Lupus
SLE | Systemic Lupus Erythematosus

Overview
- Chronic inflammatory autoimmune disease with unknown etiology
- Possible provocative agents: UV light, infections, hormones, drugs, emotional or physical stress; genetic factors involved
- Epidemiology: more common in females and in blacks, Hispanics, Native Americans, and Asians

Pathogenesis
- Immunologic abnormalities
  - Production of antinuclear antibodies against dsDNA (specific for SLE), ssDNA, RNA
  - RNA associated antigens present: Smith (Sm), snRNP, Ro (SS-A), and La (SS-B) antigens
- B-cell abnormalities
  - Excessive antibody production → hyperactive B lymphocytes → loss of self-tolerance + excessive antigenic load
  - Th1 cells → Th2 cells → ↑ B-cell antibody production
  - Defective B-cell suppression
- Involvement from other players: T cells, cytokines, and natural killer cells

Clinical presentation
- Diagnosis: need ≥ 4 of 11 criteria
- Possible symptoms
  - Cutaneous: cheek butterfly rash, mouth ulcers, hair loss
  - Joints: pain, erythema, swelling
  - Membrane lining: polyserositis (combination of pleurisy, pericarditis, peritonitis)
  - Blood: hemolytic anemia, leukopenia, thrombocytopenia
  - Lungs: infiltrates, pulmonary hypertension, pulmonary embolism
  - Nervous system: headaches, psychosis, depression, anxiety, seizure, stroke, peripheral neuropathy, cognitive impairment
- Possible clinical signs:

<table>
<thead>
<tr>
<th>Lab ↑</th>
<th>ESR, CRP, gammaglobulin, BUN, SCr, muscle Es</th>
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</thead>
<tbody>
<tr>
<td>Lab ↓</td>
<td>Albumin, platelets, WBCs, anemia</td>
</tr>
<tr>
<td>Routine chem. panels</td>
<td>Abnormal LFTs</td>
</tr>
<tr>
<td>ANA titers</td>
<td>Titer &gt; 1:80 considered + ; (ANA titers go up/down during disease and a high/low titer does not necessarily mean the disease is more/less active); + ANA test, by itself, not proof of lupus</td>
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</tbody>
</table>
  - Positive ANA test may be true of other diseases: scleroderma, Sjogren’s, RA, thyroid, liver, juvenile arthritis
- Hematologic manifestations:
  - Anemia: common; usually mild, normochromic, normocytic sear and low serum [Fe], but adequate Fe stores; some pts develop hemolytic anemia (+ Coombs test)
  - Milk leucopenia: present in ½ of SLE pts
  - Thrombocytopenia: usually mild, more common during disease exacerbation
  - Antiphospholipid Abs: lupus anticoagulant and anticardiolipin Abs

DILE | Drug-Induced Lupus Erythematosus
- Criteria: no prior SLE history + ANAs + ≥1 clinical feature + improvement upon drug discontinuation (days to weeks)
- Differential diagnosis: DILE vs. idiopathic lupus

<table>
<thead>
<tr>
<th>DILE</th>
<th>Idiopathic lupus</th>
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<tbody>
<tr>
<td>Antibodies against ssDNA</td>
<td>Antibodies against dsDNA</td>
</tr>
<tr>
<td>Symptoms: musculoskeletal</td>
<td>Symptoms: renal, CNS</td>
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</tbody>
</table>
- Common symptoms: fever, fatigue, pericarditis, pleurisy, weight loss, malar rash
- Culprits: procainamide, hydralazine, isoniazid, chlorpromazine, methyl dopa, quinidine

Treatment
- Goals: prevent flares, ↓ symptoms, preserve organ functions, ↓ drug toxicity
- Non-pharmacological: rest, exercise, smoking cessation, sunscreen, vaccinations to prevent infections
  - Algorithm
    o Mild to moderate: NSAIDs, antimalarials, low dose corticosteroids
    o Severe: high dose corticosteroids and/or cytotoxic drugs
- Pharmacological therapy: overview of classes

