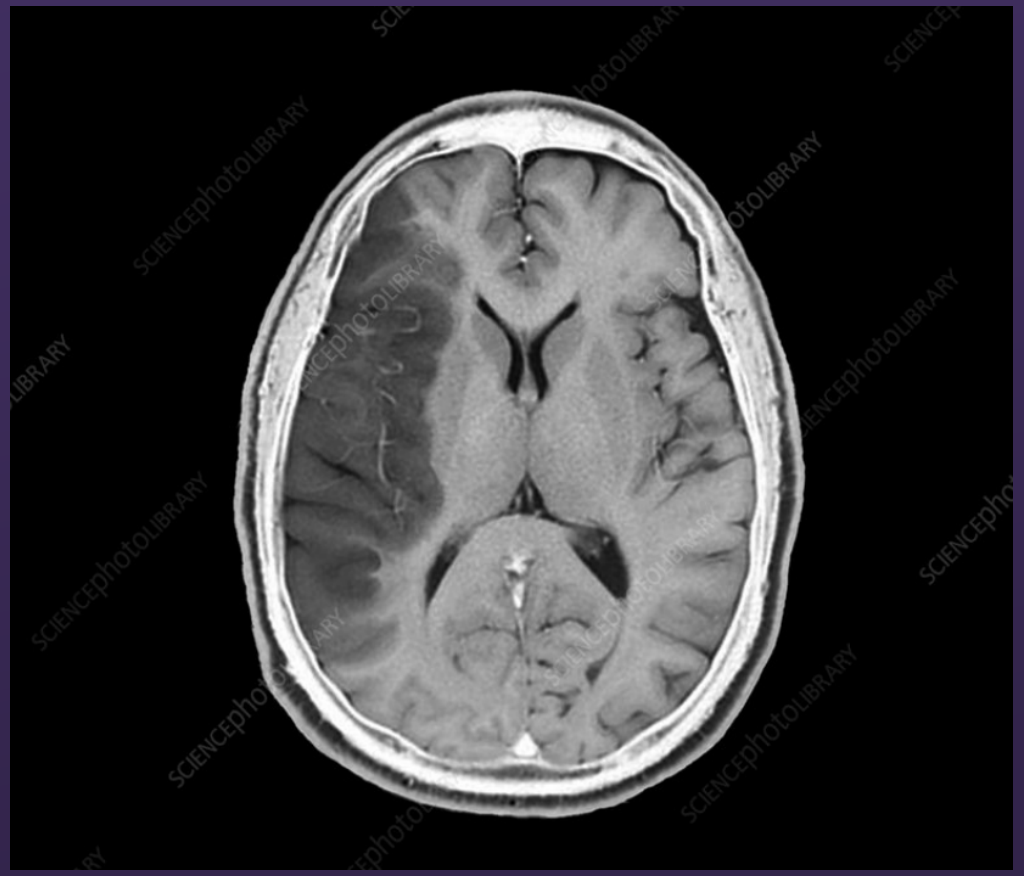


B. 4 months later, there is significant cerebral atrophy, characterized by a loss of brain volume, along with multiple high-intensity areas.

Katsumata Y, Kawaguchi Y, Yamanaka H. *J Rheumatol*. 2011;38;2689.

Vascular Abnormalities in NPSLE

- Associated clinical syndromes
  - Acute – headache, stroke, and seizures
  - Chronic cognitive impairment due to recurrent microinfarcts
- Vascular lesions include:
  - Hemorrhages
  - Ischemic stroke and microinfarcts
    - Associated with antiphospholipid antibodies
  - Vasculopathy with perivascular lymphocytic infiltrate and endothelial cell proliferation
  - Vasculitis (rare)



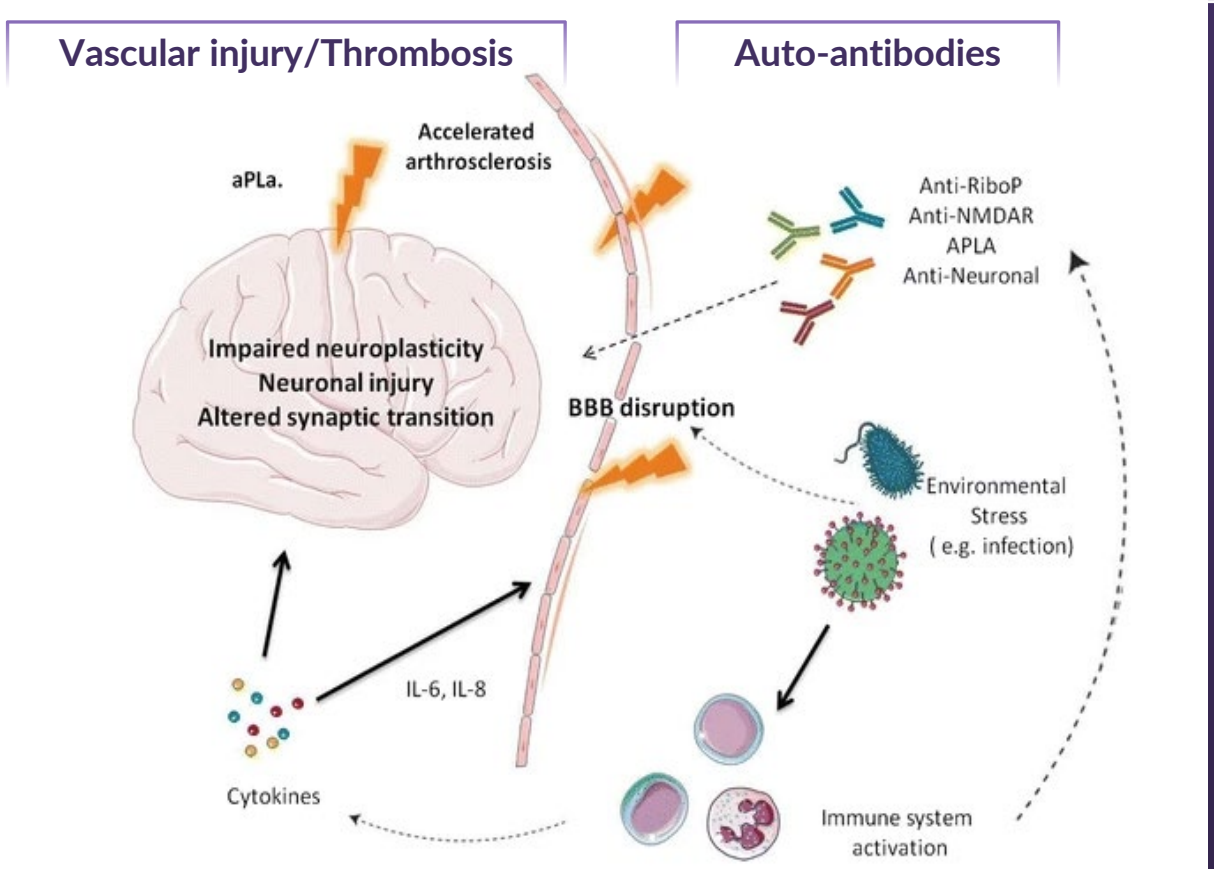
Stroke

Injury to the Brain Parenchyma

- Associated clinical syndromes
  - Acute confusional state, psychosis, and mood disorders
  - Often wax and wane, suggesting temporary neuronal dysfunction
- CSF analysis may indicate local inflammation
  - Increased lymphocytes
  - Elevated protein levels, specifically IgG index and oligoclonal bands
  - Presence of autoantibodies (e.g., CSF anti-neuronal antibody)

Zhang, X, et al. Ann Rheum Dis. 2007 Apr; 66(4): 530–532.

