Systemic Lupus Erythematosus
Objective 1

- Define lupus and its various presentations:
  - Historical perspective
  - Working definition of SLE
  - Time to diagnosis
  - Common presentations
  - ACR criteria for diagnosis
SLE: A Historical Perspective

- 460-375 BCE Cutaneous ulcers have been described since the time of Hippocrates and were termed “herpes esthimenos”
- 916 CE Herbernus of Tours first used the term ”Lupus” to describe a skin disease
- During the Middle Ages various terms for skin disorders were used
- 1757-1812 Willan further classified skin disorders as “herpes” meaning vesicular or “lupus” meaning destructive or ulcerative
- 1833 Biett provided the first clear description of DLE and termed it “erythema centrifugum”
- 1846 Hebra first used the term “butterfly rash”
- 1851 Cazenave first coined the term lupus erythematosus
- 1872 Kaposi sub classified DLE and SLE and was the first to describe systemic manifestations and fatal outcomes.

(Smith, Rheum Dis Clin North Am 1988)
SLE: A Working Definition

• Lupus is a systemic autoimmune disease in which the body loses tolerance to self

• Can affect virtually any organ in the body and initial symptoms are often nonspecific, making it very difficult to diagnose

• Typical autoantibodies seen are those reacting against nuclear components of the cell

• Most commonly seen in women of childbearing age but 10% of patients are men

• Lupus is a clinical diagnosis made by a clinician. Most patients will have four or more ACR criteria.
SLE: Average Time to Diagnosis

SLE can be very challenging to diagnose:

• Average time of two years between initial symptomatology and definitive diagnosis. (Cervera, Medicine, 1993; Font, Semin Arthritis Rheum, 2004)
  • Eurolupus study –1000 patients, enrolled in 1990
  • University of Barcelona –600 pts, enrolled 1980-2001

• Lupus autoantibodies develop over time:
  • Analysis of stored serum of 130 military recruits who later developed lupus revealed that autoantibodies were present in the serum up to 9 years prior to the onset of clinical disease (Arbuckle, N Engl J Med 2003)
Antinuclear Antibodies— ANA

- Low titer positive ANA in normal population increases with age

- Patterns of ANA immunofluorescence vary.
  - SLE is commonly associated with peripheral or speckled patterns
  - Homogeneous patterns are associated with drug induced lupus.

- First degree relatives of patients with SLE are likely to be ANA positive
  - Analysis of 54 lupus patients, 154 of their first degree relatives and 330 controls
  - 32% of relatives had antinuclear antibodies, compared with 1.5% of the healthy controls

(Sack, Primer 2001; Van der Linden, J Rheumatol 2001)
SLE: Common Manifestations, ACR Criteria

Arthritis 83%
Malar rash 54%
Photosensitivity 41%
Nephropathy 34%
Oral Ulcers 30%
Serositis 28%
Seizure/Psychosis 12%

(Font, Semin Arthritis Rheum 2004)
SLE: Common Manifestations, Not Part of ACR Criteria

(Font, Semin Arthritis Rheum 2004)
Clustering of symptoms

• Cutaneous, articular and renal manifestations tend to appear “together”

• CNS thrombotic and muscular symptoms also cluster, although to a lesser extent

(Font, Semin Arthritis Rheum 2004)
SLE: Common Presentations Vary by Gender, Race, Ethnicity

• Does ethnicity play a role in lupus disease expression?
  – African American:
    • Discoid lesion
    • Proteinuria
    • Anti-Sm, anti-RNP
  – Caucasian:
    • Photosensitivity
    • Mucocutaneous ulcers
  – Hispanic:
    • Photosensitivity
    • Vascular thromboses, livedo reticularis

• Does gender play a role in lupus disease expression?
  – Male:
    • Proteinuria
    • Hematologic (leukopenia, lymphopenia, thrombocytopenia)

(Cooper, Lupus 2002; Molina, Lupus 1997)
ACR Criteria for Classification of SLE

- Initially published in 1971
  - Purpose: to provide a standardized definition of SLE for use in research
- Revised in 1982
- Clarifications made in 1997
  - Revised the immunologic criteria to reflect the growing knowledge and new diagnostic tests available

- Rules for using the criteria:
  - A patient who exhibits any 4 of these 11 criteria is classified as having SLE
  - Criteria need not be present simultaneously; SLE evolves over time.

- Criteria as detailed on the following slides are listed almost verbatim from the Primer on Rheumatic Diseases. Original sources: (Tan, 1982; Hochberg, 1997)
1. Malar Rash

😊 Erythematous

😊 May be hyperpigmented in darker skinned individuals

😊 Flat or raised

😊 May occur on exposure to sunlight

😊 SPARES NASOLABIAL FOLDS!
2. Discoid Rash

- Erythematous
- Raised patches
- Adherent keratotic scale
- Follicular plugging
- Atrophic scarring may occur as lesions age

**LOOK IN EARS!**
3. Photosensitivity

Pathophysiology:

- UV light damage
- epidermal/dermal cells apoptosis
- nuclear autoantigen exposed
- immune system sensitized
- autoantibodies production

malar rash → multiorgan flares


Clinical Correlation:

29 lupus patients (Finland)

- Disease activity increased significantly in spring and summer
- Most due to renal disease, low complements, hematologic
- Flares in “photosensitive” patients and in “not-photosensitive” pts
- No difference in sun-avoidant behaviors or sun protection use between “photosensitive” pts and “not-photosensitive” pts

(Hansen, Ann Rheum Dis 2004)
4. Mucocutaneous Ulcers

- Oral or nasopharyngeal ulcerations
- Must be observed by physician/health care provider
- Often painless
5. Arthritis

• Predominantly nonerosive arthritis

• Involving 2 or more peripheral joints

• Characterized by:
  – Tenderness
  – Swelling
  – Effusion

• May culminate in Jaccoud’s arthropathy, reducible deformities caused by periarticular fibrosis and ligamentous laxity.
6. Serositis

• Pleuritis:
  – a convincing history of pleuritic pain
  – or rub heard by an examiner
  – or evidence of pleural effusion

  OR

• Pericarditis:
  – documented by ECG
  – or rub
  – or evidence of pericardial effusion

Left sided pleural effusion

Free- flowing; with some underlying consolidation
7. Renal Disorder

- Persistent proteinuria
  - greater than 0.5 grams per day
  - or greater than 3+ if quantitation is not performed

