Systemic Lupus Erythematosus Overview

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Definition

• An autoimmune disease characterized by:
  • Systemic inflammatory response in many organ systems
  • Dysregulated autoimmune response involving many arms of the immune system including T cells, B cells and macrophages
Autoantibodies in SLE: Anti-Nuclear Antibodies (ANA)

- Sensitive but not specific for SLE
  - Seen in many inflammatory, infectious, and neoplastic diseases
  - Seen in 5% to 15% of normal persons
  - Its usefulness increases with high pretest probability

Incidence of Positive ANA

- Normal subjects 3-4%
- SLE 95-99%
- Drug-Induced Lupus 100%
- Discoid Lupus 30-40%
- Sub-acute cutaneous lupus 60-80%
- Incidence increases with age, chronic infections and other chronic conditions
### Autoantibodies in SLE: Anti-ds DNA

- Seen in 60% of patients with SLE
- Highly specific for SLE but not diagnostic
- Strongest clinical association is with nephritis
- Titer tends to fluctuate with disease activity
- Methods vary
  - Crithidia IFA - relatively specific
  - ELISA - higher false positives

### Anti Extractable Nuclear Antigen (Anti-ENA)

- Panel of antibodies that includes anti-RNP, anti-Sm, anti-SSA and anti-SSB
  - Anti ribonucleoprotein antibody (Anti RNP)
    - Found in mixed connective tissue disease and in low titers in a variety of other autoimmune diseases
  - Anti Smith antibody (Anti Sm)
    - Seen in 10% to 30% of SLE patients
    - Highly specific for SLE not diagnostic
Anti-ENA

- Anti-SSA
  - Incidence: SLE (25-57%) Also found in patients with Sjogren’s
  - In SLE, anti-SSA are often associated with a photosensitive skin rash
  - Not uncommonly found in healthy subjects
- Anti-SSB
  - Incidence: SLE (15-30%). Also found in patients with Sjogren’s

Epidemiology

- Etiology is unknown
- More common in Females (7:1-15:1)
- Both geography and race affect the prevalence of SLE
  - More common in urban areas
  - In the US prevalence ranges from:
    - 106 white women per 100,000 women
    - 406 African American women per 100,000 women
- Peak age of onset between 15-40
Genetics

- High concordance rate in monozygotic twins
  - 14-57%
- First degree relatives have a 17-fold increase risk of SLE compared to the general population
- 27% of children who have mothers with SLE will have ANA positivity
- Multiple polymorphisms have been identified
  - Deficiency of complement components (C1q, C2, C4 a/b)
  - Mutated TREX 1 gene

Diagnosis of SLE
Diagnosis

• A diagnosis of SLE should be based on the patient’s symptoms and physical exam
  • A diagnosis of SLE is confirmed by laboratory tests
• Many versions of SLE criteria have been proposed:
  • 1997 ACR Criteria
  • 2012 SLICC Criteria: incorporates clinical features not included in the ACR criteria
  • 2015 Combined ACR/SLICC criteria to maximize positive predictive values
  • Most developed as clinical research tools for epidemiologic studies but not for diagnosis
### 1997 ACR Criteria for Identifying SLE

<table>
<thead>
<tr>
<th>Skin Criteria</th>
<th>Systemic Criteria</th>
<th>Laboratory Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Butterfly rash</td>
<td>➢ Arthritis (≥2 joints)</td>
<td>➢ Hematologic disorders</td>
</tr>
<tr>
<td>• Rash over cheeks</td>
<td>➢ Serositis</td>
<td>➢ Immunologic tests</td>
</tr>
<tr>
<td>• Sparing nasolabial folds</td>
<td>➢ Kidney involvement</td>
<td>➢ Anti-Sm</td>
</tr>
<tr>
<td>• Discoid Rash</td>
<td>➢ Abnormal urine sediment +/-</td>
<td>➢ Anti-DSDNA</td>
</tr>
<tr>
<td>• Scarring rash</td>
<td>proteinuria</td>
<td>➢ False positive for syphilis</td>
</tr>
<tr>
<td>• Sun sensitivity</td>
<td>➢ Neurologic</td>
<td>➢ ANA positive</td>
</tr>
<tr>
<td>• Oral ulcerations</td>
<td>➢ Seizures, psychosis</td>
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</tr>
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</table>