Parenchymal Brain Lesions Often Indicate Penetration of the Blood-Brain Barrier (BBB)



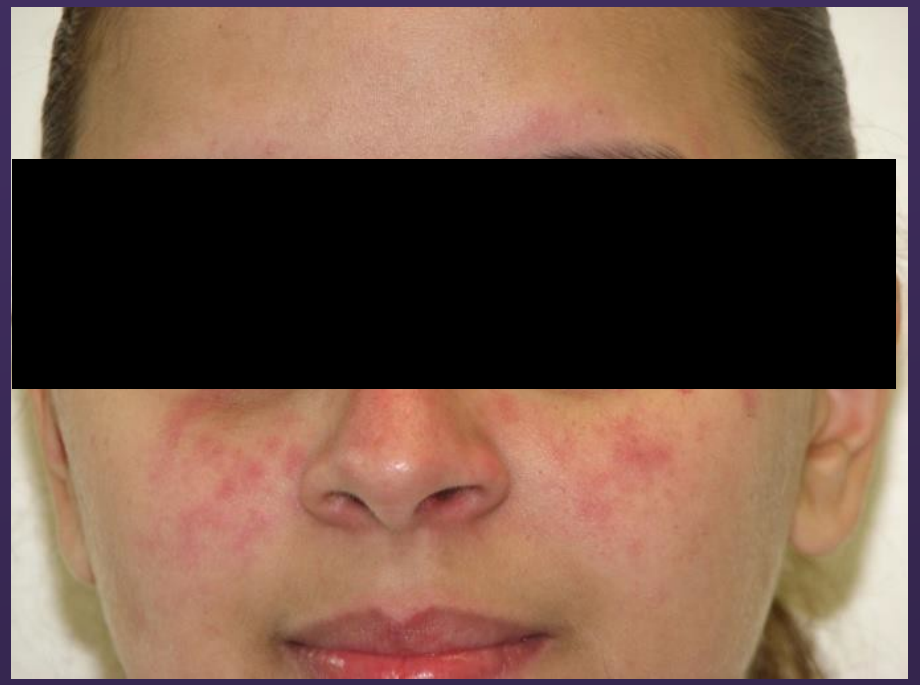
8-Abbo8-Abbott NJ, Mendonca LL, Dolman DE. Lupus. 2003;12:908-915. Kivity et al. BMC Medicine March 2015

tt NJ, Mendonca LL, Dolman DE. Lupus. 2003;12:908-915. Kivity et al. BMC Medicine March 2015

- Tight junctions between endothelial cells control BBB and can be disrupted by:
  - Infection
  - Inflammatory cytokines
  - Hypertension
- Disrupted BBB allows auto-antibodies to enter brain causing neuronal damage, e.g., impaired neuroplasticity, synaptic transition and cytokines
- Vascular injury can be mediated by antiphospholipid antibodies (aPLa) or accelerated atherosclerosis

Cognitive Dysfunction in NPSLE

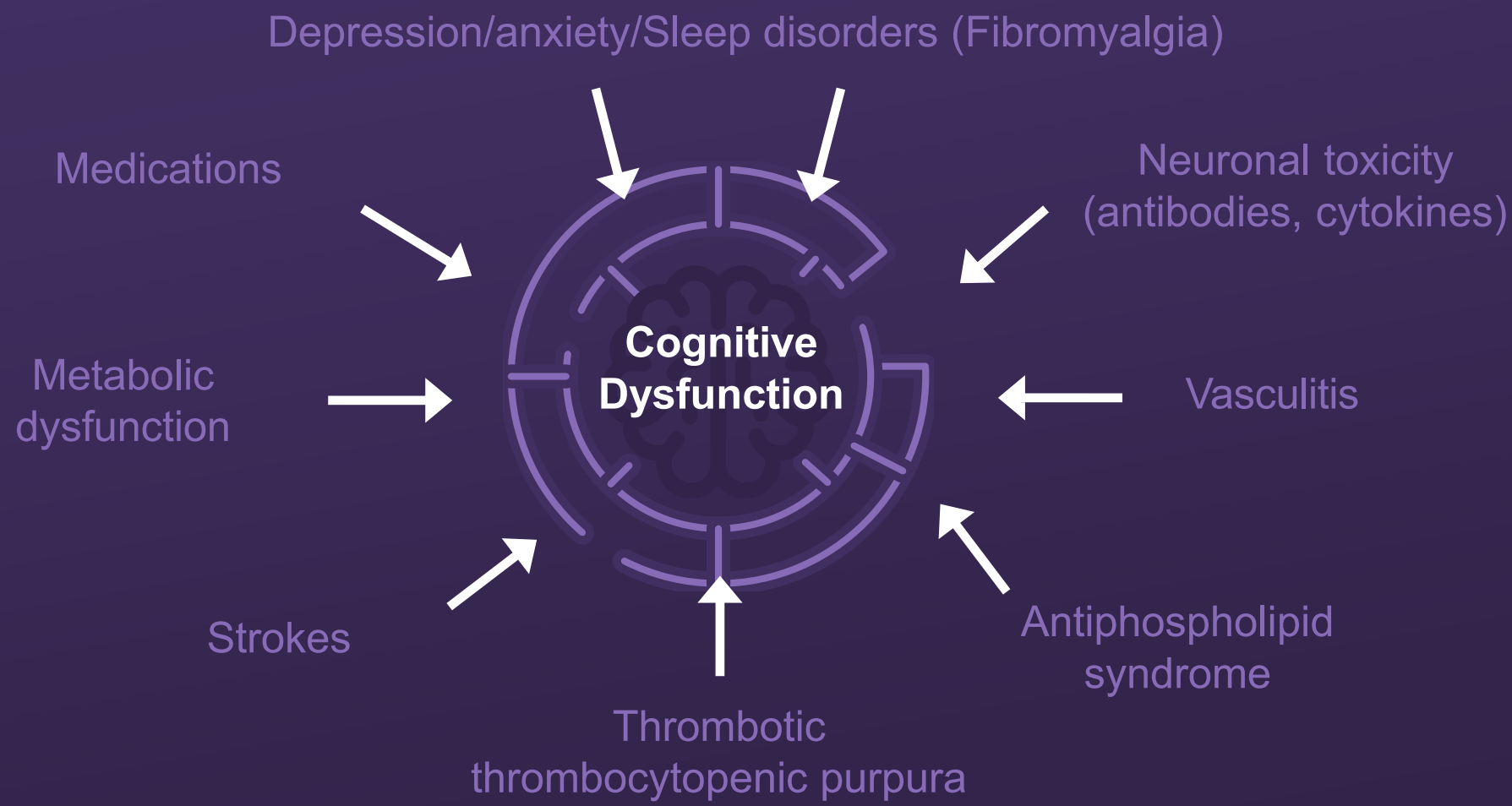
- Common (50%–80%) but difficult to attribute directly to SLE
- Problems with:
  - Attention
  - Concentration
  - Memory
  - Word-finding



"I have to squeeze my brain *really* hard to get a thought out!"

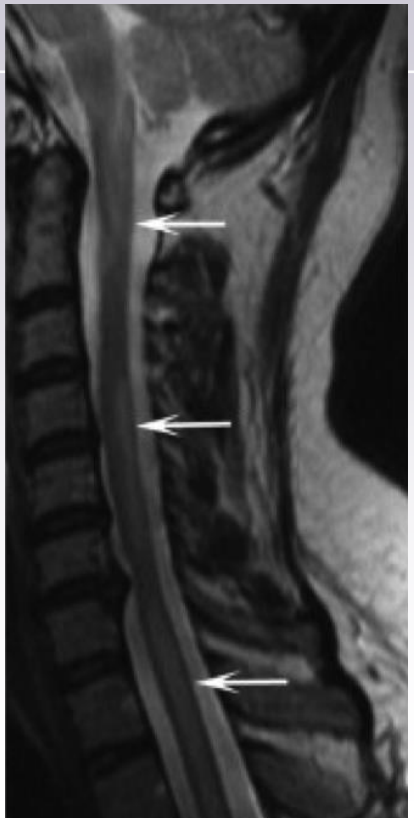
Benedict RH, Shucard JL, Zivadinov R, Shucard DW. Neuropsychol Rev. 2008;18(2):149-166. Rayes HA, et al. Semin Arthritis Rheum. 2018;48(2):240. Kello, N, et al. Arthritis Rheumatol. 2019 Sep;71(9):1413-1425.

