**Systemic Lupus Erythematosus**

**Definition:**
Multisystem autoimmune disorder

**Drug-induced lupus:** Hydralazine, Procainamide, Isoniazid, Methyldopa, Quinidine, and Chlorpromazine
- Sx resolve when drug is discontinued (ANA may persist for years)
- Primarily in older pts
- No CNS or renal involvement
- (+) antihistone, (-) anti-ds DNA

**Epidemiology and risk factors:**
- Women of child bearing age (90%). Female-to-male ratio is 8:1
- Ethnicity: african-american, asians, hispanics. African-american:Caucasian ratio is 4:1
- Appears in late childhood or adolescence
- Mild in elderly, severe in children
- Genetics:
  - HLA DR2 and DR3
  - Congenital def of complemtns components: C1, C2, and C4

**Pathogenesis:**
- A combination of type II and III hypersensitivity
- Production of auto-Ab against nuclear, cytoplasmic, and cell-surface Ag
- Defective clearing of apoptotic cells + blebs containing surface proteins (act as auto-Ag)
- Tissue injury involves:
  1. Immune complex deposition: MC Id is anti-dsDNA -> form in circulation then deposit in kidney, or form in situ
  2. Cell specific Ab: don’t destroy cells directly, but mark cells for premature destruction by reticuloendothelial system -> hemolytic anemia, leukopenia, and thrombocytopenia
Presentation:

1. **Constitutional symptoms**: fatigue, malaise, fever, wt loss

2. **Skin**:  
   - **Malar rash**: butterfly rash over cheeks and bridge of nose, sparing the nasolabial folds, nonscarring  
   - **Discoid lesions**: typically occur over exposed areas (face and scalp) -> deeper, often scarring  
   - **Subacute cutaneous lupus**: erythematous, annular, polycyclic lesions, slightly scaling border with central clearing  
   - Most rashes are photosensitivite (esp if + anti-Ro)  
   - Oral or nasopharyngeal ulcers  
   - Alopecia

3. **Raynaud’s phenomenon**:  
   - Vasospasm of small vessels when exposed to cold (usually in fingers)  
   - Needs to be differentiated from primary Raynaud’s -> common in health young women

4. **Lungs**:  
   - Pneumonitis and pleural effusion  
   - Pneumonia, atelectasis, pulmn fibrosis, alveolar hemorrhage, restrictive lung ds -> common in SLE but not diagnostic  
   - Shrinking lung syndrome: smaller lung volumes due to diaphragm weakness

5. **Cardiovascular**:  
   - Pericarditis, endocarditis, myocarditis  
   - **Libman-Sacks endocarditis** is a serious complication: a form of nonbacterial endocarditis, that causes vegetations on the valves (mitral mainly) which can embolize

6. **Joints and muscles**:  
   - Arthralgia w\ morning stiffness: episodic, migratory, nonerosive, symmetrical distribution (similar to RA; peripheral joints)  
   - Jaccoud’s arthropathy: joint deformity bc tendon damage (w\out joint erosion)  
   - Mayalgia (50%), myositis (<5%)
7. **Kidneys:**
   - Hematuria, proteinuria, high BUN and Cr, and urinary casts
   - The most common and severe: diffuse proliferative GN -> rapidly prog renal failure

8. **CNS:**
   - Psychosis, seizures, headache, depression, TIA, stroke (from vasculitis)
   - Commonest finding in MRI: increased white matter signal

9. **Hematologic:**
   - Hemolytic anemia
   - Anemia of chronic ds (normocytic, normochromic)
   - **Lymphopenia**, leukopenia, thrombocytopenia

10. **GI:**
    - N\V, dyspepsia, dysphagia, peptic ulcer disease

11. **Ocular:**
    - Photophobia, conjunctivitis, retinal lesions (cotton wool spots), blindness

12. **Other:**
    - Antiphospholipid syndromes
    - Sjögren syndrome AKA Sicca syndrome
    - Mesenteric vasculitis: can present w/ abdominal pain, bowel infarction, perforation

13. **Immunologic:**
    - **ANA** (90%): to multiple nuclear Ags. Sensitive, not specific. Screening test. Not diagnostic w/ out clinical features. “Don’t treat asymptomatic (+) ANA”
    - **Anti-DNA** (60%): to native ds DNA, Poor prog (renal ds). Highly specific
    - **Anti-Smith (Sm)** (30%): to smith nuclear ribonuclearprotein. Most specific
    - **Antihistone**: to DNA\protein complex. Sensitive for drug-induced lupus
    - **Anti-RNP**: to ribonuclearprotein. Overlap SLE, scleroderma, and myositis
    - **Anti-Ro (SS-A)\La (SS-B)**: in Sjögren\SLE overlap and neonatal lupus
    - Decreased C3, C4, and CH50 bc immune complex formation. Drop further with acute exacerbations!
    - **Anti-phospholipid Abs** (anti-cardiolipin and SLE anti-coagulant): ↑ risk of clotting and aPTT
    - False-positive test for syphilis
    - Positive LE preparations: ANAs bind to nuclei of damaged cells -> LE bodies