At least 4 out of 11 criteria needed for diagnosis

### SLICC: Systemic Lupus International Collaborating Clinics Classification Criteria for SLE

<table>
<thead>
<tr>
<th>Clinical Criteria</th>
<th>Immunologic Criteria</th>
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<tr>
<td>• Acute cutaneous lupus</td>
<td>• Positive ANA</td>
</tr>
<tr>
<td>• i.e. Malar rash</td>
<td>• Positive Anti-ds DNA</td>
</tr>
<tr>
<td>• Chronic cutaneous lupus</td>
<td>• Positive Anti-Sm</td>
</tr>
<tr>
<td>• i.e. Discoid rash</td>
<td>• Positive APS labs</td>
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<tr>
<td>• Oral or nasal ulcers</td>
<td>• Lupus anticoagulant</td>
</tr>
<tr>
<td>• Non-scarring alopecia</td>
<td>• Anti-cardiolipin</td>
</tr>
<tr>
<td>• Arthritis</td>
<td>• Anti-beta2glycoprotein</td>
</tr>
<tr>
<td>• Serositis</td>
<td>• Low complements</td>
</tr>
<tr>
<td>• Neurological involvement</td>
<td>• Positive direct coombs</td>
</tr>
<tr>
<td>• Renal involvement</td>
<td>• Without presence of hemolytic anemia</td>
</tr>
<tr>
<td>• Hemolytic anemia</td>
<td></td>
</tr>
<tr>
<td>• Leukopenia (WBC &lt; 4000)</td>
<td></td>
</tr>
<tr>
<td>• Thrombocytopenia (WBC &lt; 100,000)</td>
<td></td>
</tr>
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<td>• Positive ANA</td>
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### SLICC: Systemic Lupus International Collaborating Clinics Classification Criteria for SLE

- ≥4 criteria needed for SLE diagnosis
  - At least 1 clinical and 1 laboratory criteria
  - Biopsy proven lupus nephritis with:
    - Positive ANA or positive anti-dsDNA

### Revised 2015 Criteria for diagnosis of SLE

- Revised 2015 Criteria endorsed by the ACR
- Combines 1997 criteria and SLICC criteria
- 4 out of 16 points, definite SLE
- 3 out of 16 points, probable SLE
Revised 2015 ACR/SLICC Combined Criteria for Diagnosis SLE

SKIN MANIFESTATIONS
- Acute/sub-acute lupus rash:
  - up to 2 points
  - Malar Rash: 2 points
  - Subacute SLE rash: 1 point
  - Palpable purpura/Urticaria: 1 point
  - Photosensitivity: 1 point
- Discoid lupus: 1 point
- Non scarring alopecia: 1 point
- Oral ulcers: 1 point

Revised 2015 ACR/SLICC Combined Criteria for Diagnosis SLE

ORGAN INVOLVEMENT
- Joint disease: 1 point
- Serositis: 1 point
  - Pleurisy
  - Pericarditis
- Neurological involvement: 1 point
  - Seizure
  - Acute psychosis
  - Acute confusion
- Kidney involvement: up to 2 points
  - Biopsy proven SLE: 2 points
  - Proteinuria >3+ grams or > 500mg/day: 1 point
  - Urinary casts: 1 point
Revised 2015 ACR/SLICC Combined Criteria for Diagnosis SLE

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<th>Hematologic Tests: up to 3 points</th>
<th>Serologic Tests: up to 3 points</th>
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<td>• Hemolytic anemia: 1 point</td>
<td>• Low titer ANA: 1 point</td>
</tr>
<tr>
<td>• Thrombocytopenia: 1 point</td>
<td>• High titer ANA: 2 points</td>
</tr>
<tr>
<td>• &lt;100,000</td>
<td>• Positive Anti-dsDNA: 2 points</td>
</tr>
<tr>
<td>• WBC count &lt; 4000 mm³ with &lt; 1500 lymphocyte count: 1 point</td>
<td>• Positive Anti-SM: 2 points</td>
</tr>
<tr>
<td></td>
<td>• Positive Antiphospholipid antibodies: 1 point</td>
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Drug-induced lupus: definite drug associations

- Hydralazine
- Procainamide
- Minocycline
- Chlorpromazine
- Isoniazid
- Penicillamine
- Methyldopa
- Interferon-alpha
Systemic Lupus Erythematosus Overview

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Treatment Principles

• Goals:
  • To control and reverse ongoing inflammation
  • To limit irreversible end-organ damage
  • Tailor therapy based on extent of the disease and the specific organ(s) involved

• Potential toxicities of immunosuppressive drugs require vigilance

• Biologic therapies are very promising because of the possibility of targeting pathogenic mechanisms
Treatment Principles

- Induction therapy
  - The initial treatment that is administered to a patient with moderate-severe disease activity with the intention of rapidly suppressing the inflammatory process
  - Can be associated with significant toxicity
  - Short duration (months)
- Maintenances
  - Used to prolong the remission using drugs that have a lower toxicity profile