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Agent</th>
<th>Indication</th>
<th>MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID</td>
<td>Various agents at anti-inflammatory dose</td>
<td>Mild: fever, arthritis, rash, serositis</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Antimalarial</td>
<td>Hydroxychloroquine, Chloroquine</td>
<td>Mild: arthritis, rash, serositis</td>
<td>Interferes with T-cell activation</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>Prednisone, Methylprednisolone</td>
<td>Initial control of severe disease; or mild disease control or maintenance Life-threatening disease</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Cytotoxic</td>
<td>-Cyclophosphamide, -Azathioprine, -Mycophenolate mofetil</td>
<td>Most commonly used in severe lupus nephritis; may be necessary for other severe disease manifestations</td>
<td>-Alkylating agent, (→) protein synthesis -Immunosuppressive antimetabolite -Immunosuppressant, (→) IMPDH → (→) B-cell &amp; T-cell proliferation</td>
</tr>
</tbody>
</table>

- Pharmacological therapy: agents

<table>
<thead>
<tr>
<th>Toxocities to monitor</th>
<th>Comparisons</th>
</tr>
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<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>Myelosuppression, myeloproliferative disorders, malignancy, immunosuppression, hemorrhagic cystitis, infertility</td>
</tr>
<tr>
<td>Myelosuppression, hepatotoxicity, lymphoproliferative disorders, malignancy</td>
<td>Need good hydration, monitor WBC</td>
</tr>
<tr>
<td>Myosupression, hepatotoxicity, lymphoproliferative disorders, malignancy</td>
<td>Better AE profile overall compared to cyclophosphamide: ↓ovarian toxicity, ↓nephrotoxicity, ↓amenorrhea, ↓leukopenia</td>
</tr>
<tr>
<td>Macular damage (cycloplegia, corneal deposits), headache, insomnia, rashes, dermatitis, skin pigment changes, nausea</td>
<td>Best used for longer term management (max response: 3-6 months); need ophthalmology exam at baseline and q6-months; useful for cutaneous symptoms, arthralgia, pleuritis, mild pericardial inflammation, fatigue, leukopenia</td>
</tr>
<tr>
<td>Myelosuppression, hepatotoxicity, lymphoproliferative disorders</td>
<td>Little data on use in lupus nephritis, slightly more effective than prednisone alone, less toxic than cyclophosphamide</td>
</tr>
</tbody>
</table>

Lupus nephritis

- Symptoms: ↑SCr, proteinuria
- Diagnosis: kidney biopsy
- Predictors of poor outcome: AA race, ↑SCr, poor response to immunosuppressive agents, hypertension, persistent nephrotic syndrome
- Guidelines:
  o All patients: biopsy, hydroxychloroquine, maintain BP < 130/80
  o Patients with concomitant conditions:
    ▪ Patients with proteinuria > 0.5 g/day: ACEI or ARB
    ▪ Patients with LDL > 100 mg/dL: statins
    ▪ Fertile women: pregnancy counseling
    ▪ Pregnant women:
      ▪ ≥Class III: don’t require treatment
      ▪ Mild: hydroxychloroquine 200-400 mg/day
      ▪ Active disease: prednisone to suppress activity + azathioprine if necessary (≤2 mg/kg/day)
  o For class III/IV nephritis induction tx:
    ▪ Choice of MMF or CYC; MMF 2-3 g/day x 6 mo preferred over CYC for AA and Hispanic pts
    ▪ IV glucocorticoid pulse for 3d followed by pred 0.5-1mg/kg/d tapered over a few weeks
    ▪ Pts who fail 1st induction tx switch to other option; after failure to MMF and CYC, suggest rituximab or CNI
    ▪ Pts who improve can go to maintenance w/MMF 1-2 g/d OR AZA 2 mg/kg/d
  o Class V membranous lupus nephritis
    ▪ Induction tx: should start on MMF 2-3 g/d x 6 mo PLUS pred 0.5 mg/kg/d x 6 mo
    ▪ If improve, maintenance tx w/MMF OR AZA
    ▪ If NOT improved, start CYC 500-1000 mg/m2 monthly x 6 mo PLUS glucocorticoid pulse followed by pred 0.5-1mg/kg/d
    ▪ Patients with proteinuria > 0.5 g/day: ACEI or ARB
Patients with LDL > 100 mg/dL: statins
Fertile women: pregnancy counseling
Pregnant women:
  • ≥Class III: don’t require treatment
  • Mild: hydroxychloroquine 200-400 mg/day