  OR

- Cellular casts
  - may be red cell,
  - hemoglobin,
  - granular,
  - tubular
  - or mixed

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8. Neurologic Disorder

- Seizures

  **OR**

- Psychosis
  
  - With no other possible causes such as drugs or metabolic derangements (uremia, ketoacidosis, electrolyte imbalance)
9. Hematologic Disorder

• Hemolytic anemia with reticulocytosis

  \textbf{OR}

• Leukopenia—less than 4000/mm\(^3\) total on two separate occasions

  \textbf{OR}

• Lymphopenia—less than 1500/m\(^3\) on two or more occasions

  \textbf{OR}

• Thrombocytopenia—less than 100,000/m\(^3\) in the absence of offending drugs

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10. Immunologic Disorder

- Anti-DNA antibody

  **OR**

- Anti-SM antibody

  **OR**

- Positive finding of antiphospholipid antibodies based on
  - Anticardiolipin IgG or IgM
  - Positive Lupus Anticoagulant
  - False positive serologic test for syphilis known to be positive for at least 6 months and confirmed by T. pallidum immobilization or florescent treponemal antibody absorption test

LE cell, the first clinical “test” for lupus
11. Antinuclear Antibody

- Abnormal titer of ANA
- By immunoflorescence or an equivalent assay
- At any point in time
- In the absence of drugs known to be associated with “drug induced lupus” syndrome
  - See postscript 2 to Objective 1 for further discussion of drug-induced lupus

ANA Patterns:

- Peripheral
- Diffuse
- Speckled
- Nucleolar

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Lupus-Related Syndromes:

1. **Cutaneous lupus**

   - Presents only with skin involvement (usually DLE).
   - Some will evolve into SLE
   - It is important to screen these patients for autoantibodies and for signs of hematologic or renal involvement.

(Werth, Autoimmun Rev 2005)
Postscripts to Objective 1

2. **Drug-induced lupus**

- Presentation: fever, myalgia, rash, arthritis and serositis.
- Associated with: procainimide, isoniazid and hydralazine
  however has been reported with many other drugs, including TNF alpha inhibitors.
- Lab findings: Antihistone antibody is positive in 95%, ANA homogenous pattern, usually anti-DNA is negative and complements are normal (except if caused by anti-TNFs).
- Organ systems: Rarely associated with hematologic, renal and CNS involvement.
- Treatment: remove precipitating agent; use of NSAIDs (symptomatic relief); rarely may require prednisone to resolve serositis.

(Sarzi-Puttini, Autoimmunity 2005; Schur. Drug-induced lupus. Up to date v.14.2)
Objective 2

Describe the epidemiology and pathogenesis of SLE.
SLE Epidemiology: Incidence and Prevalence

Incidence: there are an estimated 2-8 new cases of SLE per 100,000 people in North America, South America and Europe.

Prevalence: 40-50 cases per 100,000 people; approximately 750,000 cases of SLE exist in US today.

Much more common in developed countries and in urban areas.

(Schur. Epidemiology and pathogenesis of SLE. Up to date v.14.2; Petri. SLE. Current Rheumatology. Chapter 19)
SLE Epidemiology: Race, Gender and Age

Race: SLE disproportionately affects minority populations: It is more prevalent among African-Americans, Afro-Caribbeans, Hispanic-Americans and Asians.

Gender: Female to male ratio of approximately 10:1 in those diagnosed between 20-50 years old. In the pediatric and older (postmenopausal) population, the ratio declines somewhat

Age distribution: SLE is most common in women between 20-40 years old

(Schur. Epidemiology and pathogenesis of SLE. Up to date v.14.2; Petri. SLE. Current Rheumatology. Chapter 19)
SLE Epidemiology: Quality of Life and Disability

Quality of life (QOL):

90 patients with SLE (University of Chicago) compared with general US population

- Lupus patients have significantly worse QOL than age matched controls
- Lupus patients had worse QOL than did patients suffering from hypertension, diabetes, or myocardial infarction.
- Lupus patients scored lower than patients with CHF regarding physical function, bodily pain and perceived general health. (Jolly, J Rheumatol 2005)

Disability:

273 patients with SLE for more than five years in the LUMINA cohort, 19% overall disability rate: (Bertoli, Ann Rheum Dis 2006)
Pathogenesis of SLE

• Immune abnormalities
• Genetic Predisposition
• Hormonal
• Environmental factors
• FYI: Impact of smoking
  – SLE disease activity
  – Efficacy of antimalarial agents
Immune Dysregulation in SLE

Pathogenesis: Disorder of humeral immunity (Th2):

- Loss of B cell tolerance to self
- B cell production of autoantibodies.

(Mevorach, Rheum Dis Clin North Am 2004; also refer to Pascual, Curr Opin Immunol 2006)

Proposed mechanism: Altered clearing of apoptotic cells

- Apoptotic cell
  - Antigenic intracellular components abut cell surface
  - Dysfunctional removal of blebs
    - Immune system sensitized
      - B cell loss of tolerance
        - T cell dysfunction
Immune Dysregulation—Some Details

(Disordered Phagocytosis)

- Apoptotic Cell
- Blebs

B Cell sensitization

BAFF/BLyS moderate B Cell activity

Polyclonal B Cell activation

1. Hyperglobulinemia
2. Autoantibody production (→immune complex formation → inflammatory response)
3. Presents autoantigens
4. Secretes IL 10, IL 6, IL T2, TNF alpha

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Heritability/ Genetic Predisposition

- Concordance rates in monozygotic twins ranges from 14-57%
- 5-12% of relatives of lupus patients develop SLE
- In one study of 50 lupus patients and 154 unaffected first degree relatives, 32% of healthy relatives were ANA positive (van der Linden, 2001)
- 27% of children whose mothers have SLE test positive for ANA
- Lupus patients are more likely to have a variety of genetic markers including some HLA markers, some forms of complement deficiency, and polymorphisms of antibody Fc receptor, cytokines and cytokine receptors.
- Studies of “lupus families” suggest that genetic predisposition likely involves complex combinations of an estimated 4-8 discrete genes

(Schur PH. Epidemiology and pathogenesis of SLE. Up to Date v 14.2 ; Van der Linden J Rheumatol 2001)
Hormonal Issues

Hormonal influences on the pathogenesis of lupus are poorly understood.