**During an acute exacerbation:**
- Anti-DNA levels ↑
- Complement levels ↓
Diagnosis:

2012: “SOAP BRAIN MD” 4 out of 11; at least 1 clinical and 1 immunologic

- Indications for renal biopsy:
  - Increasing serum creatinine in the absence of strong evidence for another etiology (eg, sepsis, hypovolemia, medication)
  - Proteinuria of more than 1 g/24 hr
  - Proteinuria of ≥0.5 g/24 hr, along with either (1) hematuria (≥5 RBCs/hpf) or (2) cellular casts

Treatment:

- Treat the ds, not the serologic activity
- Avoid sun exposure

- For mild sx: NSAIDs (ibuprofen 400-800 mg 3-4 tx/d)

- For acute exacerbations: corticosteroids (either systemic or local)

- For mild nephritis: 1st line: Mycophenolate mofetil 2-3 g/d. 2nd line: Azathioprine (AZA) – steroid sparing

- For severe nephritis/serious SLE: cytotoxic agents\immunosuppressive agents (cyclophosphamide IV pulse 500-750 mg/M² x 6 mo, followed by maintenance w\ Mycophenolate mofetil or AZA) added to steroids. SE: Myelosuppression, hemorrhagic cystitis, bladder Ca, teratogen.

- For long-term\preventive (for cutaneous, constitutional and articular manifestations): antimalarial agents (Hydroxychloroquine; 400 mg/d). Requires annual eye exam for possible retinal toxicity. Other SE is Stevens-Johnson synd

Complications\Prognosis:

- Bimodal mortality pattern:
  - Early (w\in 2 yrs): infections (50% are opportunistic; PCP and candida), or active ds (renal or CNS)
  - Late (>10 yrs): atherosclerosis and accelerated coronary artery ds (MI)

- Prognosis: 10-yr survival is > 85%
Pregnancy and SLE:

- Normal fertility rates, but they have increased spontaneous abortions and stillbirths compared with normal pts
  - Why? Anti-phospholipid Abs -> placental infarcts
  - How to treat? Low-molecular weight heparin (LMWH) during pregnancy
- In case of a lupus flare during pregnancy -> safely use steroids
- All preg ladies should be screened for Anti-Ro (SS-A)
  - Why? These Abs cross placenta -> passively transferred to fetus -> neonatal lupus + heart block

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>Arthralgias/arthritis, myalgias, mild serositis</td>
<td>Gastritis, UGIB, Renal failure</td>
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<tr>
<td>Hydroxychloroquine</td>
<td>Mild disease complicated by serositis, arthritis, skin Δs</td>
<td>Retinal damage, Stevens-Johnson synd., Myopathy</td>
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<tr>
<td>Corticosteroids</td>
<td>Low doses for mild disease</td>
<td>Adrenal suppression, osteopenia, avascular necrosis of bone, myopathy</td>
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<td></td>
<td>High doses for major manifestations including renal, hematologic, CNS</td>
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<tr>
<td>Mycophenolate</td>
<td>Nephritis (induction and/or maintenance); N Engl J Med 2004;350:971 &amp; 2005;353:2219</td>
<td>Myelosuppression, Immunosuppression/infection, teratogen</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Severe nephritis, vasculitis or CNS disease (induction = maintenance)</td>
<td>Myelosuppression, Myeloproliferative disorders, Immunosuppression/infection, Hemorrhagic cystitis, bladder cancer, Infertility, teratogen</td>
</tr>
<tr>
<td>Azathioprine (AZA)</td>
<td>Mild nephritis (2nd line) Steroid-sparing agent</td>
<td>Myelosuppression, Hepatotoxicity, Lymphoproliferative disorders</td>
</tr>
<tr>
<td>Methotrexate (MTX)</td>
<td>Skin and joint disease Serositis</td>
<td>Myelosuppression, Hepatotoxicity, Pneumonitis = fibrosis, Alopecia, stomatitis</td>
</tr>
<tr>
<td>Cyclosporine (CsA)</td>
<td>Renal disease</td>
<td>Hyperplastic gums, HTN, Hirsutism, Renal impairment, anemia</td>
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<tr>
<td>Rituximab</td>
<td>? Refractory ITP or AIHA</td>
<td>B-cell depletion; PML (?)</td>
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<tr>
<td>Belimumab</td>
<td>Refractory SLE; compassionate use only (Arthritis Rheum 2010;62:201)</td>
<td>B-cell depletion</td>
</tr>
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References:
- Pocket medicine
- Toronto notes
- Step up to medicine
- Master the boards
- The Johns Hopkins Internal Medicine Board Review
- Davidson’s Principles and Practice of Medicine