The Office of Lifelong Learning, the Division of Rheumatology & the Physician Learning Program

Rheumatology Revealed 2.0: Advanced Insights and Evolving Best Practices for Family Physicians | Pearls for practice

Navigating Lupus: The Latest in Diagnosis, Management, and When to Refer

Dr. Stephanie Keeling

Introduction

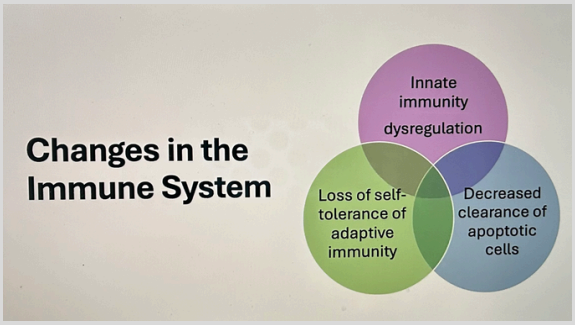
- Who gets Systemic Lupus Erythematosus (SLE)?
  - Women of child-bearing age
  - Most common age: 15-44 years old
  - Men, children, teenagers, elderly
  - Male gender associated with higher level of disease activity at the time of diagnosis independent of age, race, ethnicitiy
  - Increased mortality in men than women in retrospective cohort
    - 20-39 yo – lupus causes death
    - > 40 yo – cardiovascular disease and malignancy

- Environmental
  - Infection: viruses (EBV), Mycobacterial, Trypanosomiasis
  - Ultraviolet light:
    - Interfere with antigen processing
    - Activate macrophages
    - Decrease T-cell methylation
    - Promote auto reactivity
  - Medications: Antibiotics
  - Silica Dust:
    - Cleaning powders
    - Soil, Pottery materials, Cement
    - Cigarette smoke (dose–response association between the number of cigarettes smoked per year and the development of SLE50.

- Genetics
  - Different lupus genes confer risk for diverse manifestations
    - Twin concordance: Monozygotic (24-58%) vs dizygotic (2-5%)
    - Autoantibodies show familial aggregation
    - Genome wide association studies (GWAS)
      - European
      - Asian
      - African American study underway

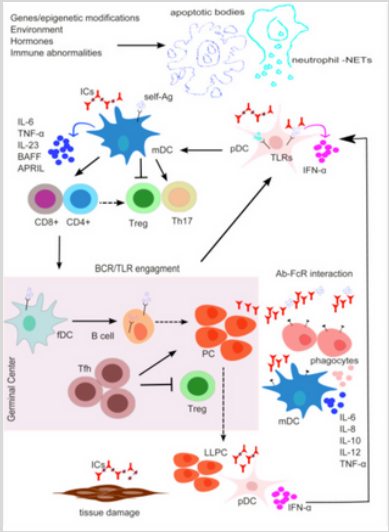
- Lupus in Canada
  - 1 in 1000 Canadians affected
  - Incidence is 3 per 100 000person-years (2003)
  - Prevalence:
    - 32.8 per 100 000 persons (2003)(Quebec)
    - 27.3 per 10 000 females
    - 3.2 cases per 10 000 males
    - 2x more prevalent in First Nations females >45 yo

Etiology



- Hormonal Factors
  - Estrogens, Testosterone, Progesterone, Prolactin
  - Thyroid hormone
  - Hypothalamus-pituitary-adrenal axis

Pathogenesis & pathophysiology



Concetta Ferretti, Antonio La Cava, Chapter 8 - Overview of the Pathogenesis of Systemic Lupus Erythematosus 2016, P 55-62

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IEULAR/ACR Classification Criteria for SLE

Additional criteria items within the same domain will not be counted.

***Note: In an assay with at least 90% specificity against relevant disease controls.**

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	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		

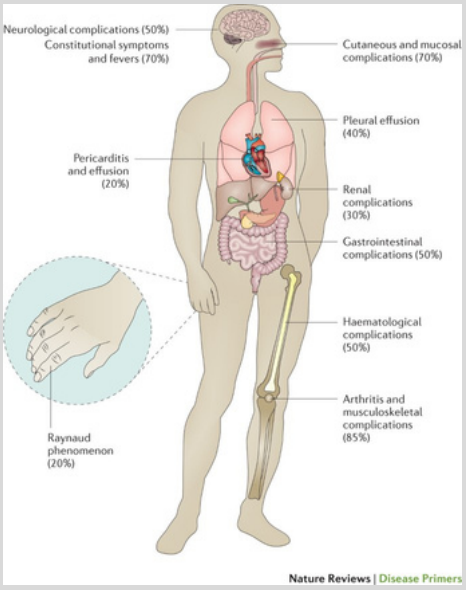
Total score:

↓

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

Martin Aringer et al. Ann Rheum Dis 2019;78:1151-1159

Clinical Manifestations



Kaul, A.,et al. Systemic lupus erythematosus. Nat Rev Dis Primers 2, 16039 (2016). https://doi.org/10.1038/nrdp.2016.39

Labs for disease diagnosis and activity

- **Baseline (not ongoing):**
  - **Antinuclear antibodies (ANA), extractable nuclear antigens (ENA), Lupus anticoagulant, anticardiolipin, Beta2 glycoprotein-1**
- **Baseline & ongoing: (frequency depends on disease severity)**
  - **C-reactive protein**
  - **CBC and differential**
  - **Renal function (Creatinine, urinalysis, spot urine protein:creatinine ratio)**
  - **Double stranded DNA**
  - **Complements (C3, C4)**
  - **Creatine kinase (CK) (sometimes)**

Extractable Nuclear Antigens (ENA) profile

Autoantibody	Disease Associations
Anti-ds DNA	SLE
Chromatin	Drug-induced SLE, SLE
Ribosomal P	
Sm (Smith)	SLE
SmRNP	SLE
RNP 68	MCTD
RNP A	MCTD
SS-A/Ro-52 Trim21	Sjogren's Syndrome, SLE
SSA/Ro-60	Sjogren's Syndrome, SLE
SS-B/La	Sjogren's Syndrome, SLE
Centromere B	Scleroderma CREST variant
Scl-70	Scleroderma
Jo-1	Myositis

ENA's & dsDNA: How helpful are they?