**Women of childbearing age**
- No association between estrogen exposure on the risk of developing SLE (Cooper, Arthritis Rheum 2002)

**HOWEVER:**
- Only enrolled stable patients
- Greater risk of thromboses if antiphospholipid antibodies present

**Postmenopausal women**
- Nurses Health Study: RR 2.1, CI 1.1-4.0, for developing lupus with HRT (Sanchez-Guerrero, Ann Intern Med 1995)
- Stable active or inactive lupus patients on HRT have minimal increased risk of lupus flare, most flares mild to moderate (Buyon, Ann Intern Med 2005)

Environmental Factors

- Communicable diseases: molecular mimicry of foreign antigens with discrete HLA regions might lead to the development of autoreactivity
  - People with SLE have higher titers of Epstein-Barr virus antibodies
  - Trypanosomiasis and mycobacterial infections can stimulate anti-DNA antibodies
  - People with lupus may flare after acute bacterial infection

- UV light damages skin cells which then can potentially increase autoreactivity

- Drugs such as sulfonamide antibiotics and the herbal supplement echinacea have been associated with the onset of and exacerbations of SLE

- Silica dust and cigarette smoking are associated with an increased risk of SLE in case-control studies

- Vitamin D deficiency may trigger autoimmunity

- Of note, there is no known association between SLE and hair dyes, pesticides or occupational solvents

(Petri, J Clin Rheum 2006; Schur PH. Epidemiology and pathogenesis of SLE. Up to Date v.14.2, Kamen, Autoimmun Rev 2006)
Cigarette Smoking

Recent studies have raised the issue of whether cigarette smoking impacts SLE disease activity or features. In addition, cigarette smoking may affect the efficacy of common treatments:

- Freemer et al examined sera of 410 patients with SLE
  - 12% current smokers, 22% former smokers
  - Current cigarette smoking increases the risk of being anti DNA positive, OR of 4.1
    ** Anti DNA antibodies are highly correlated with lupus nephritis**

- Jewel et al examined the records of 61 patients with cutaneous lupus
  - Smoking decreased the efficacy of antimalarials in treatment of cutaneous lupus
  - Dose-response relationship (heaviest smokers had the least improvement)

- In addition, smoking definitely increases risk of cardiovascular events which SLE patients are already at heightened risk for.

Mechanisms by which Cigarette Smoking can be Linked to SLE:

Cigarette smoking leads to an influx of ‘sick’ neutrophils into the lung which rapidly undergo apoptosis.

Smoking also impairs the ability of the macrophages to clear cellular debris via phagocytosis.

This leads to high level of exposed intracellular antigens in the extracellular space.

Current smoking is the real risk: Stop smoking!

(Majka, Ann Rheum Dis 2006)
Objective 3
Describe the clinical course of SLE.
Clinical Course—Remission Rates

Patterns of disease activity:

**Chronic active**— at least a year of continuous disease activity
**Relapsing remitting**— periods of disease activity interspersed with periods of disease inactivity during two or more visits during one year
**Quiescent disease**— remained quiet for at least one year

204 lupus patients followed quarterly for 2-7.5 years:

**Quiescent disease** 16-25% of patients
**Relapsing remitting** 26-35% of patients
**Chronic active** 40-60% of patients

In other words, given a cohort of 100 lupus patients, expect only 16-25 patients to have quiescent disease for one or more years.

(Barr, Arthritis Rheum 1999)
Mucocutaneous Concerns—Rashes

• Malar rash: present in up to 50% of patients associated with exposure to ultraviolet light
• Discoid lupus: present in 25% of pts:
  – Discrete, erythematous, with adherent scale and follicular plugging;
  – Active inflammation at edges (peripherally)
  – Central depressed scars; atrophy, telangiectasias and changes in pigmentation
  – Commonly seen on head, neck, scalp, ears (sometimes upper torso)

(Schur. Cutaneous manifestations of SLE. Up to Date v.14.2; Callen Best Pract Res Clin Rheumatol 2005)
Subacute cutaneous lupus:
Present in 10% of patients. Can be caused or exacerbated by hydrochlorothiazide or other antihypertensives, interferon, statins or other medications in some patients with anti-Ro (SSA) antibodies, and does not leave a scar when healing (unlike DLE).

(Schur. Cutaneous manifestations of SLE. Up to Date v.14.2; Callen, Best Pract Res Clin Rheumatol 2005)
Mucocutaneous Concerns—Rashes (3)

- Rare: lupus may also be associated with several rare rashes including:
  - Lupus profundus: painful, firm, nodular lesions causing panniculitis, with resultant atrophic skin changes and scarring
  - Bullous skin lesions: subepidermal bullous (blistering) lesions not only on sun-exposed areas
  - Lupus tumidus: photosensitive pink to violaceous rash

(Schur. Cutaneous manifestations of SLE. Up to Date v.14.2; Callen, Best Pract Res Clin Rheumatol 2005)
Mucocutaneous Concerns—Alopecia

• **Alopecia**
  – Scarring: discoid lupus lesions
    • Discrete inflammatory areas of alopecia
    • Can use intralesional steroid injections to increase chances of hair regrowth.
  – Nonscarring:
    • Telogen effluvium, stress-related diffuse thinning of the scalp hair
      – will regrow spontaneously
    • “Lupus hair” thin fragile hair, usually at forehead edge of hairline
      – grows back normally when disease controlled.

(Schur. Cutaneous manifestations of SLE. Up to Date v.14.2)
Mucocutaneous concerns—Mucous Membranes and Sicca Symptoms

- Oral ulcers, may be painless
- Nasal ulcers,
  - Bilateral
  - At lower nasal septa
- Sicca symptoms
  - 9.2% of lupus patients
  - May precede the diagnosis of SLE
  - Associated with:
    - Older-onset SLE
    - Anti-Ro and anti-La antibodies (secondary Sjögren’s syndrome)
    - Raynaud’s phenomenon
    - More likely to have a positive rheumatoid factor (Manoussakis, 2004)

(Schur. Cutaneous manifestations of SLE. Up to Date v.14.2 Manoussakis, Arthritis Rheum 2004)
Mucocutaneous Concerns—Vascular Lesions

• Livedo reticularis: vasospasm of dermal arterioles (associated with antiphospholipid antibodies)

• Urticarial or purpuric vasculitis: immune complex deposition
  – parallels lupus activity
  – (decreased complement levels; increased anti DNA antibodies)

(Schur. Cutaneous manifestations of SLE. Up to Date v.14.2)
Mucocutaneous Concerns—Vascular Lesions (2)

