Systemic Lupus Erythematosus

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Mary Schira PhD, RN, ACNP–BC
The University of Texas at Arlington
College of Nursing and Health Innovation
Outcomes/Focus

- Etiology and multisystem effects of Lupus
- Therapy options – Lupus and Lupus nephritis
- Pharmacologic and non-pharmacologic management approaches for lupus nephritis.
Lupus

- Autoimmune disease
  - Body produces antibodies against cell nucleus
  - Immune system hypersensitive, hyperactive

- Characterized by exacerbations (flares) and remissions

- Variable course and prognosis

- Multiple genetic influences + environment; ? clear pattern of inheritance
Incidence, Prevalence

- 1.5 million in US (Lupus Foundation of America)
- 15,000 – 16,000 develop each year
- 90% women of childbearing age
- 2–3 times more prevalent in African American, Hispanic, and Asian women
Variability of Lupus

- **Variable severity**
  - Mild, moderate, severe
  - Increased severity associated with: abrupt onset, race/ethnicity, younger age onset

- **Variable organ system involvement**
  - Skin
  - Musculoskeletal
  - Kidney
  - Cardiac/vascular
Lupus on the Outside

- Synovitis
- Malar rash
- Oral ulcer
- Discoid rash
- Jaccoud’s arthropathy
- Vasculitis
- Lupus profundus

The Lupus Initiative
(www.thelupusinitiative.org)
Lupus on the Inside

Serositis

Pericardial effusion

Cerebral infarct

Brain atrophy

Spherocytes

Glomerulonephritis

The Lupus Initiative
(www.thelupusinitiative.org)
Diagnostic Criteria – SLE

- American College of Rheumatology
- [www.lupus.org](http://www.lupus.org)
- Meet 4 of 11 diagnostic criteria
Diagnosis – Lupus

- Abnormal antinuclear antibodies (ANA)*
- Arthritis (abnormal swelling, pain of at least 2 joints)
- Discoid rash (raise, red, disk-shaped patches)
- Malar rash (nose and cheeks; butterfly shape)
- Photosensitivity (rash appears with or worsens with sunlight)
- Oral ulcers
Diagnosis, cont.

- Immunological disorder (positive antiphospholipid antibodies, anti-Sm, or antidouble-stranded DNA)
- Blood disorder (thrombocytopenia, lymphopenia, leukopenia or anemia)
- Neurological disorder (seizure, psychosis)
- Serositis (pericarditis or pleuritis)
- Kidney disorder (persistent cellular casts or proteinuria)
Treatment – SLE

- Mild disease
  - Lifestyle changes, management
  - Protection from direct sunlight
  - Treat infections
  - Treat symptoms (e.g. NSAIDS for joint pain)
  - Hydroxychloroquine (Plaquenil)
    - Initiate early in disease prior to organ damage
Treatment – SLE

- Moderate to severe disease
  - Immunosuppressants
    - Cyclophosphamide
    - Myophenolate mofetil
    - Azathioprine
    - Belimumab (FDA approved 2011)
    - Rituximab (not FDA approved for Lupus)
  - Steroid-sparing strategies
    - “high dose” = > 6mg qd
    - Risk of organ damage greater with higher doses (increased by 50%)
Goals of Therapy – Lupus

- Decrease disease activity
- Prevent flares/exacerbations
- Prevent multisystem/organ damage
- Prevent/lessen toxic effects of medicines
- Promote positive quality of life
Lupus Nephritis

- Incidence, scope
  - 35% individuals with Lupus have clinical evidence of nephritis at time of diagnosis
  - 50–60% will develop during 1st 10 years of the disease
  - Higher in African American and Hispanics
  - Higher in males than females

- Survival
  - Lupus = 95% at 5 yrs; 92% at 10 yrs
  - Lupus Nephritis = 88% at 10 yrs (lower in African Americans)
Lupus Nephritis

- American College of Rheumatology 2012. *Arthritis Care and Research, 64*, 797–808.

- Glomerular disease; immune deposits in mesangium

- Diagnostic criteria
  - Anti–ds DNA highly positively associated with lupus nephritis
  - Proteinuria
    - Spot urine protein/creatinine ratio > 0.5
    - Persistent proteinuria (> 0.5 gm/day)
  - Urine abnormalities
    - *And/or* cellular casts (RBCs, WBCs, hemoglobin, granular, tubular, mixed)
    - “active” urine sediment (>5 RBCs or > 5 WBCs per hpf) in absence infection
Kidney Biopsy – Lupus Nephritis

- Immune complex mediated glomerulonephritis consistent with lupus nephritis
- All patients with clinical evidence active lupus nephritis, previously untreated
- Evaluate disease activity, chronicity, tubular, vascular changes; ? for disease classification
- ESPECIALLY needed:
  - Increased serum creatinine
  - Proteinuria > 1 gm/day
  - Proteinuria > 0.5 gm/day + > 5 RBCs/hpf OR casts
Classification – Lupus Nephritis