- **Clinically quiet, serologically active lupus:**
  - **Low C3, c4, positive ds DNA but no clinically active disease**
- **Positive dsDNA, anti-Smith is very specific for Lupus**
- **Some patients have lupus with no positive ENAs or dsDNA but they have + ANA and meet criteria with their other manifestations**
- **ENA's not used over time as disease activity marker**

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Diagnosis and referral

- Early presentations of lupus can be non-specific & take time
- Positive ANA's can be associated with other conditions
- Joint pain can be more diffuse and caused by other mechanisms
- Beyond the serologies, consider referrals if you see:
  - Low C3, C4
  - Cytopenias (eg. lymphopenia)
  - Abnormal urinalysis, renal function
  - Abnormal nailfold changes

Goals of treatment

Important Considerations

- Mortality in Lupus patients:
  - 1st few years: Infection, CNS or renal lupus
  - > 2 years: Cardiovascular disease
- Always consider the disease activity and disease damage and medication toxicity
- Pregnancy: consider when prolonged period of low disease activity state and no teratogenic medications

- Supportive treatment with:
  - Sunblock
  - Calcium channel blockers
  - Bone protection (from osteoporosis)
  - Cardiovascular risk reduction
  - Dyslipidemia
  - Hypertension treatment
  - Smoking cessation
  - Physical activity, exercise
- Age and gender appropriate malignancy screening

Treatment options for Lupus

ALL PATIENTS	MILD TO MODERATE DISEASE ACTIVITY	MODERATE TO SEVERE DISEASE ACTIVITY
Antimalarials (eg. hydroxychloroquine)	Topical or systemic corticosteroids	Systemic corticosteroids
*unless contraindicated	Methotrexate	Mycophenolate mofetil
	Azathioprine	Cyclophosphamide
		Rituximab
		Belimumab
		Anifrolumab

Steroids: the love-hate relationship

- Glucocorticoids (GCs)
  - Intravenous, oral, intramuscular, intra-articular
  - Treatment for organ-threatening lupus flares

- Hopkins Lupus Cohort:
  - Dose-response relationship between prednisone & risk of new organ damage
  - Reduction of 1 mg/day or more in mean prednisone dose reduces the risk for future organ damage by 3%

Sawah et al. 2015

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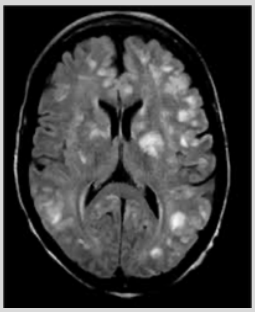
Neuropsychiatric Lupus

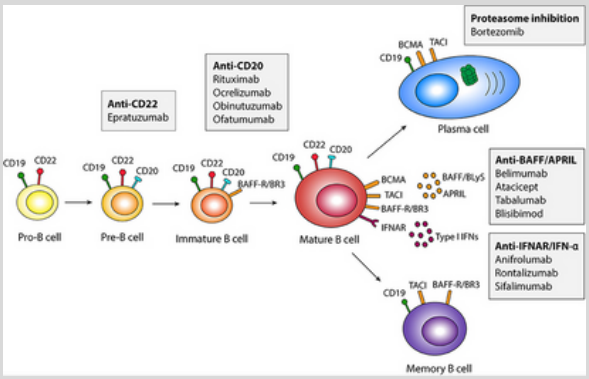


- Possible manifestations:
  - CNS, Peripheral nervous system, transverse mielitis, mononeuritis multiplex
- Initial treatment (s):
  - Glucocorticoids (systemic) iv or oral prednisone
  - Steroid sparing agents: Mycophenolate mofetil, cyclophosphamide, rituximab

Lupus Nephritis

ACR Lupus Nephritis Guidelines

Biologics in Lupus



- Rituximab:
  - Off label
  - Helpful for:
    - Cytopenias-ITP, hemolyticanemia
    - Arthritis (especially if erosive, deforming, overlap syndromes
    - Rashes
    - Interstitial lung disease
    - Inflammatory Myositis
    - Class 4 Nephritis in fail first line can be added to MMF
  - May be covered by 3rd party insurances
- Benlysta (Belimumab):
  - Works well when seropositive (+ENA, +dsDNA), joints, skin, cytopenias, lupus nephritis
  - Slow acting- minimum of 6 months and up to a year to evaluate benefits
  - Covered by some 3rd party insurances

Biologics in Lupus. cont

- Saphnelo (Anifrolumab)
  - Type 1 interferon receptor antagonist
  - Prevents signaling by all type 1 interferons
  - MUSE study (Phase 2b) & Tulip phase 3 trials
  - Significant reduction in SLE activity
  - iv medication every 4 weeks
  - Improvement in mucocutaneous and MSK domains at week 52 vs placebo
  - Herpes zoster higher in anifrolumab group

Furie et al 2017; Morand et al 2020