- Raynaud’s Phenomenon: (vasospasm of nail beds or digital arterioles)
  - Diagnostic clues: loss of digital pulp (fingertips), ulceration or scarring
  - May lead to gangrene and loss of digits.
- Periungual erythema: dilated nailfold capillaries (anticardiolipin antibodies)

(Schur. Cutaneous manifestations of SLE. Up to Date v.14.2)
Vascular Involvement

- Vasculitic skin lesions:
  - Blood extravasation from injured vessels
  - Palpable purpura—
    • Slightly raised
    • Non-blanching
    • Ulcerations may be present.
- Prevalence: 11%
  - 89% cutaneous vasculitis
  - 11% had isolated visceral vasculitis
  - Vasculitis associated with:
    • Active disease
    • Livedo reticularis
    • Anemia
    • High ESR
    • Anti-La/SSB antibodies (Ramos-Casals, 2006)

(Ramos-Casals, Medicine 2006)

Palmar cutaneous vasculitis
Cardiopulmonary involvement—overall

**Pulmonary:**
- Pleuritis
- Acute reversible hypoxia
- Pneumonitis with or without hemorrhage
- Pulmonary hypertension
- Shrinking lung syndrome (diaphragmatic dysfunction)
- Pulmonary infections
- Pulmonary embolism

**Cardiac:**
- Pericarditis
- Cardiomyopathy
- Myocarditis
- Libman-Sacks (nonbacterial) verrucous endocarditis
- Atherosclerosis
- Coronary arteritis
- Congenital heart block

(Kao, Best Pract Res Clin Rheumatol 2002)
Cardiopulmonary Involvement — Most Common Concerns

- Symptomatic pericarditis is seen in 25% of patients and presents as positional precordial or substernal chest pain, fever, tachycardia, pericardial rub; significant effusion may present with muffled heart sounds and pulsus paridoxus.
- Myocarditis is found in 14% of patients and presents as dyspnea, tachycardia, arrhythmia and occasionally as CHF.
- Libman Sacks endocarditis affects 30% patients and is seen even without antiphospholipid syndrome. Affected patients need SBE prophylaxis.
- Pleuritis affects 45-60% patients and is likely to be accompanied by fever.
- Interstitial lung disease affects 3-8% patients
- Secondary pulmonary hypertension affects 5-14% patients.

(Kao, Best Pract Res Clin Rheumatol 2002)
Late Cardiopulmonary Involvement — Atherosclerosis

- Women with lupus who are between 35-44 years old have an incidence of myocardial infarction more than 50 times that of age matched controls from Framingham study.  
  (Manzi, Am J Epidemiol 1997)

- Case-control study: The prevalence of atherosclerosis (identified by carotid plaque on ultrasonography) in a cross-section of lupus patients less than 50 years old is 33%.  
Anemia in Lupus

Prospective study of 132 lupus patients with anemia:

- Iron deficiency anemia and anemia of chronic disease each accounted for slightly more than 33% of cases
- Autoimmune hemolytic anemia was relatively rare, seen in less than 15% of patients
- Autoimmune hemolytic anemia associated with:
  - More severe anemia
  - Positive anticardiolipin antibodies
  - Lower complement levels
  - Higher anti DNA levels

  - Diagnostic tests:
    - Elevated reticulocyte count
    - Low haptoglobin levels
    - Increased indirect bilirubin
    - Positive direct Coombs’ test
    - Increased LDH
    - Peripheral smear- may show RBC fragments

(Voulgarelis, Ann Rheum Dis 2000)
Other Causes of Anemia

BEWARE:

• Anemia can also be a side effect of immunosuppressants.
• Screen for occult pernicious anemia. (Many patients are receiving folate supplementation due to methotrexate use, etc.)
• Consider whether renal insufficiency is the cause of impaired red cell erythropoiesis
• Screen for occult blood loss (NSAID gastropathy; menorrhagia; pulmonary hemorrhage)

(Schur. Hematologic manifestations of SLE in adults. Up to Date v.14.2)
Leukopenia

Leukopenia occurs in 15-20% of patients and appears to be associated with increased risk of infection, especially when patient is also on immunosuppressive medication:

- **Lymphopenia:**
  - 6 lupus patients who developed Pneumocystis carinii pneumonia after IV cyclophosphamide or azathioprine; cases had significantly lower lymphocyte count and were on higher doses of prednisone than a cohort of similar patients used for comparison
  - Retrospective analysis of recently diagnosed lupus patients in China; lymphopenia was positively associated with increased risk of infection (hazard ratio 4.7)

- **Neutropenia:**
  - Retrospective case-control study with 33 neutropenic patients and 65 controls
    - Neutropenia likely associated with immunosuppressant use
    - Neutropenic patients more likely to be hospitalized for infection
    - However neutropenic patients have less lupus activity and no differences in mortality

Antiphospholipid Antibody Syndrome

- Arterial or venous thromboses
  - Can cause catastrophic thrombosis in any organ including myocardial, cerebrovascular, pulmonary and deep vein
- Placental thromboses
  - Recurrent pregnancy loss or preterm birth (<34 weeks) due to pre-eclampsia, eclampsia or placental insufficiency
- Antiphospholipid antibody levels can fluctuate and be false-positive – to confirm you should have elevated titers on at least two occasions 6 or more weeks apart.

(Bermas, Clinical manifestations and diagnosis of antiphospholipid syndrome. Up to Date v.14.2)

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Renal Involvement—Lupus Nephritis (LN)

• Present in: 40-60% of lupus patients
  – Higher percentage in minorities

• Lupus nephritis:
  – Rising anti DNA antibodies
  – Lowering of complement levels (C3, C4, CH50)

  – HOWEVER: Rising anti DNA levels and decreasing serum complement levels do not always predict flares.
  – Serum indicators signal need for more frequent monitoring

(Ho, Arthritis Rheum 2001; Ter Borg, Arthritis Rheum 1990)
Summary of ISN LN Classification:

- **Class I Minimal Mesangial LN:**
  - normal light microscopy (LM), immune deposits visible only by immunoflorescence

- **Class II, Mesangial Proliferative LN:**
  - mesangial hypercellularity, no subepithelial or subendothelial deposits visible with LM

- **Class III Focal LN**
  - subendothelial deposits in <50% of all glomeruli (active-proliferative; chronic-sclerosing)

- **Class IV Diffuse LN**
  - subendothelial deposits in >50% of all glomeruli (diffuse segmental-many glomeruli have segmental lesions (involves less than half the glomerular tuft); diffuse global-many glomeruli are globally affected); also subdivided as active or chronic

