SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)
Other Types of “Lupus”

- Discoid Lupus Erythematosus
- Lupus Pernio --- Sarcoidosis
- Lupus Vulgaris --- Tuberculosis of the face

Manifestations of SLE

- Fever
- Rashes
- Arthritis
- Fatigue
- Weight loss
- Lung
  - Pleurisy, pneumonia
- Heart
  - Pericarditis, heart failure

Kidneys
- Nephritis
- Nervous system
  - Stroke, cerebritis
  - Seizures
- Blood count
  - Anemia
  - Thrombocytopenia
  - Abnormal clotting or bleeding
### American College of Rheumatology Criteria

| 1. Malar rash  | 8. Seizures, psychosis |
| 3. Photosensitivity | 10. Antinuclear antibody |
| 4. Oral/nasal ulcers | 11. Other abnormal antibodies (e.g., anti-DNA antibodies) |
| 5. Nonerosive arthritis |  |
| 6. Pleurisy/pericarditis |  |
| 7. Renal abnormalities |  |

### Manifestations of SLE

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<tr>
<th>Fever</th>
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Anti-Cardiolipin Syndrome (Anti-phospholipid Syndrome, Lupus Anticoagulant)

- Occasional feature of Lupus, or occurs alone
- Frequent miscarriages
- Tendency to form blood clots
  - Stroke
  - Blood clots in legs or lungs

**INCIDENCE (FREQUENCY)** –
- Number of new cases in a given population over a certain period of time, usually a year

**PREVALENCE** –
- Number of active cases in a given population at a certain point in time (cross-section)
### Annual Incidence per 100,000

<table>
<thead>
<tr>
<th>Region</th>
<th>Incidence</th>
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</thead>
<tbody>
<tr>
<td>US</td>
<td>1.0</td>
</tr>
<tr>
<td>US</td>
<td>2.0</td>
</tr>
<tr>
<td>US</td>
<td>7.6</td>
</tr>
<tr>
<td>US</td>
<td>4.6</td>
</tr>
<tr>
<td>US</td>
<td>1.8</td>
</tr>
<tr>
<td>Curacao</td>
<td>4.6</td>
</tr>
<tr>
<td>US</td>
<td>2.4</td>
</tr>
<tr>
<td>US</td>
<td>5.6</td>
</tr>
<tr>
<td>Brazil</td>
<td>8.7</td>
</tr>
<tr>
<td>Sweden</td>
<td>4.8</td>
</tr>
<tr>
<td>UK</td>
<td>6.5</td>
</tr>
<tr>
<td>Sweden</td>
<td>4.8</td>
</tr>
<tr>
<td>Denmark</td>
<td>2.5</td>
</tr>
<tr>
<td>UK</td>
<td>2.5</td>
</tr>
<tr>
<td>Finland</td>
<td>0.37</td>
</tr>
<tr>
<td>Norway</td>
<td>2.6</td>
</tr>
</tbody>
</table>

### Gender – Age of Onset

- **F:M**
- **Children** = 1:1
- **Teen/Middle Age** = 9:1
- **65 & Older** = 1:1
### NATURE (GENETICS)

- Overall likelihood = 0.04 - 0.1?
- Sister = 2-5%
- Fraternal twin = 2-5%
- Identical twin = 24-58%

### NURTURE (ENVIRONMENTAL)

<table>
<thead>
<tr>
<th>Category</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>Hydralazine</td>
</tr>
<tr>
<td>Foods</td>
<td>Flaxseed?</td>
</tr>
<tr>
<td>Viruses</td>
<td>Epstein-Barr Virus</td>
</tr>
<tr>
<td>Toxins</td>
<td>Sunlight</td>
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</table>
Mechanisms – How does SLE develop?

• Autoimmunity – Failure of the immune system to recognize “self”.
• Genetic background
• Triggered by ?

SLE -- Diagnosis

• Symptoms
  – Fatigue, joint pain, fever, etc.
• Physical findings
  – Rashes, swollen joints, etc.
• Laboratory findings
  – Antinuclear Antibody (ANA), Abnormal urinalysis, etc.
### Antinuclear Antibody (ANA)

- We’ve all got some
- Screening test – Very sensitive
- Most individuals with a positive ANA test do not have SLE
- May lead to over-diagnosis

### Other antibodies – Less sensitive but more specific for SLE

- Anti-DNA Antibodies***
- Anti-Smith (Sm) Antibodies***
- SSA, SSB, RNP antibodies
### MARKERS OF DISEASE ACTIVITY

- Depressed complement levels
- Elevated anti-DNA levels
- Elevated erythrocyte sedimentation rate
- Elevated C-Reactive Protein
- Urine abnormalities
  - Protein
  - Blood cell casts

### Complement

- A system of proteins normally involved in healthy immune reactions, e.g., killing bacteria
- Over-activated in Lupus, results in abnormal immune reactions, e.g., destroying red blood cells or damaging the kidneys.
- Levels are below normal in active Lupus, complement is used up, or “consumed”.
### Anti-DNA Antibodies

- Abnormal antibodies directed against a person’s own body tissues.
- Anti-DNA antibody levels frequently parallel Lupus disease activity, particularly kidney inflammation.
- Rising levels can help to predict a flare.
- Anti-DNA levels can be used to monitor response to treatment

### Treatment

- Aspirin, Non-steroidal anti-inflammatory drugs (NSAID’s)
- Cortisone
  - Prednisone
  - Medrol
  - Etc.
### Anti-Malarial Drugs