Cognitive Dysfunction in SLE is Multifactorial

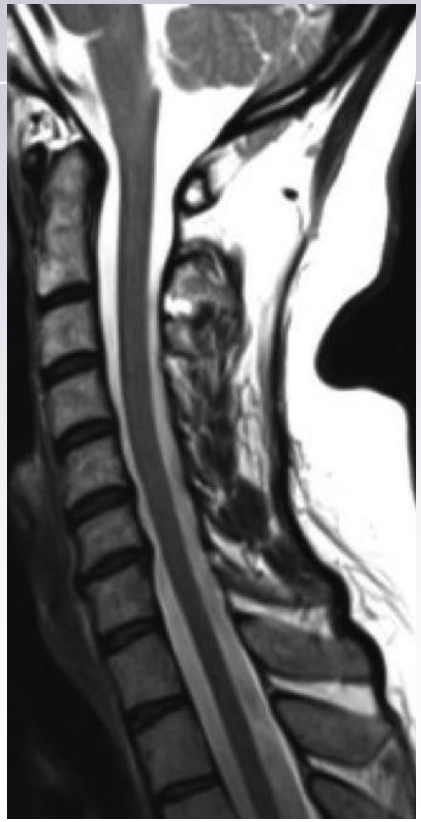


Transverse Myelitis in NPSLE Requires Prompt Attention

- Can occur across the life span of SLE including at presentation
- Most patients, but not all, demonstrate a sensory level with spastic weakness and sphincter dysfunction (urinary/bowel retention or incontinence)
- Though rare, its consequences are serious, so it is critical to not overlook this possibility



Sagittal MRI spine (T2-weighted, gadolinium-enhanced) showing cord enlargement & hyperintense signal in C2, C4–C6, C7–T1



Posttreatment spine MRI demonstrates complete resolution of the T2 hyperintense signal

Birnbaum J, Petri M, Thomson R, Izbudak I, Kerr D. Arthritis Rheum. 2009;60(11):3378-3387. Espinosa G, Mendizábal A, Minguez S, et al. Semin Arthritis Rheum. 2010;39(4):246-256. Simeon-Aznar CP, Tolosa-Vilella C, Cuenca-Luque R, Jordana-Comajuncosa R, Ordi-Ros J, Bosch-Gil JA. Br J Rheumatol. 1992;31(8):555-558. Goh YP, Naidoo P, Ngian GS. Clin Radiol. 2013;68(2):181-191.

Peripheral Nervous System Involvement

- Neuropathies (motor or autonomic) or myasthenia gravis-like syndrome
- SLE/myasthenia overlap is associated with antiacetylcholine receptor antibodies
- Circulating antibodies and inflammatory mediators have direct access to peripheral nerves

NPSLE Treatment

- Accurate evaluation and assessment are critical
  - e.g., ischemic stroke due to long-standing diabetes and hypertension should not be treated with immunosuppression
- Immunosuppression for inflammatory manifestations
- Traditional medications for headache, seizures, stroke, mood disorders
- Stress management and psychotherapy

NPSLE Conclusions

- The most common causes of neuropsychiatric involvement are non-lupus related.

  Rule out other causes first

- NPSLE encompasses a broad range of clinical presentations and pathologies
  - Vascular lesions can cause both acute focal and chronic diffuse impairment
  - Autoantibodies and other proinflammatory molecules that cross the blood-brain barrier may have direct effects on neurons, resulting in altered cellular function or death
  - Peripheral nerves are exposed to the circulation
- Correct diagnosis is critically important to ensure that appropriate therapy is used

Patient EM

- She experienced resolution of symptoms and decrease in anti-dsDNA antibodies over 6–8 weeks. She was treated by steroid taper over the next 6 months and was maintained on hydroxychloroquine. She was followed every 3 months but lost to follow-up after 2 years.
- 3 years later, at age 23, she presents with fever and joint pains. In the last 3 days, she has noticed mild swelling of both ankles.

Laboratory Test, Units	Result	Reference Range
Anti–double-stranded DNA antibodies, IU/mL	30	0–7
Complements, serum C3, mg/dL C4, mg/dL	 67 4	 100–233 14–48
Creatinine, serum, mg/dL	0.9	0.7–1.5
Urinalysis	5 WBCs/hpf, 2+ protein	0-3 WBCs, no protein
Protein-to-creatinine ratio, urine, mg/mg	600mg/mg	<200mg/mg

Epidemiology of Lupus Nephritis

- Prevalence: 30%–65% in adults and 80% in children
- 10% annual incidence in large cohort studies
- More frequent and severe in children, Blacks, Hispanics, Asians, and males
- Strong predictor of morbidity and mortality, lupus nephritis reduces survival rate from 92% to 88% at 10 years
- Nearly 20% of those with lupus nephritis will develop ESKD within 10 year

Bastian HM, et al; LUMINA Study Group. Lupus. 2002;11(3):152-160. Danchenko N, Satia JA, Anthony MS. Lupus. 2006; 15:308-318. Fernández M, et al; LUMINA Study Group. Arthritis Rheum. 2007;57(4):576-584. Hiraki LT, et al. Arthritis Rheum. 2012;64(8):2669-2676. Patel M, et al. Arthritis Rheum. 2006;54(9):2963-2969. Petri M. Lupus. 2005;14(12):970-973. Hahn et al. Arthritis Care Res. 2012;64(6):797-808. Mahajan A. Lupus. 2020 Aug;29(9):1011-1020

Mortality in Patients With Lupus Nephritis

Hong Kong Cohort

- 694 Chinese SLE patients, 368 with LN.
- Age and sex-adjusted HR for mortality in SLE patients with LN vs. those without LN.

SLICC Cohort

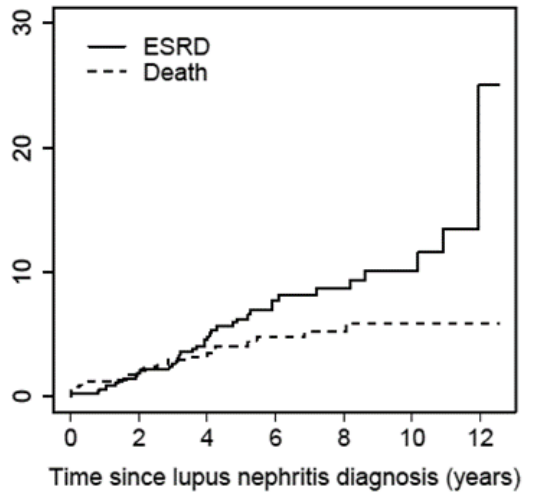
- 1827 patients enrolled into SLICC inception longitudinal cohort.
- Mean follow-up 4.6 yrs.
- LN occurred in 38% patients (81% at enrollment visit).
- After development of LN, higher risk of ESKD (HR 44.7) and death (HR 3.2).
- In patients with LN, cumulative incidence of ESKD at 10 yrs.= 10% (vs. 0.5% in non-LN patients).

Hanly J et al., Rheumatol., 2016

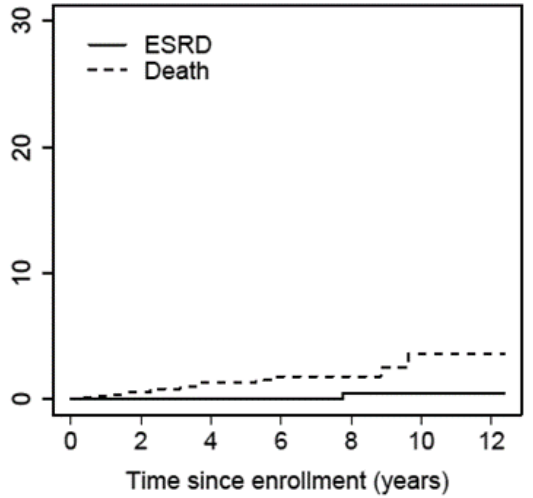
Mok C.C. et al. Arthritis Rheum, 2013

	Hazard Ratio (95% CI)
Kidney Disease	2.23 (1.29-3.85)
Kidney Damage	3.59 (2.20-5.97)
ESKD	9.20 (4.92-17.2)
Proliferative LN	2.28 (1.22-4.24)
Pure membranous LN	1.09 (0.38-3.14)