- **Class V Membranous LN**
  - Subepithelial immune deposits; +/- mesangial changes, global or segmental

- **Class VI Advanced Sclerosing LN**
  - > 90% of glomeruli sclerosed with no residual activity

(Weening, Kidney Int 2004)
Indications for Renal Biopsy

• Suspect lupus nephritis
  – Estimated or 24 hour protein excretion has risen sharply
• Biopsy in order to:
  – Establish a diagnosis of lupus nephritis versus other causes of renal disease
  – Stage the degree of nephritis (patterns of nephritis activity are associated with prognosis)
  – Distinguish new lupus nephritis activity (inflammation) versus chronic changes

(Schur. Overview of … lupus nephritis. Up to Date v.14.2.)
Urine Protein: Creatinine Ratio

• Easier to procure than are 24 hour urine samples.
  – Less opportunity for patient noncompliance.
  – Fewer errors
  – Quicker sample procurement

• Are quite accurate in general
  – Accuracy may decrease in patients with severely elevated urinary protein excretion
  – And in patients who have creatinine clearances ≤10

• Controversy exists as to whether it is best to examine the protein:creatinine ratio from the first morning void versus a random sample or a timed (eg, 4 hour) collection

Urine Protein: Creatinine Ratio (continued)

• A bit of math:
  • Example: spot urine protein: 81 mg/dl
  • Spot urine creatinine: 75 mg/dl

  – Make a ratio: urine protein/urine creatinine = x/1000. Here, 81/75 = x/1000. Answer: approximate protein excretion of 1080 mg/day which clearly is abnormal (> 200 mg/day indicates pathology with renal protein filtering)

  – Alternatively, one can use a straight ratio: 81/75 = 1.08; greater than 0.2 is abnormal

Neuropsychiatric lupus—ACR definitions

• Central:
  – Aseptic meningitis, cerebrovascular disease, demyelinating syndrome, headache, movement disorder, myelopathy, seizure disorder, acute confusional state, anxiety disorder, cognitive dysfunction, mood disorder, psychoses
• Peripheral:
  – Peripheral: Guillain Barre syndrome, autonomic neuropathy, mononeuropathy, myasthenia gravis, cranial neuropathy, plexopathy, polyneuropathy
• Prevalence of NP-SLE using ACR criteria ranges from 37-91%, depending on the study.
  – Most common manifestations of NP-SLE were cognitive dysfunction, headache, mood disorder, and cerebrovascular disease
• Possible relationship with antiphospholipid antibodies

• A comprehensive review may be found at:

Other Concerns

• Higher rates of some cancers seen in SLE patients:
  – Non-Hodgkin's lymphoma
  – Lung cancer

• Higher risk of infections
  – Altered immunity
  – Immunosuppressive medications

• Other illnesses:
  – Higher incidence of osteoporosis and avascular necrosis
  – Unclear whether due only to glucocorticoids or whether there is any contribution from SLE or antiphospholipid syndrome

(Bernatsky, Arthritis Rheum 2006)
Mortality in SLE

- More active disease and worse prognosis seen in ethnic minorities
- Lupus manifestations and disease activity also vary by region

- Example:
  Consider Hispanics in Texas versus Hispanics in Puerto Rico.

  Hispanics in Texas exhibit increased disease activity, more major organ involvement, higher titers of anti-DNA, and accrue more damage.

  This fascinating phenomenon can also be seen when comparing other countries and may possibly point to environmental or stress-related factor(s).

(Vila, Rheumatology 2004)
Early and Late Causes of Mortality

• Overall lupus mortality rates have declined over the past 50 years however:
  – Rates remain 3 times that of age and gender matched controls
  – Mortality in African American women with SLE has increased in the last 20 years
  – Change in the mortality patterns (causes of death).
    • Most common causes of death:
      – Heart disease
      – Malignancy
      – Infections

• Currently lupus has a bimodal pattern of mortality:
  – Early causes: active SLE and infection
  – Late causes: thrombotic (cardiovascular), primarily due to accelerated atherosclerosis

(Borchers, Autoimm Rev 2004; Cervera, Medicine 2003; Bernatsky, Arthritis Rheum 2006)
Survival Rates and Risk Factors

• Retrospective analysis of the Hopkins lupus cohort—
  – 1378 patients
  – 39% African-American, followed since 1987

• Current 10 year survival rates are up to 91%, 20 yr survival rates are up to 78%

• Risk factors for poor survival include:
  » Male gender (20 yr survival rate 68%)
  » Age >50 at diagnosis
  » African American
  » Lower socioeconomic status
  » Low complement levels
  » Higher disease activity at diagnosis (measured by SLEDAI score)
  » Hemolytic anemia at any point

(Kasitanon, Medicine 2006)
Late onset SLE—prognosis in older patients

- Late onset SLE
  - More quiescent disease
  - Higher damage accrual and higher mortality rates

- In a nested case control study, lupus patients diagnosed after age 50 were more likely to have:
  » Neurologic involvement
  » Arterial thrombotic events
  » Osteoporosis
  » Hypertriglyceridemia
  » Cardiovascular damage
  » Ocular damage
  - But were less likely to have renal involvement and anti-Sm antibodies.

(Bertoli, Arthritis Rheum 2006)
Objective 4

Determine differential diagnoses associated with SLE.
Differential Diagnosis of Lupus:

SLE has been termed “the great imitator” for its propensity to mimic various other disorders. Here are a few common differential diagnoses to consider when a patient presents with polyarticular joint pain:

<table>
<thead>
<tr>
<th>Early Rheumatoid Arthritis</th>
<th>Primary Sjogren’s Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed Connective Tissue Disease</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Undifferentiated Connective Tissue Disease</td>
<td>Scleroderma</td>
</tr>
<tr>
<td>Antiphospholipid antibody syndrome</td>
<td>Drug induced lupus</td>
</tr>
<tr>
<td>Fibromyalgia with positive ANA</td>
<td></td>
</tr>
</tbody>
</table>

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Differential Diagnosis of Malar Rash

- Malar rash, flushing or hyperpigmentation of bilateral cheeks and bridge of nose which spares the nasolabial folds, is pathognomic of lupus. Nevertheless, similar rashes may be present in a variety of other disorders including:
  - Rosacea
  - Dermatitis
    - Seborrheic
    - Atopic
    - Contact
  - Glucocorticoid-induced atrophy
  - Chloasma/ Melasma
  - Benign flushing