Current Approved Therapeutic Options

- Corticosteroids
  - Rapid action in most patients
  - Common adverse events
- Hydroxychloroquine
  - Useful for almost all lupus patients
  - Rare adverse events but requires periodic monitoring
- Belimumab
  - A biologic agent: the only one approved in lupus
  - Targets B cells
  - Modest effect in some patients
**Current Unapproved Therapy: Induction Therapy**

- **Mycophenolate mofetil**
  - Used for moderate/severe disease
  - Lower adverse event risk profile than cyclophosphamide
- **Cyclophosphamide**
  - Important drug used for life threatening and severe disease
  - Significant short term and long term adverse events
  - Toxicity depends on multiple factors: route, accumulative dose
- **Tacrolimus**
  - Used for moderate/severe disease
  - Lower adverse event risk profile than cyclophosphamide

**Current Unapproved Therapy**

- **Methotrexate**
  - Used especially for the inflammatory arthritis and skin disease
  - Not in renal disease
- **Azathioprine**
  - Moderate disease
  - During pregnancy for moderate/severe disease
  - Maintenance of remission after induction therapy
- **Mycophenolate mofetil**
  - Used for moderate to life threatening/severe disease
  - Contraindicated in pregnancy
  - Maintenance of remission after induction therapy
## Current Therapy: Limitations

In addition to drug specific toxicity, immunosuppressive drugs share the following to varying degrees:

- Increased risk of infection
- Increased risk of cancer
- Infertility
- Hematologic abnormalities
- Osteopenia

## Current Therapy: Limitations

- Side effects of corticosteroids include:
  - Diabetes
  - Cushingoid appearance
  - Osteoporosis
  - Osteonecrosis
  - Weight gain
### Guiding Therapeutic Principles

- Use therapeutic combinations aimed at induction of remission, maintenance of remission, and supportive care
- Titrate to smallest possible dose to achieve the desired effect with least toxicity
- Strategic use of preventive therapies; antibiotics, vaccinations

### Comorbidities of SLE
Atherosclerosis in patients with autoimmune disorders

- The risk of Cardiovascular disease (CVD) is very high in a prototypic autoimmune disease, systemic lupus erythematosus (SLE), and is also raised in other autoimmune diseases such as rheumatoid arthritis.
- A combination of traditional and nontraditional risk factors, including dyslipidemia (and to a varying degree, hypertension, diabetes, and smoking), inflammation, antiphospholipid antibodies (aPLs), and lipid oxidation, contribute to CVD in autoimmune diseases.


Atherosclerosis in patients with autoimmune disorders

- Premature atherosclerosis is likely to be a major underlying mechanism, however other factors distinctive features may be playing a role (plaque rupture, thrombosis).
- Control of modifiable risk factors (blood pressure, glucose, tobacco exposure, cholesterol, sedentary life style).

Reproductive issues

- Lupus does not significantly affect fertility
- Increased incidence of premature births
- Offspring of lupus patients have an increased prevalence of learning disability

Contraception:

Risks for lupus patients and benefits need to be considered

- IUD: increased risk of upper genital infections
- Oral contraceptive pill containing estrogen:
  - increased risk of thrombosis
  - increased risk for flare of disease
- Depo-provera injections and progestin-only pills are safer than traditional OCP in lupus
# Bone Health

- Treatment and prevention of osteoporosis is problematic for lupus patients on chronic corticosteroids
  - Calcium and vitamin D
  - Long term effects of bisphosphonates on future fetal growth are unknown
  - Use of estrogen is associated with increased risk of flares in some studies

# Diet and Exercise

- Heart healthy diet
- Avoid alfalfa sprouts (significant evidence) garlic, melatonin and rozerem, echinacea (very little evidence)
- Moderate exercise has significant beneficial effect
### Infection prevention/monitoring

- Vigilance in evaluating suspected infectious processes
- Vaccination
  - Live virus vaccines: contraindicated
- Vigilance with screening studies
- Use prophylaxis while on aggressive immunosuppressive regimen

### Sun exposure avoidance

- Sunlight exposure increases risk of lupus flare.
- Recommend use of SPF 45 or greater sunscreen throughout the year.
Autoimmune Diseases at a Glance

- Spectrum of diseases that vary from organ specific to systemic
- Almost every organ can be involved
- Autoimmune diseases’ clinical manifestations can evolve over time
- A patient may have multiple autoimmune diagnoses

Autoimmune Diseases at a Glance

- Therapy is only partially driven by data and the guidelines are largely consensus based
- Comorbidities are multiple and require vigilance