With LN

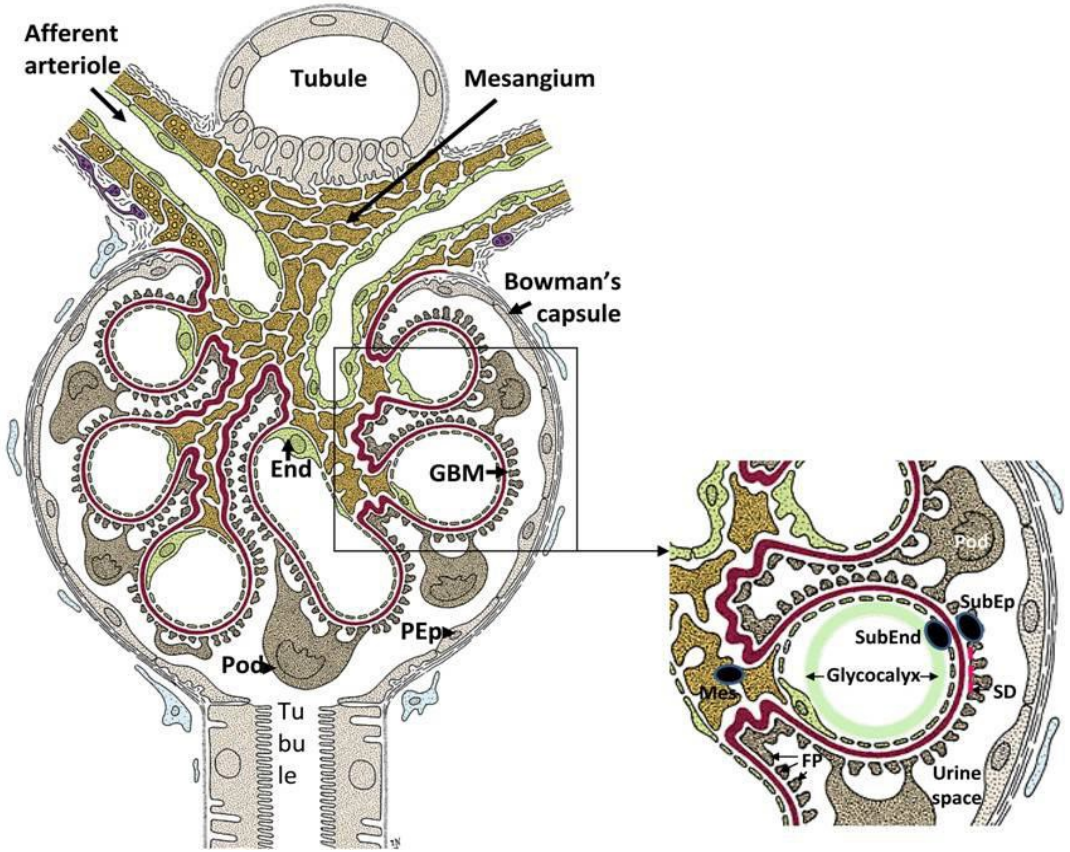


Without LN



Nephritis Is Induced by Renal Deposition of Immune Complexes

- **The glomerulus consists of a tuft of capillary loops fed by the *afferent arteriole*.**
- **The *mesangium* (Mes) holds the tuft together.**
- Glomerular filtration barrier is formed by *glycocalyx*, *fenestrated endothelial cells* (End), *glomerular basement membrane* (GBM), *podocyte foot processes* (Pod and FP), and *slit diaphragm* (SD).
- The podocyte layer is contiguous with the *parietal epithelial layer* (PEp), which is surrounded by the *Bowman capsule*.
- Immune deposits may be found on either side of the GBM (SubEnd or SubEp) or in the mesangium.
- Tubular and vascular deposits may also occur.



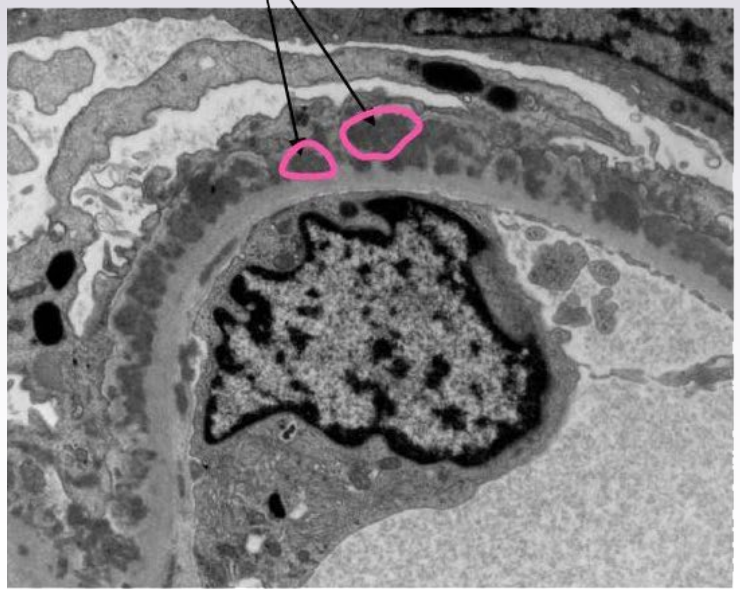
Anatomy of the glomerulus

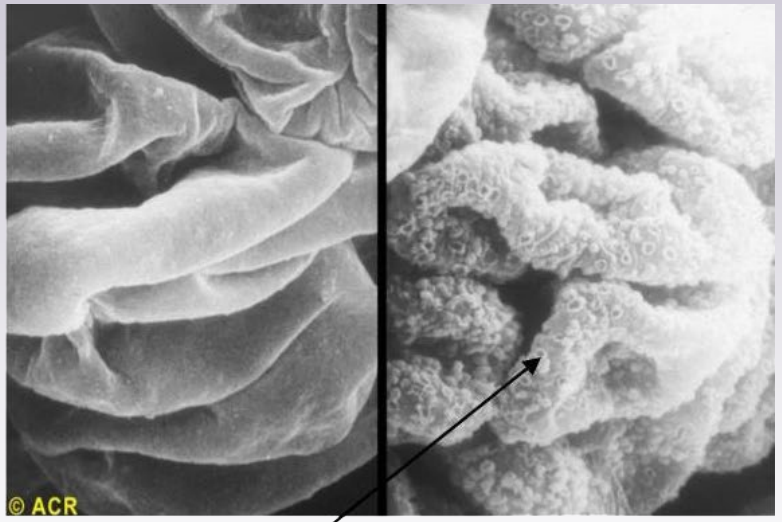
Davidson A, Berthier C, Kretzler M. In: Dubois' Lupus Erythematosus and Related Syndromes (8th Ed). Philadelphia, PA: Saunders; 2013:237-255.

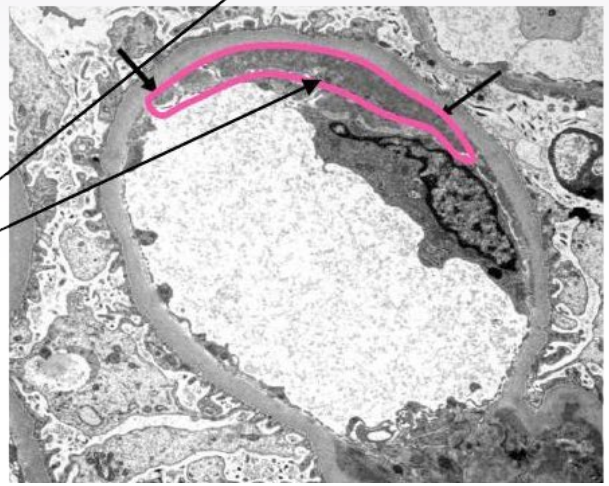
Immune Complex Deposits

Subepithelial deposits found in membranous disease

(Class V)







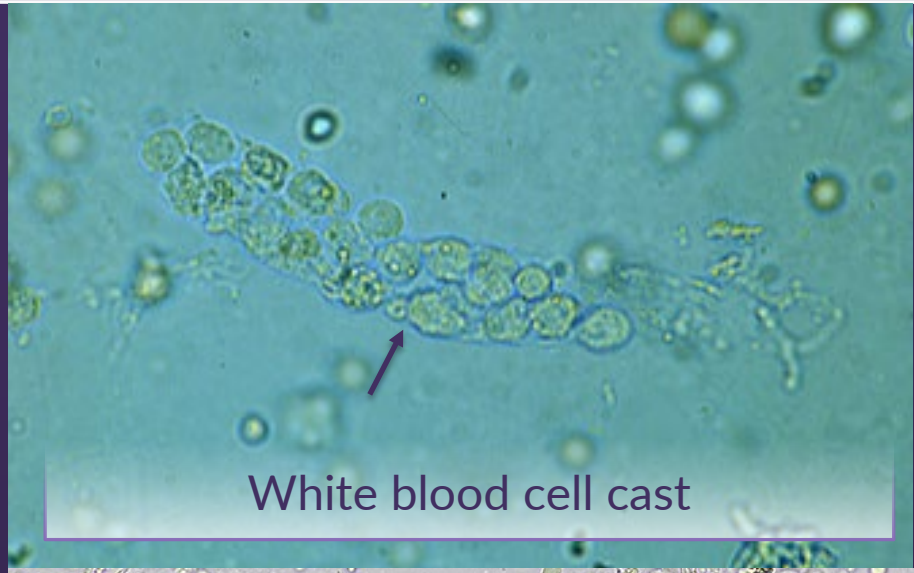
Subepithelial deposits found in prolifeative disease

(Class III/IV)

Image courtesy of the Rheumatology Image Bank

Diagnosis of Lupus Nephritis

- Proteinuria is
  - Measured by spot protein: creatinine ratio >500mg/mg or 24-hour collection >500mg (arbitrarily defined values)
- Active urinary sediment on urine microscopy
  - >5 WBCs or RBCs per high power field in the absence of infection or other causes
  - Cellular casts (white or red cells), less frequently seen than WBCs and RBCs
- Kidney biopsy is used routinely (unless strongly contraindicated) to classify disease type and severity and to direct management



White blood cell cast

Free red cells and a red cell cast that is tightly packed with red cells

Hahn BH, McMahon MA, Wilkinson A, et al. Arthritis Care Res. 2012;64(6):797-808.