- Chloroquine
- **HYDROXYCHLOROQUINE (PLAQUENIL)**
- Quinacrine

### Treatment

- **Immunosuppressants**
  - Cyclophosphamide (Cytoxan)
  - Azathioprine (Imuran)
  - Mycophenylate mofetile (CellCept)
- **Biologic agents**
  - Belimumab
  - Rituximab
Treatment - Biologic agents

Belimumab (Benlysta)

Rituximab (Rituxin)

Morbidity – Early Phase

- Severe Lupus flare
- Renal failure
- Brain disease (Cerebritis, stroke)
- Vasculitis, gangrene
- Myocarditis
- Pneumonitis
- Bleeding/Thrombosis
- Infection
Morbidity – Late Phase
“Disease Burden” “Treatment Burden”

- “Metabolic Syndrome”
  - Diabetes
  - Hyperlipidemia
  - Arteriosclerosis, myocardial infarction, stroke
- Fracture complications
- Infections
- Malignancy

Five Year Survival Rates 1950-2011
Changing Patterns of Mortality
Journal of Rheumatology 2008

• 1241 Subjects
• Standard Mortality Ratio (SMR)
• Cohorts
  – 1970-1978
  – 1979-1987
  – 1988-1996
  – 1997-2005
Why improved outlook?

• Increased awareness
• More sensitive screening – earlier diagnosis
• Improved management of first phase
  — Immunosuppression
  — Improved treatments for complications (e.g., infections)
• Improved management of second phase
  — Blood pressure control, statins, etc.

Mortality in SLE
Bertansky S et al 2006

• 9,547 subjects
• Overall Standard Mortality Rate 2.4
• “Relative High Risk”
• High Mortality for
  — Circulatory disease, infections, renal disease, non-Hodgkin’s Lymphoma, lung cancer
• Highest Risk
  — Female sex, younger age onset, SLE duration <1 year, African-American
### Medicine (2003)

- 1000 subjects followed for 10 years
- 10 year survival
  - Overall 92%
  - Renal 88%
  - Non-renal 94%
- Causes of death
  - First 5 years -- Active Lupus, Infection 29% each
  - Second 5 years -- Thrombosis, ASCVD 26%  

### Kasitanon et al.

*Medicine (2006)*

- 1378 subjects
- Medial follow-up 6.1 years. 8.6% died
- Probability of survival
  - 5 years – 95%
  - 10 years – 91%
  - 15 years – 85%
  - 20 years - 78%
- Worse prognosis
  - Onset >50 years old
  - M>F
  - Annual income <$25,000
### Prognostic Factors


- Renal Disease
- Hypertension
- Male sex
- Young age
- Poor SE status
- Cerebritis
- Cerebrovascular disease

- AA (SE?)
- Antiphospholipid antibodies
- Hemolytic anemia
- Thrombocytopenia
- Pulmonary hypertension
- Pulmonary hemorrhage

### Lupus Nephritis

- **Class I** -- Normal or minimal change
- **Class II** -- Mesangial nephritis
  - **Class III** -- Focal membranoproliferative
  - **Class IV** -- Diffuse membranoproliferative
  - **Class V** -- Membranous glomerulonephritis
  - **Class VI** -- End-stage
### PROGNOSIS OF VARYING SEVERITY

<table>
<thead>
<tr>
<th>Worse</th>
<th>Better</th>
</tr>
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<tbody>
<tr>
<td>• 18 year old presents with glomerulonephritis</td>
<td>• 40 year old presents with rash and arthritis</td>
</tr>
<tr>
<td>• 36 year old with pulmonary hemorrhage</td>
<td>• 38 year old with chronic stable thrombocytopenia</td>
</tr>
<tr>
<td>• 28 year old with organic brain syndrome, early dementia</td>
<td>• 32 year old with extreme fatigue and muscle aches</td>
</tr>
<tr>
<td>• 40 year old presents with stroke</td>
<td>• 58 year old with pleurisy</td>
</tr>
</tbody>
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### MALIGNANCY

- Non-Hodgkins Lymphoma
- Hodgkins Lymphoma
- Lung Cancer
- Breast Cancer
- Squamous cell skin cancer
- Cervical cancer
- Vulvar/Vaginal cancer
### Non-Hodgkins Lymphoma

**Annals of Rheumatic Diseases (2005)**

- 42 cases over 76,948 patient years
- Mean age at diagnosis 57 years
- Females 86%
- Diffuse Large B-cell type, i.e., aggressive
- 22/42 died within 1.2 years

### Non-Hodgkins Lymphoma

**Archives of Internal Medicine (2005)**

- Standardized Incident Rate (SIR) 7.4
- Considered “moderate”
### Non-Hodgkin's Lymphoma

**Annals of Rheumatic Diseases (2007)**

- Swedish study
- 16 subjects identified over 30 year period
- Conclusion:
  - Chemotherapy (cyclophosphamide, azathioprine) no increased risk
  - Hematological, pulmonary or sicca features higher risk

### Breast Cancer

**Rheumatology (2004)**

- 871 subjects
- 15 breast cancers vs. 7.2 predicted (SIR 2.1)
- No relation to family history or hormone use
| Skin Cancer  
| ---  
| **Lupus (2003)**  
| • Icelandic SLE Registry  
| • 238 subjects 1957-2001 (44 years)  
| • 39 malignancies in 36 subjects (16%)  
| • Odds Ratio (OR)  
|   – Squamous cell cancer **6.43** (p=0.012) – Significant  
|   – Lymphoma **5.48** (p=0.052) – “Not significant”  
|   – Uterine cancer **2.46**  
|   – Ovarian cancer **2.0**  
|   – Lung cancer **1.72**  
|   – Breast cancer **1.6** |