- Class I  Minimal mesangial lupus nephritis (LN)
- Class II  Mesangial proliferative LN
- Class III  Focal LN (< 50% glomeruli)
- Class IV  Diffuse LN (> 50% glomeruli)
- Class V  Membranous
- Class VI  Advanced sclerosing LN (> 90% sclerosed glomeruli without residual activity)

Based on classification, biopsy results

- Class I: Not require immunosuppressants
- Class II: Not require immunosuppressants unless proteinuria > 3 g/d
- Class III, IV: Aggressive therapy with immunosuppressants and steroids
- Class V: Generally as in III, IV unless pure membranous, then add therapies
- Class VI: Prepare for RRT rather than immunosuppression
Hydroxychloroquine: 200–400 mg/day
- Flare rates lower than placebo
- Less kidney damage

All with proteinuria > 0.5 gm/day – RAS blockade
- Goal = 30% reduction proteinuria
- Delays increased creatinine and progression

Control hypertension – goal < 130/80
- Delays progression kidney damage

Control lipids – treat if LDL > 100
- SLE is independent risk factor for accelerated atherosclerosis

Fertility, pregnancy counseling
Induction Therapy – Class III, IV

- **Mycophenolate mofetil (MMF)**
  - 2–3 gm/d po x 6 mo, then decreased doses x 3 yrs.
  - Similar efficacy across genders, races
  - Asians generally require lower doses

  OR

- **Cyclophosphamide (CYC)**
  - 500 mg IV x 1 weekly for 2 weeks x 6 doses, then Azathioprine or MMF po qd  **OR**
  - 1000 mg IV q mo x 6 doses, then Azathioprine or MMF po qd
PLUS Methylprednisolone

- 500–1000 mg IV or 10mg/kg qd x 3 days, then 0.5 mg/kg/day
- Taper to minimum dose to control disease activity (no recommendations)
- Advantages, disadvantages of steroid therapy in treatment of lupus and lupus nephritis
Clinical Outcomes

- Decrease in serum creatinine
- Decrease in proteinuria < 0.5 gm/24 hrs
- 50% individuals with LN show improvement after 6 mo; 65–80% with improvement 12–24 mo of treatment MMF OR CYC
  - Similar complete and partial remission rates
  - Need prospective studies to determine if MMF has same renal preservation long term as CYC
Positive Response to Induction

- MMF (2 gm/d) or Azathioprine (2mg/kg/d)
- Prednisone up to 10 mg/day
- MMF superior to Azathioprine (multiethnic group)
- Azathioprine with more adverse events than MMF
- **BUT** no significant difference between MMF and Azathioprine outcomes (renal flares, end stage kidney disease, doubling creatinine, death)
No/Poor Response Induction

- Look at 6 month results
- “Resistant lupus nephritis” – no clear, consistent, nor accepted definition
- Change to “other” agent (MMF vs CYC) + IV glucocorticoids x 3 days
- ? Consider Rituximab
- ? Calcineurin inhibitors
- ? Replacement or additive
## Monitoring Activity of LN

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Active LN</th>
<th>Previous Active LN</th>
<th>No prior or current LN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>1 mo</td>
<td>3 mo</td>
<td>3 mo</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>1 mo</td>
<td>3 mo</td>
<td>6 mo</td>
</tr>
<tr>
<td>Pro/Creat ratio</td>
<td>1 mo</td>
<td>3 mo</td>
<td>6 mo</td>
</tr>
<tr>
<td>Serum Creat</td>
<td>1 mo</td>
<td>3 mo</td>
<td>6 mo</td>
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Kidney Replacement Therapy

- 11,317 individuals with LN started RRT 1995–2006
- 82% HD, 12% PD, 3% transplant
- All therapies appropriate for individuals with Lupus
- Recurrent LN after transplant 2–5%
Education and Counseling Lupus, Lupus Nephritis

- Inter, multi disciplinary team that includes rheumatology colleagues
- Managing stress, unsure nature of disease with exacerbations, remissions
- Screen for depression every visit
- ? Value/need for genetic counseling
- Medication adherence
- Vigilance regarding end organ effects
Fertility Concerns/Issues

- Population most affected = women childbearing age
- MMF preferred over CYC for preservation of fertility
  - High dose CYC can cause permanent infertility in both genders
- MMF teratogenic
  - Stop MMF 6 wks prior to attempt pregnancy
- LN treatment during pregnancy
  - No active disease – no treatment
  - Mild disease – hydroxychloroquine
  - Active disease – steroids; Azathioprine if needed
Summary

- Lupus has potential to affect numerous organs – kidneys most commonly affected.
- Lupus Nephritis is a glomerular disease marked by proteinuria.
- Lupus Nephritis is treated with immunosuppressants to achieve remission.
- Progression of Lupus Nephritis to end stage kidney disease is non-linear but more likely to occur with frequent flares of lupus.