Classes of Lupus Nephritis (LN)

LN Class*	Prognosis
I: Minimal mesangial • Deposits but normal light microscopy	Good
II: Mesangial proliferative	Good
III: Focal proliferative • <50% glomeruli involved	Severe
IV: Diffuse proliferative • ≥50% glomeruli involved	Severe
V: Membranous	Intermediate
VI: Advanced sclerosing • >90% sclerotic glomeruli	End-stage renal disease

*Patients can have mixed classes; for example, class IV/V (proliferative and membranous) lupus nephritis.

Hahn BH, et al. Arthritis Care Res. 2012;64(6):797-808. Markowitz GS, D'Agati VD. Kidney Int. 2007;71:491-495. Weening JJ, et al. Kidney Int. 2004;65:521-530.

Kidney Pathology

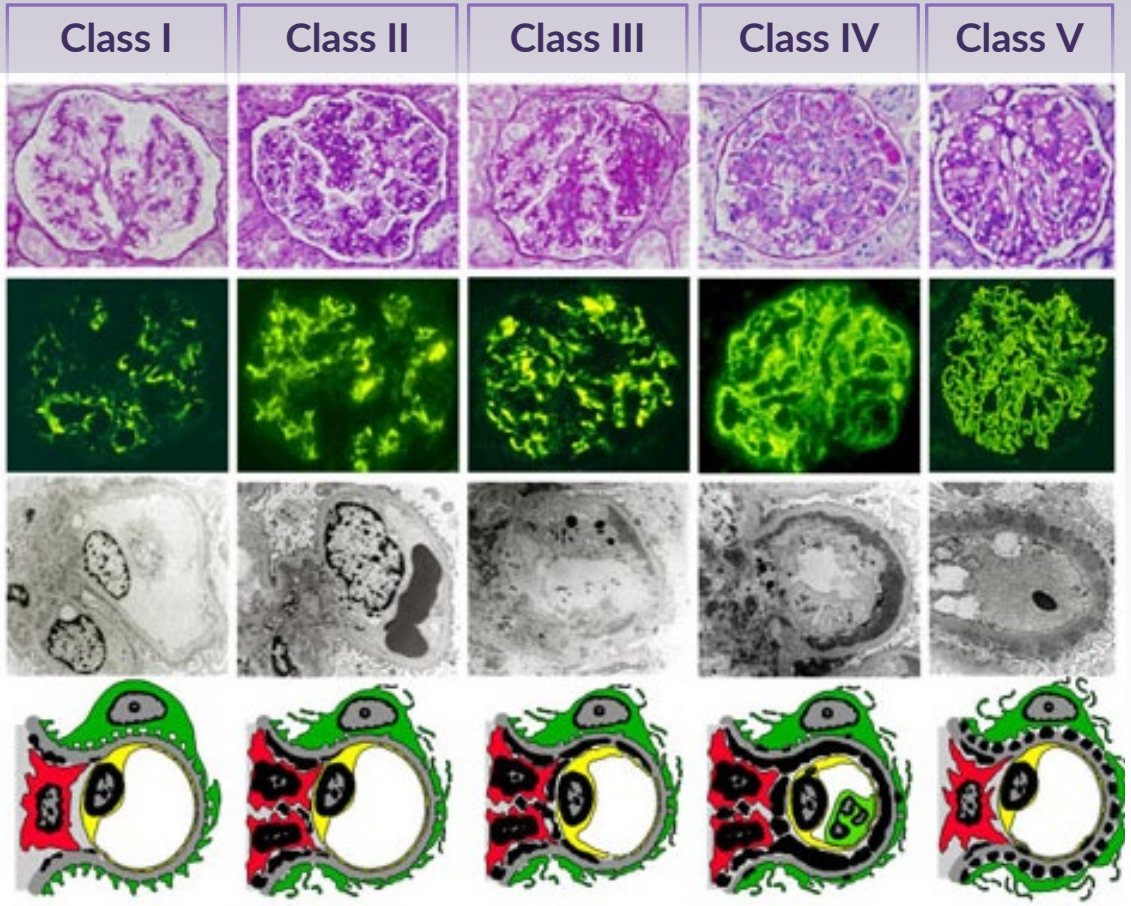


Image curtesy of https://unckidneycenter.org/kidneyhealthlibrary/glomerular-disease/lupus/

Janette JC, Olson, JL, Schwartz MM, Silva FG. In: Heptinstall's Pathology of the Kidney (6th Ed). Philadelphia, PA; Lippincott Williams & Wilkins; 2007.
Bajema IM, et al. Kidney Int. 2018;93(4):789

Treatment of Proliferative LN Class III/IV

- Initial – Intensive immunosuppression for 3-6 months to reduce inflammation by controlling immunologic causes of injury
- Cyclophosphamide or mycophenolate mofetil with steroids
- Generally, mycophenolate mofetil is preferred first choice, especially for Black and Hispanic patients, and patients who desire to preserve fertility
- Two new medications were FDA approved in 2021 to be used in combination with the above standard of care
  - Voclosporin (calcineurin inhibitor)
  - Belimumab (monoclonal antibody again BlyS (B lymphocyte stimulator protein)

Hahn BH, et al. Arthritis Care Res. 2012;64(6):797-808. Furie R, et al. N Engl J Med. 2020 Sept 17;383(12);1117-1128.
Rovin BH, et al. Lancet. 2021 May 29;397(10289):2070-2080.

Treatment of Proliferative LN Class III/IV (cont.)

- Subsequent therapy – longer period of less-intensive therapy to prevent flare
  - Mycophenolate mofetil is the current standard of care; azathioprine can be an alternative
  - Length of time needed is not well defined (at least 3 years)
- Adjunct therapy
  - Hydroxychloroquine
  - ACE inhibitors or ARBs
  - Control blood pressure to goal of ≤130/80 mm
  - Correct Vit D level to 40 ng/mL
  - Cholesterol lowering agents to treat dyslipidemia

Hahn BH, et al. Arthritis Care Res. 2012;64(6):797-808. Petri M, Bello KJ, Fang H, Magder LS. Arthritis Rheum. 2013 Jul;65(7):1865-71

Treatment of Pure Membranous LN Class V

- Adjunct treatment
  - ACE inhibitors and ARBs can decrease proteinuria
  - Hypercoagulability due to nephrotic range proteinuria requires anticoagulation on an individualized basis
  - Rigorous control of blood pressure
  - Aggressive treatment of dyslipidemia
- Immunosuppression (e.g., mycophenolate mofetil) and steroids are used for patients with nephrotic range proteinuria or progressive disease
- For mixed-type pathological process, treatment is tailored to the more aggressive type of process (Class III or IV–V)

Hahn BH, et al. Arthritis Care Res. 2012;64(6):797-808.

Limitations of Current Therapies

- Side effects and Toxicities including:
  - GI intolerance
  - Infections (especially in leukopenia patients)
  - Infertility (cyclophosphamide)
  - Malignancy – bladder (cyclophosphamide), cervical dysplasia
  - Multiple toxicities of long-term or high-dose steroid use
- Pill Burden
- Insufficient Efficacy
  - Remission rates ~50%
  - Relapse rates 30%–50% by 2–3 years

Costenbader KH, Desai A, Alarcón GS, et al. Arthritis Rheum. 2011;63(6):1681-1688.

Progression to End Stage Kidney Disease (ESKD)

- 10%–30% progress within 15 years
- Rate of ESKD in the United States due to SLE appears to be increasing (especially in younger age groups, Blacks, and the Southeast)
- Mortality rates from ESKD are stable
- 5-year mortality of children with ESKD is 22%
- Many disparities exist in access to treatment and kidney transplantation

Costenbader KH, Desai A, Alarcón GS, et al. Arthritis Rheum. 2011;63(6):1681-1688; Hiraki LT, Feldman CH, Liu J, et al. Arthritis Rheum. 2012;64(8):2669-2676. Hiraki LT, Lu B, Alexander SR, et al. Arthritis Rheum. 2011;63(7):1988-1997.

