LUPUS & LUPUS NEPHRITIS in CHILDREN & VASCULITIS

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Systemic Lupus Erythematosus in Children (cSLE)

- cSLE: onset of disease before 18 years of age
- Approximately 15-20% of SLE cases begin before age 18
- Incidence and prevalence rates vary by ethnicity
- US administrative database showed higher in Asians followed by African Americans, Native Americans & Hispanic children
- The prevalence in White children is lowest 2.4-4.9
- Incidence of childhood onset SLE 6-30/100,000 children/year
- The mean age at diagnosis is 12-13 years
- F/M ratio increase from 2:1 in prepubertal children to 4.5:1 in adolescents
Systemic Lupus Erythematosus in Children (cSLE)

- More acute onset of SLE in children
- More fever and lymphadenopathy (+10-20% in children)
- More kidney involvement (+20-30% in children)
- More hematological disease (+10% in children)
Malar rash
Discoid rash
Photosensitivity
Oral or nasal ulcers
Arthritis
  Nonerosive, ≥2 joints
Serositis
  Pleuritis, pericarditis or peritonitis
Renal manifestations†
  Consistent renal biopsy
  Persistent proteinuria or renal casts
Seizure or psychosis
Hematologic manifestations†
  Hemolytic anemia
  Leukopenia (<4,000 leukocytes/mm³)
  Lymphopenia (<1,500 leukocytes/mm³)
  Thrombocytopenia (<100,000 thrombocytes/mm³)
Immunologic abnormalities†
  Positive anti–double-stranded or anti-Smith antibody
  False-positive rapid plasma reagin test result, positive lupus anticoagulant test result, or elevated anticardiolipin immunoglobulin (Ig) G or IgM antibody
  Positive antinuclear antibody test result
# Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for Systemic Lupus Erythematosus

<table>
<thead>
<tr>
<th><strong>CLINICAL CRITERIA</strong></th>
<th><strong>IMMUNOLOGIC CRITERIA</strong></th>
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</table>
| **Acute cutaneous lupus**  
  Malar rash, bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash, or subacute cutaneous lupus | Positive antinuclear antibody  
 Positive double-stranded DNA antibody  
 Positive anti-Smith antibody  
 Antiphospholipid antibody positivity |
| **Chronic cutaneous lupus**  
  Classic discoid rash, lupus panniculitis, mucosal lupus, lupus erythematosus tumidus, chilblains lupus, discoid lupus/lichen planus overlap | Positive lupus anticoagulant, false-positive test for rapid plasma regain, medium to high titer anticardiolipin antibody level (IgA, IgG, IgM), or positive anti-β2-glycoprotein I antibody (IgA, IgG, IgM) |
| Oral or nasal ulcers  
  **Nonscarring alopecia**  
  Synovitis (≥2 joints)  
  Serositis  
  Pleurisy or pericardial pain ≥1 day, pleural effusion or rub, pericardial effusion or rub, ECG evidence of pericarditis  
  Renal  
  Presence of red blood cell casts or urine protein/creatinine ratio representing >500 mg protein/24 hours  
  Neurologic  
  Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, or acute confusional state  
  Hemolytic anemia  
  Leukopenia (<4,000/mm³) or lymphopenia (<1,000/mm³)  
  Thrombocytopenia (<100,000/mm³) | Positive direct Coombs test (in the absence of hemolytic anemia)  
 Low complement  
 Low C3, C4, or Ch50 level |

4 criteria (including at least 1 clinical and 1 immunologic criterion)

OR

A biopsy-proven lupus nephritis with positive ANA or Anti-DNA

Immune system dysregulation

- Loss of self-tolerance and activation of auto reactive B and T cells
- High levels of interferon-α production by plasmacytoid dendritic cells (main determinant of disease development)
- **Type I interferon signature**
- Other cytokines with increased expression in SLE:
  - IL-1, IL-2, IL-6, IL-10, IL-12, IL-17, IL-21, interferon-γ, B-lymphocyte stimulator (BLyS), and anti-tumor necrosis factor-α.
- Increased numbers of memory T cells
- Decreased number and function of T-regulatory cells
- Classical Complement system activation through ICs
Human studies

- Genetic factors associated to
  - SLE susceptibility
  - Development of specific antibodies
  - Clinical feature

are under investigation.
Lupus Nephritis in Children

- Renal disease is the greatest contributor to morbidity and mortality in SLE population.
- 50-55% of SLE patients have evidence of renal involvement at onset, 80% to 90% within first year of diagnosis.
- Children are at increased risk for renal involvement compared to adults with SLE.
- Children tend to have more active disease over time.
- Receive more intensive immunosuppressive treatment.
- Have more damage.
- The severity of clinical signs and symptoms may not correlate with LN.
- Renal biopsy is important for the grading.
- Renal biopsy should be graded according to ISN/RPS 2003 classification criteria which guides the treatment.
Lupus nephritis in children shows the same range of clinical and pathological phenotypes as is seen in adult:

- **Class I** Minimal mesangial lupus nephritis
- **Class II** Mesangial proliferative lupus nephritis
- **Class III** Focal lupus nephritis- Endo- or extracapillary glomerulonephritis involving <50% of all glomeruli
- **Class IV** Diffuse lupus nephritis- Endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli
- **Class V** Membranous lupus nephritis
- **Class VI** Advanced sclerotic lupus nephritis
Class I Lupus Nephritis

- Glomeruli are normal by light microscopy- Minimal mesangial lupus nephritis
- Mesangial immune deposits seen only by IF or EM
- No clinical kidney manifestations
- Is not associated with long term impairment of kidney function
Class II Lupus Nephritis

- Pure mesangial proliferative LN
- Proteinuria and/or hematuria may be seen
- If nephrotic range proteinuria is found, this may be due to concomitant podocytopathy
Class III Lupus Nephritis

- Focal lupus nephritis
  
  Active or inactive **focal**, segmental or global **endo- or extracapillary glomerulonephritis involving <50% of all glomeruli**, typically with focal subendothelial immune deposits, with or without mesangial alterations

- if >40% of the glomeruli are involved with necrosis and deposits are present)
  
  - Clinical symptoms more severe with active urine sediment, nephrotic syndrome, hypertension and moderate renal insufficiency

- if 20% of the glomeruli are affected)
  
  - mild renal symptoms with low grade proteinuria and normal GFR
Class IV Lupus Nephritis

- Active or inactive **diffuse**, segmental or global **endo- or extracapillary** glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations
- Almost all patients will have microscopic hematuria and proteinuria; nephrotic syndrome and kidney impairment are common
Membranous Lupus Nephritis - Class V

- Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations
- Patients with class V LN, normal kidney function, and non-nephrotic-range proteinuria
- Patients with pure class V LN and persistent nephrotic proteinuria
Lupus Nephritis – Class VI

- ≥90% of glomeruli globally sclerosed without residual activity
Indication for Renal Biopsy in SLE

- Increasing serum creatinine without any alternative causes (such as sepsis, hypovolemia or medication)
- Proteinuria ≥ 0.5 g/24 hr with or without glomerular hematuria and/or cellular casts
- Persisting isolated hematuria
- Treatment should not be delayed if a renal biopsy cannot be readily performed.

Arthritis Care & Research 2012; 64(6): 797-808
Guidelines in Treatment of LN

All the guidelines were developed on the basis of extensive literature searches and consensus meetings

- American College of Rheumatology Guidelines for screening, treatment and management of lupus nephritis (ACR 2012)
- Joint European League Against Rheumatism and European Renal Association (EULAR/ERA-EDTA) Recommendations for the management of adult and pediatric lupus nephritis, 2012
- KDIGO (Kidney Disease Improving Global Outcomes) Clinical Practice Guideline for Glomerulonephritis, 2012
- Consensus Treatment Plans for Induction Therapy of Newly Diagnosed proliferative lupus nephritis, CARRA 2012
- Treat to Target in SLE (T2T/SLE) 2014 recommendations
<table>
<thead>
<tr>
<th>LN</th>
<th>EULAR/ERA-EDTA 2012</th>
<th>ACR 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction treatment for Class III/IV LN</td>
<td>MMF (3g/day) or CYC + Corticosteroids (3 pulses of IV MP followed by oral prednisolone)</td>
<td>MMF (2g/day for Asians; 3g/day for others) or CYC + Corticosteroids (3 pulses of IV MP followed by oral prednisolone)</td>
</tr>
<tr>
<td>Maintenance for Class III/IV LN</td>
<td>MMF or AZA + Corticosteroids</td>
<td>MMF or AZA + Corticosteroids</td>
</tr>
<tr>
<td>Treatment of Class V LN</td>
<td>MMF+ Corticosteroids</td>
<td>MMF+ Corticosteroids</td>
</tr>
<tr>
<td>Treatment for refractory LN</td>
<td>Switching the other agent (CYC to MMF or vice versa) or RTX</td>
<td>Switching the other agent (CYC to MMF or vice versa) or RTX or CNI</td>
</tr>
</tbody>
</table>