(Schur. Cutaneous manifestations of SLE. Up to Date v.14.2)
Differential Diagnosis of Fever

• Low grade fever is a systemic sign of infection or inflammation. Common diagnoses to consider include:
  – Infection
    • Tuberculosis, Malaria, AIDS-associated infections
  – Malignancy
    • Lymphoma
  – Drug-induced
  – Inflammatory and Collagen-vascular disease
    • Sarcoidosis, SLE, Stills disease, Vasculitis

(Bor DH. Approach to patient with FUO. Up to Date v.14.2)
Differential Diagnosis of Positive ANA

- Measurement of antinuclear antibodies is not recommended as a screening test for SLE in the absence of other signs and symptoms as low titer positive ANA is prevalent in the normal population.
- In addition, other diseases commonly associated with positive ANA include:
  - Other systemic autoimmune diseases
    - scleroderma, mixed connective tissue disease, polymyositis/dermatomyositis, rheumatoid arthritis, vasculitis, Sjögren's syndrome and pauciarticular juvenile chronic arthritis
  - Specific organ autoimmune diseases
    - primary autoimmune cholangitis, autoimmune hepatitis, Graves' disease, Hashimoto's thyroiditis and primary biliary cirrhosis
  - Idiopathic pulmonary arterial hypertension
  - Chronic infectious diseases
    - mononucleosis, hepatitis C infection, subacute bacterial endocarditis, tuberculosis and HIV

(Reichlin M. Measurement and clinical significance of ANA. Up to date v.14.2)
Objective 5

Describe autoantibodies and other common laboratory tests in SLE.
Common Autoantibodies in Lupus

• ANA
  – Present at diagnosis in 76%; 94% positive at some point
  – Difficult to diagnose SLE without a positive ANA since the assay is very sensitive in most laboratories – with very few false negatives

• Anti dsDNA
  – Associated with lupus nephropathy

• Anti Ro/ anti-La
  – Associated with Sjögren’s syndrome

• Anti-Ro
  – Also associated with subacute cutaneous lupus, photosensitivity, neonatal lupus

• Anti-RNP
  – Associated with Raynaud’s phenomenon (To, Arthritis Rheum 2005)
Antiphospholipid Antibody Syndrome (APL)

• Antibodies present in ≥ 20% of lupus patients
• Types of antiphospholipid antibodies include:
  – Anti-beta2 GPI
  – Anticardiolipin antibody
  – Lupus anticoagulant
  – History of false positive syphilis serological test
• Note that anticardiolipin antibodies are found in 2-5% of normal population and in 12-52% of elderly patients

(Bermas. Clinical manifestations and diagnosis of antiphospholipid syndrome. Up to Date v.14.2)
Diagnostic Imaging

• Not valuable for diagnosis of lupus
• Used in detecting specific organ manifestations and in ruling out other disorders. For example:
  – X-ray:
    • Distinguish erosive or deforming arthritis
    • Check for cardiopulmonary involvement (cardiomegaly, interstitial lung disease, pleural effusion)
  – Echocardiogram:
    • Identify pericardial effusion
    • Identify pulmonary hypertension.
  – Pulmonary function test:
    • Useful for picking up low diffusion capacity (DLCO), suspicious for pulmonary hypertension
    • Identify restrictive versus obstructive disease

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Objective 6

Describe principles of disease management.
Pre-Medication Issues

• Collaboration
  – Research is dynamic
  – New therapeutics/ ways of using current medications

• Before prescribing immunomodulators:
  – Check tuberculosis status (PPD)
  – Check hepatitis B and C status
  – Consider baseline chest x-ray prior to methotrexate use (methotrexate can cause pulmonary fibrosis)

• When prescribing prednisone, protect bone density:
  – Consider baseline DXA (depending on age, risk factors)
  – Prescribe calcium + vitamin D

• Preventive measures:
  – Influenza vaccine and pneumovax
  – Check BhCG at each visit in any woman who is of childbearing potential if prescribing a teratogenic agent
Compliance—Ask, Explore, Understand

• Prescribe what you will, if your patient doesn’t take the medicine, the only thing you’ve gained for your effort is the writer’s cramp. At each visit:

  – **ASK** your patients: “how many doses of your medicines have you missed in the past week?”

  – **EXPLORE** the answers in a non-threatening manner and

  – Try to **UNDERSTAND** why your patient is not complying.
Principles of SLE Therapeutics

• Most SLE manifestations respond initially to varying doses of prednisone. Issues to consider are
  – When to prescribe prednisone or other agents
  – The patient’s pattern of prior response to steroids
  – How to taper
  – When to add steroid sparing agents
Side Effects of Prednisone

- Steroids: short-term moderation of inflammation.
- Common side effects include:
  - Immediate: acne, behavioral changes, sleep disturbances
  - Short-term: obesity, glucose intolerance, hypertension, hyperlipidemia
  - Long term: Osteoporosis, cardiovascular diseases, cataracts, avascular necrosis
- Steroid damage: the Hopkins Lupus Cohort (539 pts)
  - Risk of long-term sequelae increases with cumulative steroid exposure
    - Relative risk (RR) for osteoporotic fracture 2.5;
    - Symptomatic CAD RR 1.7
    - Cataract RR 1.9
    - High dose steroid exposure: increased risk of AVN, stroke

(Zanana-Nacach, Arthritis Rheum 2000)
Immunomodulators

• Steroid sparing agents
  – Hydroxychloroquine (Plaquenil)
  – Thalidomide (for mucocutaneous manifestations)
  – Dapsone (for panniculitis, vasculitis)
  – Danazol (for thrombocytopenia)
• General Immunosuppressants
  – Azathioprine (Imuran)
  – Cyclophosphamide (Cytoxan)
  – Leflunomide (Arava)
  – Methotrexate
  – Mycophenolate Mofetil (CellCept)
• Biologics
  – Abatacept (Orencia)
  – Rituximab (Rituxan)
• Other
  – IVIg
Steroid Sparing Agents:

- **Hydroxychloroquine (Plaquenil)**, an antimalarial,
  - Used for mucocutaneous manifestations, pleurisy, arthritis and fatigue.
  - Studies have shown a decrease in damage accrual and a survival advantage for patients on long-term therapy.
  - Adverse events are rare but may include macular damage and exacerbation of existing psoriasis.

General Immunosuppressants (1)

• **Azathioprine**—a purine synthesis inhibitor
  – used as steroid sparing for extrarenal lupus and also used for maintenance of remission in lupus nephritis.
  – Adverse events include infections, myelosuppression, hepatotoxicity.