Risks for Developing ESKD

- Demographics
  - Younger age, Black race, male sex
  - Poverty
- Clinical features
  - Hypertension
  - Low complement
  - Abnormal kidney function at presentation
  - Delay in proteinuria improvement
- Delay in access to treatment or non-adherence to available treatment
- Failure to respond to treatment, or flare after remission

Franco C, Yoo W, Franco D, Xu Z. Bull NYU Hosp Jt Dis. 2010;68(4):251-256; Adler M, et al. Rheumatology (Oxford). 2006 Sep;45(9):1144-7.
Plantinga L, Lim SS, Patzer R, et al. Arthritis Care Res (Hoboken). 2016 Mar;67(3):357-65

Minimizing Future Complications of Lupus Nephritis

- Address factors that contribute to poor outcomes
  - Treat hypertension aggressively, consider use of ACEIs & ARBs
  - Address psychosocial factors and ensure medication adherence
  - Manage long-term atherosclerosis risks
- Prevent adverse effects of medications
  - Consider prophylaxis for infections, ensure appropriate vaccinations
  - Cancer screening as clinically indicated, e.g., yearly Pap smears
  - Consider interventions to prevent infertility & bladder toxicity from cyclophosphamide
  - Manage bone health
  - Minimize steroid use

Kim SC. Ann Rheum Dis. 2015 Jul:74(7):1360-1367.

Conclusions — Lupus Nephritis

- Nephritis is a common manifestation of SLE
- Proliferative nephritis (class III/IV) is the most common form
- Treatment of Class III, IV, or V LN involves initial therapy to achieve a renal response followed by subsequent treatment to sustain that response and prevent renal flare, while minimizing treatment toxicity
- Current therapies are limited and ESKD still ensues in 10%–30% of patients

Patient EM

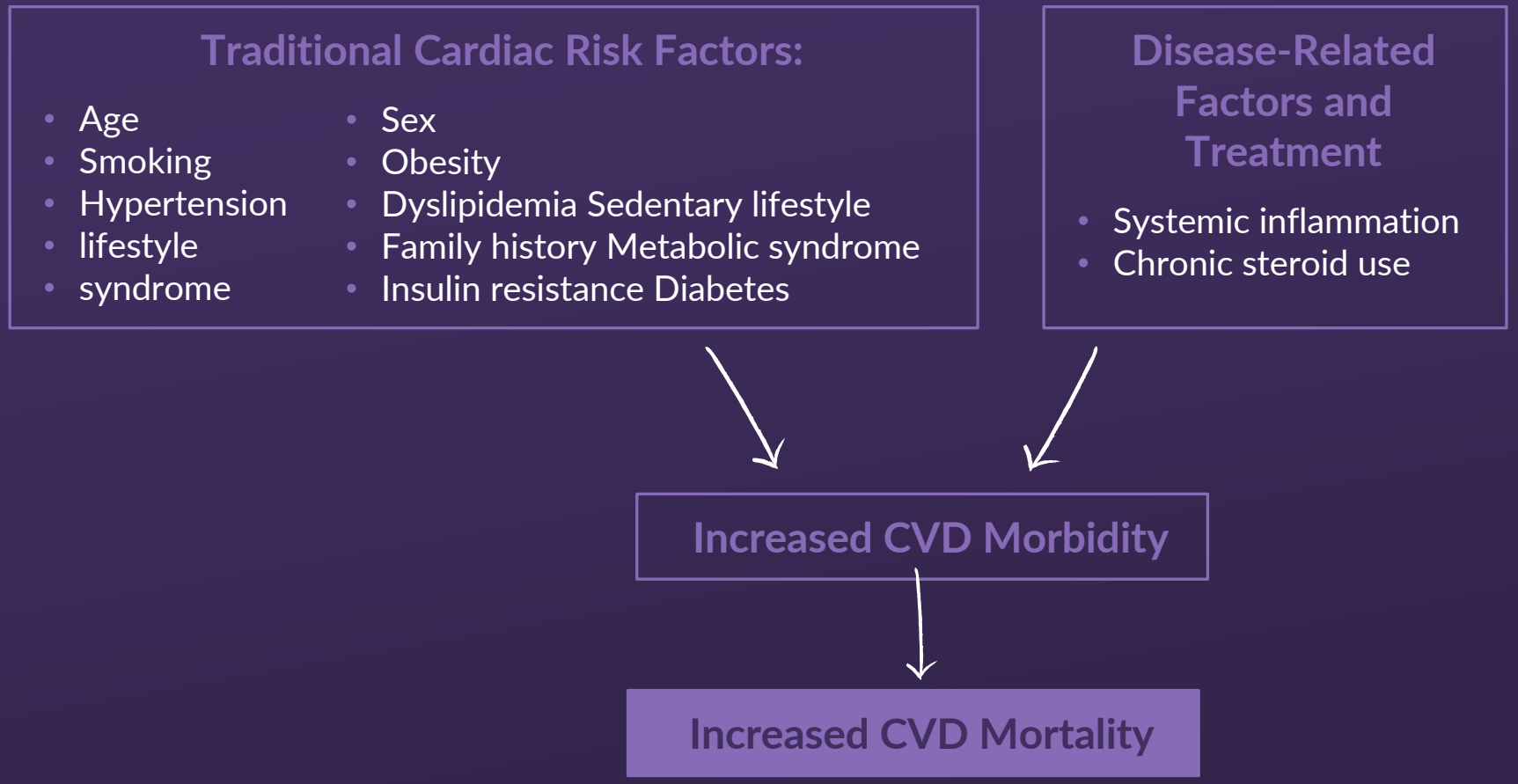
- EM responds to high-dose mycophenolate mofetil and prednisone. She is maintained on low-dose mycophenolate mofetil and 5 mg prednisone daily for 2 years, and is then switched to azathioprine as she wants to get pregnant
- She gains 50 pounds over this time, which she is unable to lose
- 2 subsequent lupus flares with inflammatory arthritis triggered by stress and sun-exposure are treated with moderate-dose prednisone. She is maintained on hydroxychloroquine and prednisone 7.5 mg daily
- She requires an ACE inhibitor for mild hypertension and at age 36 develops type 2 diabetes. Her HbA1C is always above normal
- At age 43 she presents to the ED with central chest pain on exertion and is found to have an inferior myocardial infarction

Premature Atherosclerosis and SLE

- Coronary artery disease (CAD) is a leading cause of mortality in SLE
- 5X higher risk of CAD, especially in younger patients
  - 7.5-17X higher 10-year risk for a coronary event or stroke
  - 50X higher rate of myocardial infarction in 35- to 44-year-old age group
  - 1st cardiac event occurs at ≤55 years old in more than 2/3 patients
- Pathology and clinical presentation are similar to that of general population, but outcomes are worse
- Women in general can present atypically

Elliott JR, Manzi S. Best Pract Res Clin Rheumatol. 2009;23(4):481-494. McMahon M, Hahn BH. Curr Opin Immunol. 2007;19(60):633-639.

Causes of Cardiovascular Disease Burden in SLE



Adapted from: Symmons DP, Gabriel SE. Nat Rev Rheumatol. 2011;7(7):399-408.

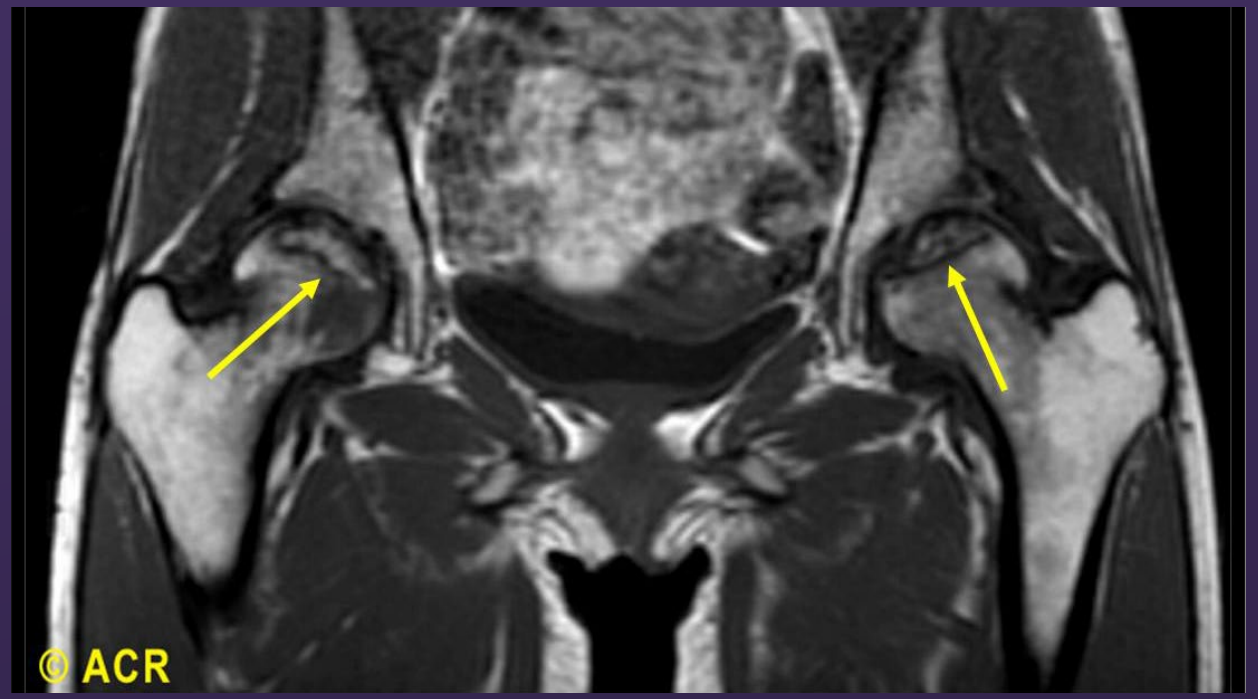
Atherosclerosis Evaluation and Management in SLE