NDT 2015;0:1-11 doi:10.1093/ndt/gfv102
Ann Rheum Dis 2012;71:1771
Arthritis Care Res 2012;64:797-808
Reduce corticosteroid use, reduce disease activity, extends the time to end-stage renal disease, and with adjunctive immunomodulatory treatment improves duration of renal remission
Other Treatment Options in LN

**Targeting B cells**
- B-cell depleting therapy: rituximab
- B-cell modulating therapy: epratuzumab
- Inhibition of B-cell survival: belimumab, atacicept
- Other potential B-cell (plasma cell) targeting strategies: bortezomb

**Targeting T cells**
- Inhibition of T-cell function: abatacept, ruplizumab, toralizumab, lupuzor

**Interleukin 6**
- Tocilizumab

**Tumour necrosis factor α inhibitors**
- Infliximab
- Etanercept

**Type I interferon inhibitors**
- Sifalimumab
- Rontalizumab

**Complement inhibitors**
- Eculizumab

*Figure: Targeted biological agents available and in present or previous clinical trials of systemic lupus erythematosus. pDC—plasmacytoid dendritic cell. Bls—B-lymphocyte stimulator. TNFα—tumour necrosis factor α. APC—antigen-presenting cell.*

**Lancet** 2014; 384: 1878–88
**Lancet** 2013; 382:809-818
Treatment For Proliferative Lupus Nephritis

- Prednisolone
  - IV 10-30 mg/kg/dose
- CYC
  - 500 mg/m² iv

What do I do?
- Vital organ involvement
- plasma exchange
  And or RTX
- Resistant Disease

AZA: 1-2 mg/kg/d
CS: 0.25 mg/kg/alternate day
MMF: 1000-1200 mg/m²

3-6 months
36 months
End Stage Renal Disease in Lupus Nephritis

- Despite immunosuppressive treatment, 10 to 30% of patients with LN will progress to ESRD within 15 years of diagnosis.
- Although clinical and serological activity tend to subside in most patients with ESRD on dialysis, flares of renal or extra renal lupus can occur.

_Nephrol Dial Transplant 2005; 20: 2797-802_  
_Am J Nephrol 2005; 25: 596-603_
Renal Transplantation

- Patients with SLE are good candidates for renal transplantation performed
  - When clinical and ideally serological lupus activity is absent, or at a low level, for at least 3-6 months
  - Best results are obtained with living donor
  - Preemptive transplantation

- Patients with moderate to high doses of antiphospholipid antibodies are at increased risk for thrombotic complications and may receive anticoagulants perioperatively

*Semin Arthritis Rheum* 1997; 1997; 27: 17-26
Lupus nephritis warrants close medical attention to avoid progression to end stage renal disease

- Its relapsing nature
- The varying clinical manifestations
- Make controlled trials difficult to set up in children

**THE GOAL SHOULD BE NEITHER TO OVERTREAT MILD DISEASE NOR TO UNDERTREAT SEVERE DISEASE**
VASCULITIS
Case

- 12 year old girl
- Weakness, periumblical abdominal pain
- Loss of appetite
- Nausea, vomiting
- Pallor
- Decreased urine output with hematuria
## Laboratory Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hb</strong></td>
<td>7.8 g/dl</td>
</tr>
<tr>
<td><strong>WBC</strong></td>
<td>7300 /mm³</td>
</tr>
<tr>
<td><strong>Platelet</strong></td>
<td>240 x10⁴/mm³</td>
</tr>
<tr>
<td><strong>CRP</strong></td>
<td>10.2 mg/dl</td>
</tr>
<tr>
<td><strong>ESR</strong></td>
<td>120 mm/hr</td>
</tr>
<tr>
<td><strong>BUN</strong></td>
<td>51 mg/dl</td>
</tr>
<tr>
<td><strong>Cr</strong></td>
<td>5.84 mg/dl</td>
</tr>
<tr>
<td><strong>T. prot</strong></td>
<td>7.3 g/dl</td>
</tr>
<tr>
<td><strong>Alb</strong></td>
<td>3.2 g/dl</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urinary pH</strong></td>
<td>6.5</td>
</tr>
<tr>
<td><strong>SG</strong></td>
<td>1020</td>
</tr>
<tr>
<td><strong>protein</strong></td>
<td>4 +</td>
</tr>
<tr>
<td><strong>7-8 RBC / hpf</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Urinary protein</strong></td>
<td>87.5 mg/m²/hr</td>
</tr>
<tr>
<td><strong>GFR</strong></td>
<td>18 ml/min/ 1.73 m²</td>
</tr>
<tr>
<td><strong>ANA</strong></td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Anti ds-DNA</strong></td>
<td>Negative</td>
</tr>
<tr>
<td><strong>C3</strong></td>
<td>Normal</td>
</tr>
<tr>
<td><strong>ANCA:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>p-ANCA:</strong></td>
<td>strong positive (IFA)</td>
</tr>
<tr>
<td><strong>MPO-ANCA:</strong></td>
<td>250 IU/ml (ELISA)</td>
</tr>
</tbody>
</table>

