Systemic Lupus Erythematosus (SLE)

- General
  - Chronic intermittently symptomatic autoimmune disorder that leads to production of antibodies that attack virtually any and every tissue resulting in dz that ranges from mild to life threatening
- Epidemiology
  - African-American, Asians, Hispanic (non-White), Childbearing (15-40yo) Female (10F:1M), +FHx, C1q, C2, C4a/b Complement Deficiency (unclear but one theory is that lupus inciting Ag cannot be cleared by complement)
- S/S
  - Precipitants (sun exposure, infection, emotional stress, surgery, sulfonamides, increased female hormones such as birth control pills, estrogen replacement therapy, pregnancy, et al)
  - Constitutional (initial findings)
    - Fatigue (usually the first sign of an impending flare), Fever, Weight Loss
  - Cutaneous (initial findings, precipitated by UV exposure)
    - Acute Cutaneous Lupus Erythematosus (ACLE): Malar Rash aka "Butterfly Rash" (erythematous raised pruritic rash over cheeks and bridge of nose sparing the nasolabial folds)
    - Subacute Cutaneous Lupus Erythematosus (SCLE): Annular/Polycyclic Papulosquamous
    - Chronic Cutaneous Lupus Erythematosus (CCLE): Discoid Rash, Hypertrophic/Verrucous, Lupus Profundus, Mucosal, Lupus Timidus, Chilblains, Lichenoid
    - Mucosal (Oral, Nasal, Vaginal) painless ulcers
    - Other: Non-Scarring (aka it grows back) Alopecia, Urticaria, Raynaud's Phenomenon, Petechiae, Purpura, Ecchymoses, Hyper/Hypopigmentation, Pruritis, Livido Reticularis, Vasculitis
  - Musculoskeletal (initial findings, most sensitive finding seen in 90%, b/c arthritis is non-erosive if a pt has pain then pursue AVN and FM rather than arthritis as the cause)
    - Arthritis/Arthralgia (nonerosive, migratory/transient (sometimes persistent/chronic) poly arthritis (hands, wrist, knees), Jacoud's Arthropathy (hand deformities mimicking RA but they are reversible and like noted above do not cause erosions))
    - Other: Myositis/Myalgia, AVN (unclear etiology)
  - Neuropsychiatric (late findings but seen in 2/3 of pts, associated with anti-ribosomal P protein, always a dx of exclusion ruling out metabolic, infection, medications causes)
    - Seizures
    - Psychosis
    - Other: though not part of the diagnostic criteria headache and cognitive dysfunction are the most common neuropsychiatric symptoms, C/PNS can be affected in various ways, Depression, TIA/CVA
  - Cardiac (late findings)
    - Premature CAD with either accelerated atherosclerosis (unclear etiology) or thrombosis (2/2 antiphospholipid syndrome) (it is the most common cause of death with ~40yo women having a 52x increased r/o MI compared to age/gender matched Framingham cohorts!!!)
    - Pericarditis w/ or w/o Effusions
    - Libman-Sacks Dz (non-bacterial verrocous vegetations on mitral/tricuspid valves) though they alone are rarely hemodynamically symptomatic they can become secondarily infected (endocarditis) such that it is recommended that these pts undergo abx prophylaxis during invasive procedures
    - Myocarditis w/ Conduction Defects and Arrhythmias and HF
  - Pulmonary (late findings)
    - Pleuritis w/ or w/o Effusions
    - Pulm Hemorrhage (uncommon but when it occurs it is likely to recur and is deadly)
    - Pneumonitis to ILD (uncommon but when it occurs it is likely to recur and is deadly)
    - PE
    - "Shrinking Lung Syndrome" (phrenic nerve damage resulting in diaphragmatic dysfxn leading to restrictive lung dz)
  - GI (late findings)
    - Non Specific Sx: Ab Pain, Anorexia, N/V
    - Peritonitis
    - Vasculitis
    - Pancreatitis
  - Renal (late findings adults but usually early finding in children) (refer)
  - Hematologic (2/2 chronic dz and/or autoimmune attack resulting in lysis)
    - Anemia
    - Leukopenia/Lymphopenia
    - Thrombocytopenia
    - Hypercoagulable State (Antiphospholipid Syndrome – APLS) (refer)
  - Immunologic
    - Immune system is dysfxnal b/c of SLE itself and also immunosuppression 2/2 medications leads to infections which is a major cause of M/M