• **Cyclophosphamide (Cytoxan)**—an alkylating agent
  – Used to treat renal disease
  – Adverse events include pancytopenia, hematuria, bladder cancer, infertility, infections.

General Immunosuppressants (2)

- **Leflunomide (Arava)**—pyrimidine synthesis inhibitor
  - has been used in small case series to treat SLE with inflammatory arthridities
  - Adverse events include infections, oral ulcers, GI disturbances

- **Methotrexate**—a folic acid antagonist
  - Used to treat active arthritis and skin disease
  - Some studies show increased toxicity in SLE pts
  - Adverse events: oral ulcer, hepatotoxicity, pancytopenia, pulmonary infiltrates and fibrosis, infections.

- **Mycophenolate mofetil (CellCept)**—inhibits inosine monophosphate dehydrogenase, a rate limiting step in the proliferation of activated lymphocytes,
  - Used in lupus nephritis
  - Adverse events include diarrhea, lymphopenia, infections

Biologics

- **Abatacept (Orencia)**—a selective costimulation modulator of T cells (binds to CD80 and CD86, blocking T cell interaction with CD28; ie, blocks T cell activation)
  - Promising results in murine models
  - Used experimentally to treat lupus nephritis
  - Adverse events include infusion reactions and increased risk of infections

- **Rituximab (Rituxan)**, a chimeric anti-CD 20 antibody, inhibits and eliminates immature B cells
  - Case studies report use in lupus nephritis and refractory systemic symptoms
  - Adverse events include infusion reactions, late infections, neutropenia, rashes

Other Immunomodulators

• IVIg (intravenous immunoglobulin)
  – Some case reports state efficacy in severe refractory lupus such as pulmonary hemorrhage, polyradiculopathy
  – BUT there have also been rare reports of severe SLE exacerbations
Treatment of Rashes and Photosensitivity

- An ounce of prevention…
  - Avoid high intensity UV light exposure: beaches and snow
  - Avoid sun exposure 10AM to 3 pm, use wide-brimmed hats and sun protective clothing
  - Sunscreen of at least SPF 30
- If only topical lesions, can try:
  - Cortisone cream BUT beware that chronic steroid application will cause skin atrophy, thinning, telangiectasia, stria, depigmentation, increase in hair growth
  - Topical tacrolimus or piocrolimus BUT linked to increased risk of skin cancer
  - Topical retinoids (still under investigation)
  - Antimalarial drugs BUT can cause flare of psoriasis and porphyria cutanea tarda; check for G6PD deficiency; check for visual field changes: baseline ophthalmologic exam then every six months
  Usual dose: hydroxychloroquine 200 mg BID in adults
- Recalcitrant lesions can be treated with systemic steroids followed by steroid sparing agents including azathioprine, methotrexate, cyclosporine, cyclophosphamide, mycophenolate mofetil, thalidomide

(Schur. Cutaneous manifestations of SLE. Up to Date v.14.2; Callen, 2005)
Treatment of Raynaud’s Phenomenon

- Avoid Triggers: smoking, caffeine, cold exposure
- Wear warm clothing including turtlenecks and scarves, gloves (may need two pairs; mittens will work better than gloves); keep torso warm to allow adequate blood flow to tips of extremities.
- Medication: Calcium channel blockers, specifically nifedipine, are used most frequently. Other vasodilators such as losartan, have also been evaluated in small trials with apparent success.
- Other agents which have been used successfully to treat recalcitrant RP include:
  - Cilostazol (Pletal)
  - Tricyclic antidepressants such as amytriptyline (Elavil)
  - Phosphodiesterase 5 inhibitors such as sildenafil (Revatio/Viagra)
- Digital sympathetic block may also afford some relief.

(Thompson, Arthritis Rheum 2001; Dziadzio, Arthritis Rheum 1999; Rosenkranz, 2003; Schur. Cutaneous manifestations of SLE. Up to Date v.14.2)
Treatment of Arthritis

- Arthritis is the most common lupus manifestation. Accordingly, there has been much opportunity to explore how to alleviate the pain and disability of joint inflammation.
  - Hydroxychloroquine and azathioprine are useful for mild arthritis/arthralgia; NSAIDs provide symptomatic relief
  - For more severe cases methotrexate is helpful
  - Refractory cases may benefit from leflunomide (Arava)

Treatment of Hematologic Disorders

- Hemolytic anemia
  Steroid-responsive in 75% of patients
  If recurs with tapering add azathioprine, cyclophosphamide, danazol, mycophenolate mofetil, rituximab, IVIG

- Severe immune thrombocytopenia (platelets less than 50,000 and symptomatic or less than 20,000 even if asymptomatic) needs treatment.
  - Steroid responsive
  - If platelet count drops may add an immunosuppressive.
  - Several case series have successfully treated with danazol, sometimes in combination with plaquenil or rituximab.

- Antiphospholipid antibody syndrome
  - Anticoagulation with coumadin to achieve an INR of between 2.5 and 3.5.
  - This is said to reduce incidence of thromboses by 75%.

(Arnal, J Rheumatol 2002; Gomard-Mennessson, Lupus 2006; Schur, Hematologic. Up to Date; Bermas, Treatment of the antiphospholipid syndrome, Up to Date)
Treatment of Lupus Nephritis (LN)

• Treatment of LN entails a stepwise approach, first to induce remission (“induction”) then to maintain remission (“maintenance”). The following is a brief summary:

• Induction
  – High dose corticosteroids initially with:
  – Cyclophosphamide (NIH protocol, IV monthly for 6 months)
  – Mycophenolate mofetil (recent research)

• Maintenance:
  – Azathioprine
  – Mycophenolate mofetil
  – Cyclophosphamide IV every 2-3 months

• Under investigation:
  – rituximab –case series, no randomized controlled trial data yet
  – Leflunomide—one small study
  – Abatacept (Orencia)—clinical trial planned, not yet underway (Buhaescu, in press; Ginzler, New Engl J Med, 2005)
Treatment of Atherosclerotic Disease

• Atherosclerosis is a significant cause of late SLE mortality
• Experts recommend considering SLE as a CHD-equivalent
• LDL cholesterol levels ought to be maintained at ≤ 100 mg/dl
• Fasting lipid profile should be checked annually
• Antimalarials have cholesterol lowering properties in addition to their disease-moderating effects
• All lupus patients with LDL >100 despite diet, exercise and antimalarial treatment, should be placed on statin therapy.