- Traditional cardiovascular disease risk calculators will underestimate the risk for SLE patients
- Have a high index for suspicion and obtain EKG and stress test when indicated based on clinical history and exam
- Assess and aggressively control modifiable cardiovascular risk factors, including obesity, smoking, hyperlipidemia, and hypertension
- Control inflammation while minimize steroid use

Haque S, Gordon C, Isenberg D, et al. J Rheumatol. 2010;37:322-329.

Bone Health in SLE - Osteonecrosis

- Osteonecrosis, or avascular necrosis, is a major cause of morbidity in some SLE patients and often requires surgical intervention
  - Frequently affects large joints including knees, hips, and shoulders
  - Risk factors include smoking, alcohol, trauma, and use of steroids
  - Diagnosis confirmed on imaging studies (X-Ray or MRI)



Coronal T1-weighted MRI shows typical lines of low signal (arrows) bordering the areas of avascular necrosis. MRI is more sensitive than plain radiographs in picking up the changes of osteonecrosis. Note crescent sign.

Gladman DD, Chaudhry-Ahluwalia V, Ibanez D, et al. J Rheumatol. 2001;28(10):2226-2229; Grossman JM, Gordon R, Ranganath VK, et al.Arthritis Care Res. 2010;62(11):1515-1526;

Bone Health in SLE - Osteoporosis

- Osteoporosis is much more common in SLE, especially in pre-menopausal women.
- Women with SLE ~ 5X more likely to experience a fragility fracture than those without SLE
- Likely contributors to this increased risk include:
  - Glucocorticoid use
  - Sun avoidance (contributing to vitamin D deficiency)
  - Disease-related mechanisms , e.g., chronic inflammation, kidney disease

Ramsey-Goldman R, Dunn JE, Huang CF, et al. Arthritis Rheum. 1999;42(5):882-890.

Bone Health in SLE – Osteoporosis Prevention and Management

- Ensure adequate calcium and vitamin D intake
- Encourage regular exercise, particularly weight-bearing
- Encourage calcium intake through diet
- Avoid smoking and heavy drinking, both worsen bone loss
- Assess risk with bone densitometry (DXA) and/or fracture risk assessment tools (FRAX) according to National Osteoporosis Foundation guidelines
- Treat with medications, such as bisphosphonates, when indicated and appropriate

Grossman J, Gordon R, Ranganath VK, et al. Arthritis Care Res. 2010;62(11):1515-1526.

Increased Malignancy Risk With SLE

- Growing amount of research show increased incidence of several types of cancers in SLE
- Regular age-appropriate cancer screening is recommended
- Additionally, consider HPV vaccination and yearly Pap smears given increased risk for cervical cancer

*Red indicates increased risk, and green indicates reduced risk

CI = confidence interval

Cancer Type	HR*	90% CI*
All	1.28	1.16-1.42
Non-Hodgkin Lymphoma	4.93	3.81-6.36
Hodgkin's Lymphoma	2.6	2.14-3.17
Multiple Myeloma	1.48	1.02-2.14
Leukemia	2.01	1.64-2.47
Breast	0.89	0.77-1.04
Ovary	0.92	0.74-1.13
Cervix	1.56	1.29-1.88
Vagina/vulva	3.48	2.69-4.50
Uterus	0.7	0.46-1.07
Lung	1.62	1.40-1.87
Hepatobiliary	2.37	1.67-3.38
Pancreatic	1.24	0.97-1.60
Esophagus	1.64	1.43-1.87
Gastric	1.31	1.04-1.63
Colorectal	0.97	0.85-1.09
Thyroid	1.8	1.46-2.23
Renal	2.1	1.11-3.96
Bladder	1.86	1.16-2.99
Prostate	0.78	0.70-0.88
Melanoma	0.72	0.56-0.93
Brain	1.08	0.64-1.81

Song L. et al. Arthritis Research & Therapy 2018 20:270.

Infections and SLE

- Infections are a major cause of hospitalizations and death
  - Higher risk for severe infections (3X), tuberculosis (6.1X), pneumonia (2.6X), herpes zoster (2.5X)
  - Factors that increase infection is:
  - Active disease
  - Immunosuppressive therapies
  - Leukopenia/lymphopenia, low complement
  - Factors that decrease infection is:
  - Prevention
  - Vaccinations (e.g., influenza, pneumococcal, no live vaccines)
  - Screening for tuberculosis, hepatitis
  - Pneumocystis pneumonia prophylaxis for patients on more intensive immunosuppressive therapies

Bernatsky S, Boivin JF, Joseph L, et al. Arthritis Rheum. 2006;54(8):2550-2557. Ginzler E, Dvorkina O. In: Wallace DJ, Hahn B. Dubois' Lupus Erythematosus (7th Ed). Philadelphia, PA: Walters Kluwer Health: Lippincott Williams & Wilkins; 2007:901-910. Sacks JJ, Helmick CG, Langmaid G, Sniezek JE. MMWR Morb Mortal Wkly Rep. 2002;51(17):371-374. Staples PJ, Gerding DN, Decker JL, Gordon RS. Arthritis Rheum. 1974;17(1):1-10. Pego-Reigosa JM, et al. Rheumatology (Oxford). 2021;60:60-72.

Hematologic Manifestations in SLE-Anemia

- Anemia is very common in SLE and is often multifactorial.
- Most common causes:
  - Anemia of chronic inflammatory disease
  - Anemia associated with kidney disease (low erythropoietin)
  - Iron deficiency
  - Side effect of medications
  - Hemolytic anemia (an ACR classification criteria)

Bertoli AM, Vila LM, Apte M, et al. Rheumatology. 2007;46:1471-1476. Kao AH, Manzi S, Ramsey-Goldman R. Lupus. 2004;13(11):865-868.

Hematologic Manifestations in SLE—Leukopenia and Lymphopenia

- Leukopenia (<4000 cells/µL)
  - Usually, an element of neutropenia (neutropenia is less common than lymphopenia)
  - Prevalence of up to 50% sometime during course
- Lymphopenia (<1500 cells/µL)
  - May be present in absence of leukopenia
  - Prevalence of up to 60%–70% sometime during course
- Can be due to active SLE or medication side effect

Kao AH, Manzi S, Ramsey-Goldman R. Lupus. 2004;13(11):865-868.

Hematologic Manifestations in SLE—Thrombocytopenia

- Thrombocytopenia (<100,000 platelets/µL) is seen in 10%–25% of patients but <10% is severe (<50,000 platelets/µL)
- Causes
  - From lupus
    - Antiplatelet antibodies
    - Antiphospholipid antibodies
    - Thrombotic microangiopathy syndromes
  - From complications
    - Drug-induced bone marrow suppression
    - Infection
- Treatment of hematologic manifestations depends upon identifying cause and assessing severity

Levine AB, Erkan D. Curr Rheumatol Rep. 2011;13:291-299.

Patient EM—What Could We Have Done Better?