Lupus nephritis: pregnant women
  • Women w/h/o Class III or higher do NOT require tx during preg if no evidence of dis activity
  • Mild dis: hydroxychloroquine 200-400 mg/d
  • Active dis: pred at doses to suppress activity and, if necessary, AZA (no more than 2 mg/kg/d)

Pregnancy and SLE associated with:
  • Exacerbation of dz during preg and early postpartum period
  • ↑ spontaneous abortion
  • ↑ chance of preeclampsia/pregnancy-induced HTN
  • Exacerbations during preg less likely if dz in remission at conception
    o Managed aggressively w/steroids
    o Hydroxychloroquine safe in preg (Cat C)
    o Cytotoxic drugs in preg: use w/caution, AZA may be safest

### APLS | Antiphospholipid Antibody Syndrome

- Need at least 1 clinical criterion & at least 1 lab criterion
  - Time between clinical and lab criteria must be > 12 weeks and < 5 y
  - Failure to satisfy criteria do NOT necessarily preclude dx of APLS
- Clinical criteria
  - Vascular thrombosis
    - Arterial, venous, or small vessel thrombosis
  - Pregnancy morbidity
    - 1/more unexplained fetal death at or after 10th week w/normal fetal morphology
    - 1/more premature births at/before 34th week due to: eclampsia/preeclampsia/placental insufficiency
    - 3/more spontaneous abortions at/before 10th week gestation
- Lab criteria: must be present on 2/more occasions, at least 12 weeks apart
  - Lupus anticoagulant present in plasma
  - Anticardiolipin (aCL) Ab of IgG and/or IgM isotype in serum/plasma present in medium/high titer
  - Anti-b2 glycoprotein-I Ab of IgG and/or IgM isotype in serum/plasma
- Clinical manifestations

<table>
<thead>
<tr>
<th>Frequent (&gt;20% of cases)</th>
<th>Less Common (10-20%)</th>
<th>Unusual</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Venous thromboembolism</td>
<td>▪ Heart valve dis</td>
<td>▪ Epilepsy</td>
<td>▪ Adrenal hemorrhage</td>
</tr>
<tr>
<td>▪ Thrombocytopenia</td>
<td>▪ Pre-eclampsia/eclampsia</td>
<td>▪ Vascular dementia</td>
<td>▪ Transverse myelitis</td>
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<tr>
<td>▪ Miscarriage/fetal loss</td>
<td>▪ Premature birth</td>
<td>▪ Chorea</td>
<td>▪ Budd-Chiari syndrome</td>
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<tr>
<td>▪ Stroke/TIA</td>
<td>▪ Hemolytic anemia</td>
<td>▪ Retinal artery/vein thrombosis</td>
<td></td>
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<tr>
<td>▪ Migraine</td>
<td>▪ CAD</td>
<td>▪ Amaurosis fugax</td>
<td></td>
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<tr>
<td>▪ Livedo reticularis</td>
<td></td>
<td>▪ Pulmonary HTN</td>
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- Classification
  - 1st: no clinical/lab evidence of other autoimmune dis
  - 2nd: in association w/another autoimmune dis (SLE most common); only other rheum dis w/proven link to APLS is RA; possibly Sjogren’s syndrome & systemic sclerosis; Sneddon’s syndrome may be undiagnosed APLS

- Epidemiology: prevalence of aPL Abs, but not all pts w/aPL have APLS; need lab PLUS clinical event
- Anticoag for APLS
  - Prophylaxis w/daily ASA for those w/out an event
  - After thrombotic event, intensity of warfarin in debate
    - If venous event (DVT, PE): INR 2-3
- If arterial event (CVA, PVD): INR 2-3.5
  - Long-term anticoag
- AP Abs ↑ risk of spontaneous abortion so to prevent recurrent pregnancy loss:
  - Pts w/standard risk: 40 mg enoxaparin qam
  - Pts w/higher thrombotic risk: 40 mg enoxaparin po bid
  - At UIC, give 40 mg po enoxaparin po bid, checking anti-factor Xa levels monthly throughout pregnancy, targeting 0.3-0.6 units/ml; dose averages ~ 0.6 mg/kg TBW