(Bruce, Best Pract Res Clin Rheumatol 2005)
Treatment of Atherosclerotic Disease, continued:

Aspirin: “an aspirin a day” therapy is indicated for the following patients:
- History of MI, angina, TIA, stroke
- APL or LAC (ACL)
- HTN
- DM
- Hypercholesterolemia
- Smokers
  **in the absence of any contraindications to aspirin therapy, including age less than 21 years.

Remember to monitor for traditional risk factors and treat appropriately:
- Hypertension
- Diet and exercise patterns
- BMI (ought to be < 25)
- Homocysteine

In addition, antimalarial agents may be helpful in decreasing cholesterol and in modulating inflammation. ACE inhibitors may have a role in treatment of known coronary heart disease.
(Bruce, Best Pract Res Clin Rheumatol 2005)
Patient Education

• Key to ensuring compliance
• Handouts (pamphlets free from CDC, fact sheets from ACR)
• Draw pictures to explain abstract concepts
• Let patient track own lab values
• Give websites where patient can find reliable information: NIH, CDC, Arthritis Foundation, Merck Manual, Lupus Foundation
• Educate about SLE
  – (Refer to “answers to JD” in Objective 2 case discussion)
• Ask if patient has any questions
• Reinforce need for:
  – Diet (eat fruits and vegetables, watch cholesterol, whole grains)
  – Exercise (bone strength, heart disease, ROM for joint/ flexibility)
  – Maintain ideal body weight
  – Stress management techniques and family/social support
Inside the Patient’s Mind

Focus on your goal: patient education to preserve or improve QOL

Ask: Why is my patient acting this way?

• **Interpretive structures**: mechanisms for explaining and giving meaning to events. The context by which the person perceives and gives meaning to his/her disease. This effects how the patient interprets the prescribed treatments and advice—everything is filtered past this!

• **Self management**: how patients attempt to promote health and limit illness. This includes medication use, CAM, doctor visits, diet/exercise...

• **Self efficacy**: confidence regarding the ability to perform a behavior or affect a change in thought/ action. This is specific to each behavior—one can have high self efficacy about driving a car and low self efficacy about taking medications, for example.

  (Ramos-Remus, Baillieres Best Pract Res Clin Rheumatol 2000)
Additional Patient Care Issues

- Culturally Sensitive Care
  Respectful communication entails understanding the cultural context
  - Interesting pilot study: culturally sensitive cholesterol lowering diet program
  - 4 patients with SLE (2 African-American and 2 Mexican-American)
  - Result: significant improvement in cholesterol and weight loss
  - Used easy to understand information, ethnically sensitive, provided strategies for adherence

- Psychosocial needs of lupus patients
  - Patients’ unmet needs: mail survey done in Australia; 386 pts
    - Tiredness (81%)
    - Pain (73%)
    - Not being able to do things one used to do (72%)
    - Fear of exacerbation (72%)
    - Sleeping problems (70%)
    - Anxiety and stress (69%)
    - Feeling down (68%)
Psychosocial Adaptation

• LUMINA (554 pts): Psychosocial factors associated with disease activity
  – Lack of social support
  – Poor illness coping skills
  – Helplessness attitudes.

• Potentially modifiable:
  – Support groups
  – Patient empowerment
  – Compliance

• Clinical Update: Randomized controlled three arm trial:
  – Stress reduction techniques reduce pain, increase psychological function and increase perceived physical function.
  – Used biofeedback-assisted cognitive support versus system monitoring support or usual medical care.
  – Psychological difference persisted at 9 month follow up

Objective 7

Discuss future directions including opportunities for research.
Research- Our Legacy to Future Patients

• Much about lupus remains unclear:
  – How to properly diagnose
  – Pathophysiology
  – Genetics/heritability
  – Course
  – Response to medications
  – Potential therapeutic options

To this end, patient participation in clinical research protocols is crucial to enhance our understanding of lupus and positively impact on the morbidity and mortality associated with SLE.
Research Issues

Other research issues of note include:

• SLE prevalence differences between Blacks in the US and Britain compared to Blacks in Africa
• Female predominance
• Causes of SLE
• Predictors of flare and predictors of the disease course
• Pharmaceutical agents:
  – immune modulators to down-regulate inflammation;
  – to interfere at the level of preventing autoantibody production
• Efficacy and safety of complementary therapeutics (CAM)
• Effects of stress and how to moderate
• Preventing and predicting flares
• Pain control
• Psychosocial adaptation and the role of social support
• Compliance with medications and prescribed regimen
• Proper exercise regimen to prevent cardiovascular disease
Research Tools

• SLEDAI-SLE disease activity index, composed of 24 items; it measures disease activity and severity of flares.
• SLAM-Systemic Lupus activity measure
• ECLAM-European community lupus activity measure
• BILAG-British Isles lupus assessment group index. It evaluates 8 different organ systems and is very sensitive at differentiating between disease activity and severity. It is recognized by the FDA and is ubiquitous in all clinical trials in the US.
• SLICC-DI –records irreversible change in an organ system that has been present for 6 months or more
• Where to find studies in progress:
  – www.clinicaltrials.gov for a listing of ongoing trials in the US
  – The Lupus Foundation and their regional chapters as well as the Arthritis Foundation and their regional chapters have listings
  – Lists of ongoing trials are posted at the ACR meetings.
Special issues: Lupus as a young person’s disease

- Young people tend to feel invincible
- Problems with compliance
- Difficulty remembering to take their meds/strategic planning to carry pills when go “out”
- Need for independence
- Friction with parents
- Need to encourage patients to finish schooling and pursue a career. A lupus diagnosis shouldn’t consign a person to a life on disability.
As a young woman grapples with her lupus diagnosis, various issues of fertility need to be addressed.

- Use of oral contraceptives nonsmoking
  - stable disease
  - no antiphospholipid antibodies nor a history of thromboses
- Pregnancy: potential for lupus flare
  - Lupus flare risk: indeterminate
- Risk of congenital heart block or neonatal lupus
  - antiRo + or antiLa + confers a 2% risk
- Risk of child developing lupus later in life (5%)
- Hormone replacement therapy
- Lupus in postmenopausal female
  - Different disease profile
Special issues: Lupus and male patients

- Stigmatizing
- How it feels to have a “woman’s disease”
- Differing presentation in male
- More virulent disease
- Support groups/ issues
- Malar rash/ DLE
  - Men don’t usually wear makeup