- Subtypes
    - SLE (1997 ACR Criteria (>4/11 "**A RASH POIN**ts **MD**"))
        - **A**NAs
        - **R**enal Dz
            - >0.5g/d/>+3 proteinuria OR
            - any type of cast
        - **A**rthritis
        - **S**erositis
            - pericarditis OR
            - pleuritis
        - **H**ematologic Dz
            - hemolytic anemia OR
            - leukopenia (<4k/mm^3) OR
            - lymphopenia (<1.5k/mm^3) OR
            - thrombocytopenia (<100k/mm^3)
        - **P**hotosensitivity
        - **O**ral Ulcers
        - **I**mmunologic Dz
            - anti-dsDNA OR
            - anti-Sm Ab OR
            - anti-phospholipid
        - **N**eurologic Dz
            - seizures OR
            - psychosis
        - t
        - s
        - **M**alar rash
        - **D**iscoid rash
    - Drug-Induced Lupus
        - Auto-Ab: + anti-histone but rarely + anti-dsDNA rather pts have + anti-ssDNA, also pts have +RF
        - Drugs
            - 1° Procainamide (30% of pts), Hydralazine (10% of pts), Isoniazid (5% of pts), Phenytoin
            - 2° Chlorpromazine, Methyldopa, Quinidine, Sulfasalazine
        - NB Minocycline has a very different picture with different autoantibodies specifically – anti-histone
        - NB Anti-TNF is an emerging one
        - Unique Clinical: rarely severe with usually only constitutional, serosal, and MS Sx (NO renal dz or neuropsych dz), pt's improve after withdrawal of agent after 4-6wks
        - RFs: old white males
    - Pregnancy and Lupus
        - VERY IMPORTANT TO DISTINGUISH LUPUS FROM ECLAMPSIA b/c they have very similar findings (cytopenias, proteinuria, HTN) and both occur later in pregnancy (lupus flares when estrogen increases)
        - Neonatal Lupus Syndrome
            - transplacental transfer of maternal IgG to the fetus causing transient photosensitive rash and congenital heart block sometimes resulting in death
            - screen for anti-Ro/La in all pregnant pts even though only 10% of these pts have babies that develop this syndrome
        - Spontaneous abortions, premature infants, and intrauterine defects are common b/c of hypercoagulable state (refer above)
- Diagnosis

NB only three markers are useful for the management of dz activity b/c changes in these markers affect the prognosis of disease

(1) Total Hemolytic Complement
(2) Anti-dsDNA
(3) Anti-Phospholipid

- + anti-Nucleic Acid (ANA)
    - Sensitivity (97%)
        - Human cells are exposed to diluting amounts of pt's serum, almost everyone has Abs in there serum that attacks some sort of antigen in the nucleus, it becomes significant as to when this attack disappears as the pt's serum is diluted such that it is meaningless when <1:40 and significant when >1:80
        - If the titer is low repeat in a few months b/c its significance becomes more significant when persistent (not transient) and/or higher titer (no lower)
        - Often SLE pts had +ANA for years prior to development of symptoms
        - Once a pt has a significantly +ANA titer then you need to determine the type of nuclear antigen aka "Extractable Nuclear Antigens" (ENA) (some labs offer reflex testing)