- Education and attention to psychosocial factors
  - Advise sun protection: year-round use of SPF-45 or higher, clothing that is UV impenetrable and avoidance of UV exposure when possible
  - Encourage weight loss and exercise
  - Encourage adherence with clinic visits and medications
- Monitor for early detection of flares
- Minimize steroid use
- Treat cardiac risk factors aggressively

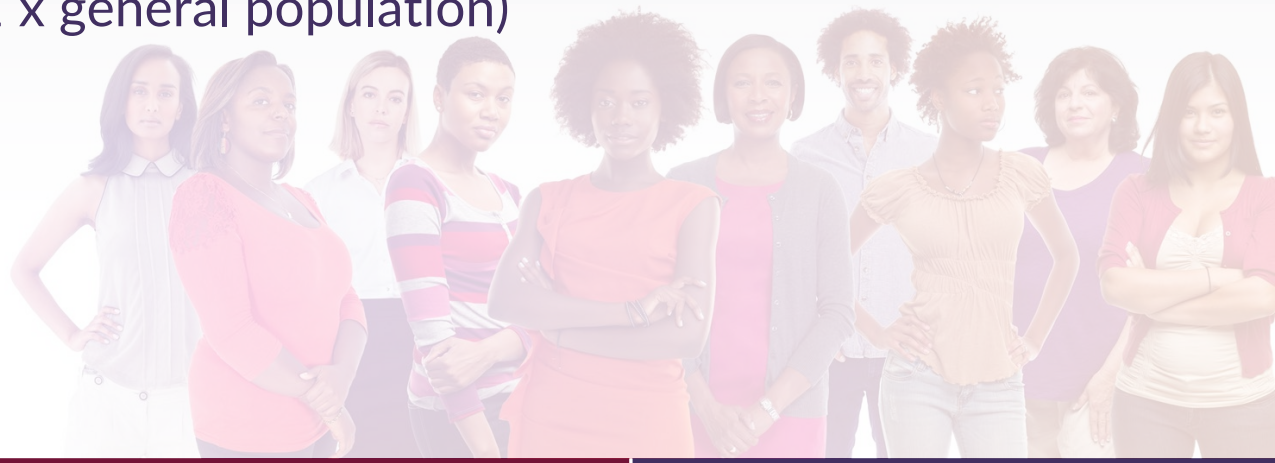
Additional Ways to Reduce Adverse Events in SLE

- Prevent infection through vaccinations
- Monitor bone health
- Regular routine Cancer screening, yearly pap smears
- Hydroxychloroquine used as a background therapy
  - Reduce mortality
  - Reduces SLE flares and SLE organ damage accrual
  - Decrease incidence of diabetes
  - Antithrombotic effects
  - Favorable lipid effects

Broder A, Putterman C. J Rheumatol. 2013;40(1):30-33. Tang C, Godfrey T, Stawell R, Nikpour M. Intern Med J. 2012 Sep;42(9):968-78.

Mortality Rate in SLE is 2-3X Higher than General Population

- Death rates have decreased by 60% in the United States since the 1970s, especially for infections and renal disease
- Risks of death increased in females, Blacks, and younger-onset patients
- Most common causes of death in SLE patients in the United States:
  - Heart disease and stroke (1.7 x general population)
  - Hematologic malignancies and lung cancer (2.1 x general population)
  - Infections (5 x general population)
  - Kidney disease (7.9 x general population)



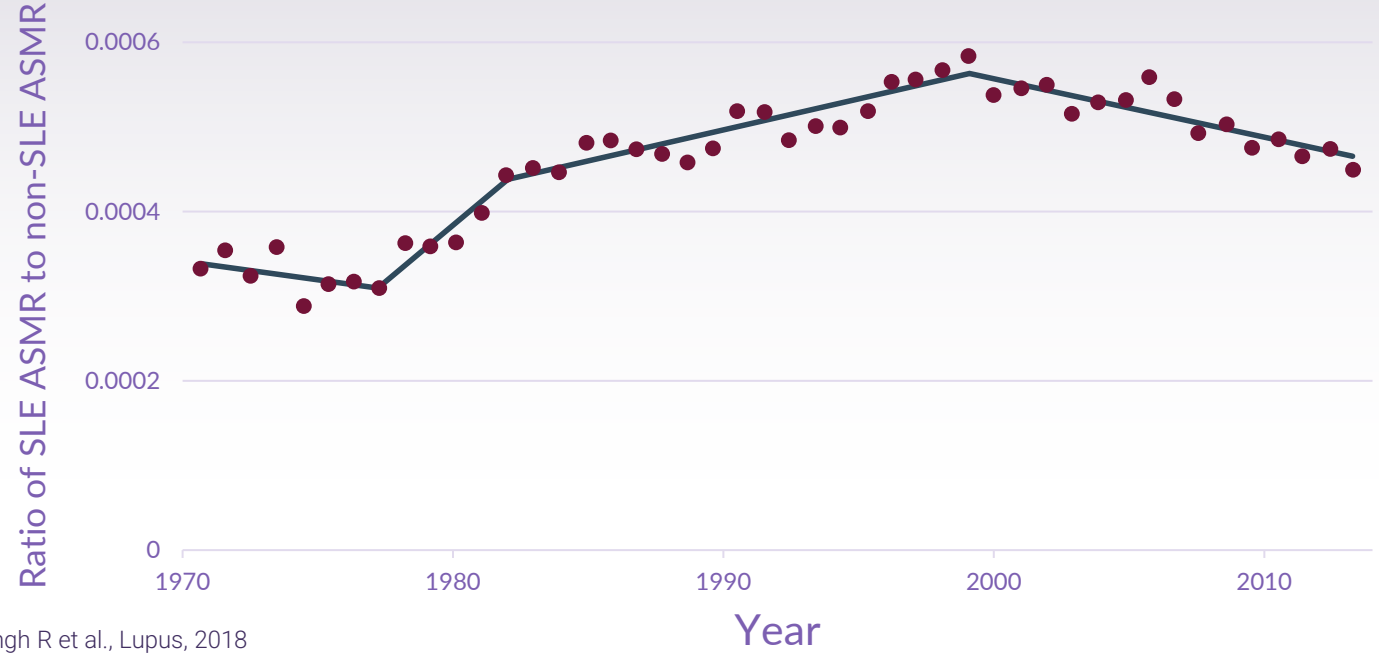
Bernatsky S, Boivin JF, Joseph L, et al. *Arthritis Rheum*. 2006;54(8):2550-2557.

SLE Mortality

Marked improvement in SLE survival over time.

1940's: 50% survival within three years after diagnosis.

1980's: 90% survival ten years after diagnosis.

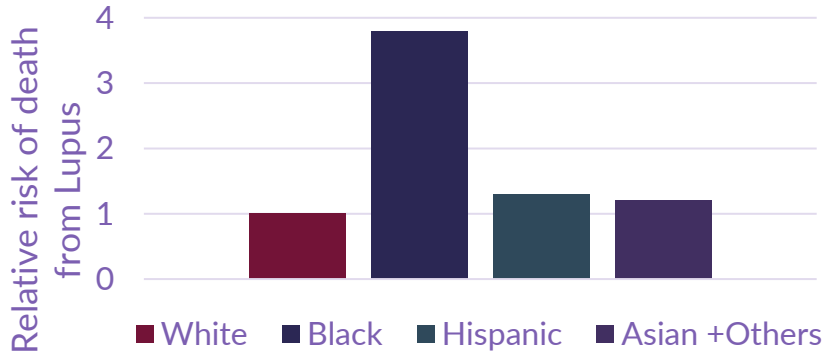


Singh R et al., Lupus, 2018

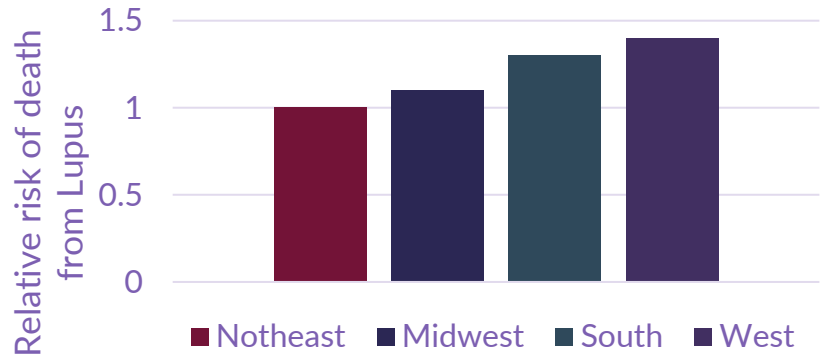
Yen E et al., Ann Intern Med, 2017

Racial/ethnic disparity in mortality.

By race/ethnicity



By place of residence



Conclusions—Mortality and Morbidity in SLE

- Morbidity and mortality in SLE are related to:
  - Active disease
  - Infectious consequences of chronic immunosuppressive therapy
  - Medication toxicities
  - Long-term sequelae of inflammation
- Each of these needs to be addressed proactively to achieve optimal long-term outcomes for individual patients

American College of Rheumatology
Empowering Rheumatology Professionals

the lupus initiative
Eliminating Health Disparities in Lupus

Visit: https://thelupusinitiative.org/

The project described is, in part, supported by the Centers for Disease Control and Prevention under Cooperative Agreement Number NU58 DP006138. Its contents are solely the responsibility of its developers/authors. Points of view or opinions do not, therefore, necessarily represent official views of the Centers for Disease Control and Prevention or the Department of Health and Human Services