*Pediatr Nephrol 2003;18: 696-699*
Dr. HOUSE

IT'S NOT LUPUS
Renal Biopsy

Circumferential fibrous – fibrocellular crescents

Microscopic polyangiitis

Serum creatinine (mg/dl)

0.5 mg/kg/d prednisone

2 mg/kg/d cyclophosphamide

2 mg/kg/d azathiopurine

Plasma exchange

Rituximab

MMF
13 years after successful renal transplantation during clinical remission and ANCA was undercontrol
- Cr: 0.98 mg/dl
- GFR: 112 ml/min/1.73 m²

Now days Tx is recommended during clinical remission, regardless of ANCA status
Microscopic Polyangiitis

MPA
Predominantly small vessel vasculitis
- Granulomatous
  - Wegener granulomatosis
  - Churg-Strauss syndrome
- Non-granulomatous
  - Microscopic polyangiitis
  - Henoch-Schönlein purpura
  - Isolated cutaneous vasculitis
  - Hypocomplementemic urticarial vasculitis

Predominantly medium vessel vasculitis
- Childhood polyarteritis nodosa
- Cutaneous polyarteritis
- Kawasaki disease

Predominantly large vessel vasculitis
- Takayasu arteritis

Other vasculitides
- Behçet disease
- Vasculitis secondary to infections, malignancy and drugs
- Vasculitis related to connective tissue disorders
- Isolated central nervous system vasculitis
- Cogan syndrome
- Unclassified

Ann Rheum Dis 2006;65(7):936-41
Chapel Hill Consensus Conference 2012 Vasculitis Classification

- **Large vessel vasculitides**
  - Takayasu Arteritis (TA)
  - Giant cell arteritis
- **Medium vessel vasculitides**
  - Polyarteritis nodosa (PAN)
  - Kawasaki disease (KD)
- **Small vessel vasculitides**
  - Anti-neutrophilic cytoplasmic associated (ANCA) vasculitis
    - Microscopic polyangiitis (MPA)
    - Granulomatosis polyangiitis (Wegener)
    - Eosinophilic granulomatous polyangiitis
  - Immune complex small vessel vasculitis
    - Anti-glomerular basal membrane disease
    - Cryoglobulinemic vasculitis
    - IgA vasculitis (Henoch-Schönlein) (IgAV)
    - Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)
- **Variable vessel vasculitis**
  - Behçet disease
  - Cogan syndrome
- **Single organ vasculitis**
  - Primary central nervous system vasculitis
  - Isolated aortitis
  - Cutaneous arteritis
  - Cutaneous leukocytoclastic vasculitis
- **Vasculitis associated with systemic disease**
  - Rheumatoid vasculitis
  - Lupus vasculitis
  - Sarcoid vasculitis
- **Vasculitis associated with possible etiology**
  - Hepatitis B associated vasculitis
  - Hepatitis C associated cryoglobulinemic vasculitis
  - Syphilis-associated aortitis
  - Cancer associated vasculitis
  - Drug-associated immune complex vasculitis
  - Drug-associated ANCA-associated vasculitis
  - Others

Clinical and laboratory features for vasculitis diagnosis

- **Clinical features**
  - Fever of unknown origin, weight loss, malaise
  - Skin findings (purpura, vasculitic urticaria, livedo reticularis, nodules, ulcers)
  - Arthralgia, arthritis, myalgia or myositis, serositis
  - Hypertension, renal involvement
  - Neurological lesions (headache, mononeuritis multiplex, focal CNS lesions)
  - Pulmonary infiltrates or bleeding

- **Laboratory features**
  - Leukocytosis, anemia
  - Eosinophilia
  - Increased ESR, CRP
  - Hematuria
  - ANCA positivity
Diagnostic Approach Of Possible Diagnosis of Vasculitis

- Complete blood count, acute phase reactants (ESR, CRP)
- Liver/Renal function tests, urinalysis
- Specific antibodies - ANCA
- MR Angiography, CT Angiography, Conventional Angiography - medium and large vessel
- Gold standard for diagnosis: Biopsy
  - Vessel size
  - Histological signs of tissue inflammation
    - Vessel wall necrosis
    - Granulomas/giant cells
    - Immune complex and/or C3 deposition

TISSUE is the ISSUE for diagnosis!
Thank you