- First Look at Pattern
    - Centromere: Limited Systemic Sclerosis
    - Homogenous, Speckled, Peripheral/Rim, Nucleolar: don't really tell much thus you must expose pt's serum to specific nuclear antigens
- Next Expose Pt's Serum to Specific Nuclear Antigens (below)
    - + anti-dsDNA (kidney dz)
        - Sensitivity (70%)
        - Specificity (97%) NB very occasionally it can be seen in other rheumatologic conditions and chronic active hepatitis
    - + anti-Histone (drug induced lupus)
        - Sensitivity (30% overall but 90% sensitive for drug induced lupus)
        - Specificity (not specific at all)
    - + anti-SM (Ag: mRNA processing protein named after pt Ms. Smith, kidney/neuropsych dz)
        - Sensitivity (5-30% depending on race)
        - Specificity (97%)
    - + anti-U1 RNP (Ag: RiboNucleotide Protein)
        - Sensitivity (50%)
    - + anti-Scl-70 (Ag: topoisomerase)
        - Sensitivity (20%)
    - + anti-Ro (SS-A) & La (SS-B) (Ag: ?, SCLE and Neonatal Lupus Syndrome)
        - Sensitivity (15%)
    - + anti-ribosomal P (neurospych dz)
        - Sensitivity (7%)
        - Specificity
    - + anti-ssDNA
        - Sensitivity
        - Specificity (not specific at all)
    - NB RF is NOT common
- Specificity (not very specific)
    - 1:40, 1:80, 1:160 titers are seen in 30%, 15%, 5% of normal adult population, respectively
    - a landmark study looked at incidence of ANA in the military recruiting population and found it to be 30%
    - rheumatologic disorders (Sjogren's, Sclerosis, PM, MCTD)
    - autoimmune disorders (thyroid dz, TIDM, cytopenias, MS)
    - infections (any recent viral infection)
    - liver (chronic hepatitis, primary biliary cirrhosis)
    - cancer (L/L, solid tumors)
    - the older the pt the more likely they have an ANA titer
- some have suggested that nuclear antigens become available as antigens during apoptosis and when there is incomplete apoptosis these antigens could be exposed for long periods of time allowing for antibodies to form

- Heme
    - CBC (leukopenia or just lymphopenia, anemia, thrombocytopenia)
        - Usually 2/2 autoantibodies therefore check Coomb's and Warm/Cold Ig
    - + anti-antiphospholipid, + anti-cardiolipin, + beta-2 glycoprotein
    - S/UPEP w/ EIF: hypergammaglobulinemia
    - decreased complement levels (C3, C4, CH50)
    - false + RPR/VRDL
- Renal
    - UA, Cr
- Acute Phase Reactants (APRs)
    - During an inflammatory process IL-1, IL-6, TNF cytokines are released by inflammatory cells BUT they are very hard to measure clinically. Fortunately, the liver also responds by increasing production of certain proteins (ferritin, fibrinogen, complement, gamma globulins, et al) and decreasing production of other proteins (albumin, transferrin, et al). These changes in protein concentration alter the rate at which RBCs fall under gravity in plasma aka Erythrocyte Sendimentation Rate (ESR).

        - NB false positives in hypoalbumic states, anemia, elevated Ig like in MM, etc

        - NB false negatives in conditions with abnormal RBCs like in SCD, polycythemia, etc.

        - NB Given that ESR might be falsely negative/positive, measuring C-Reactive Protein (CRP) becomes helpful because it typically is not affected by the above conditions. Also, unlike ESR which decreases the longer blood is analyzed after it is drawn, CRP is more stable.

- NB upper limit of normal depends on age and gender and if lab does not offer age/gender adjusted reference range then the following upper limit of normal equation can be used: Men = age/2 (mm/hr) and Women = age +10/2 (mm/hr). Hence, older women have higher normal values than younger men.

- NB similar to ESR CRP varies in age and gender: Men = age/5 (mg/dL) and Women = age+30/5 (mg/dL)

Prognosis

- 10yr survival is 80% with leading cause of early death (infection) and late death (CAD)
  - mortality rates are 3x higher than those of age/gender matched populations
- higher mortality is also associated with renal dz, lung dz, and thrombocytopenia

Treatment

- Lifestyle Modification:
  - avoid precipitants
- Symptomatic Treatment
  - Serositis/Arthritis/Cutaneous: NSAIDs, Hydroxychloroquine, Steroids
  - Major Organ Dz: Immunosuppressants (cyclophosphamide, azathioprine, methotrexate, rituxan, cyclosporine, NB anti-TNFs are not helpful)