

Lupus Related Kidney Diseases

Jason Cobb MD

Assistant Professor

Renal Division

Emory University School of Medicine

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 - Lupus Nephritis Kidney Biopsy Biomarkers Research Study
 - Co-investigator

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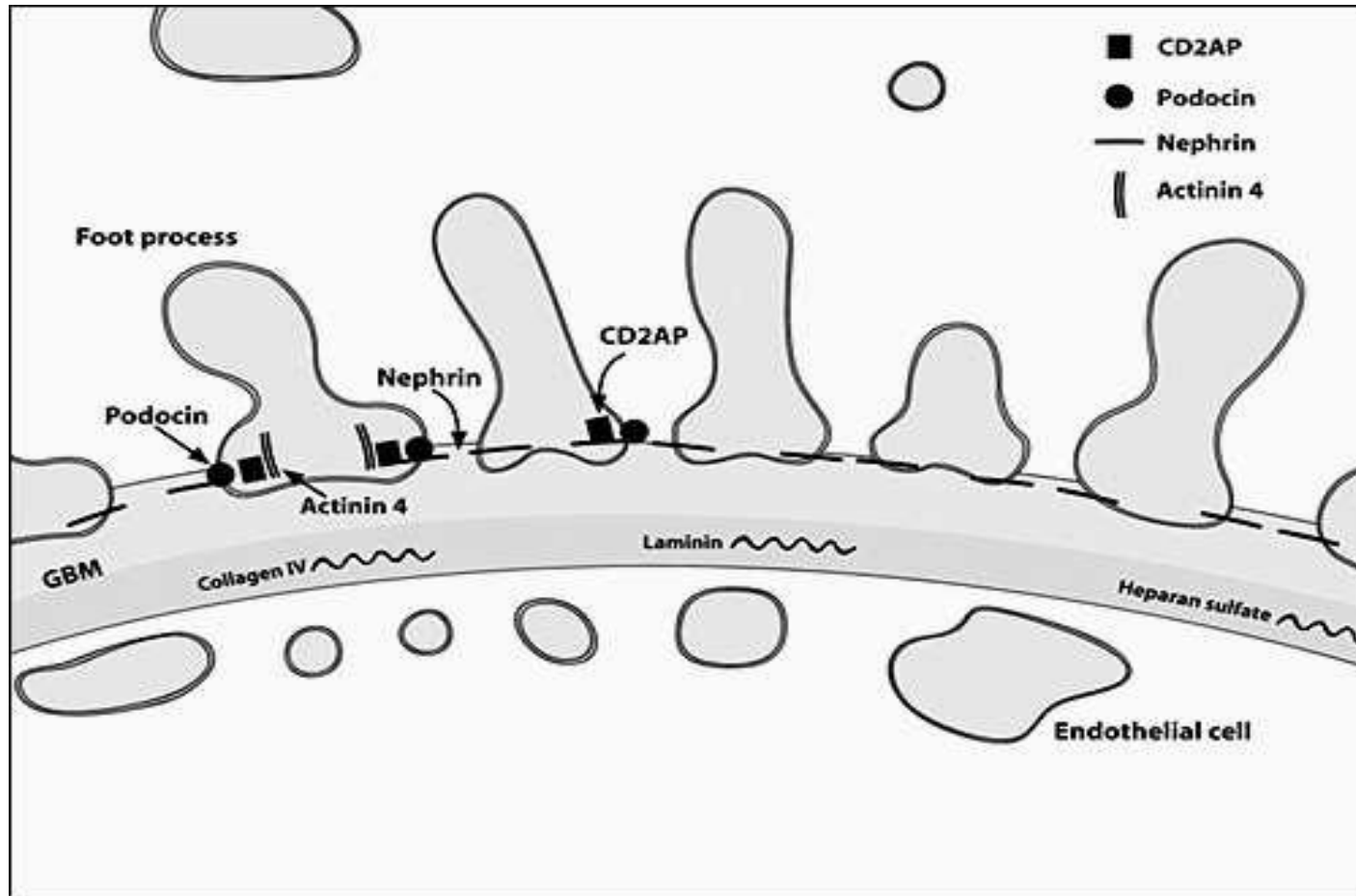
Renal Disease in SLE

- About 50% - 75% of systemic lupus erythematosus (SLE) patients have renal disease.
 - Abnormal urinalysis
 - Hematuria >5 rbc/hpf
 - Proteinuria >500 mg/day
 - Elevation of creatinine

Renal Disease in SLE

- Pathogenesis
 - Immune-complex mediated glomerulonephritis (GN) with formation of immune deposits.
 - Anti-double stranded DNA (dsDNA) antibodies against nucleosomes in the kidney.
 - Consumption of complement with low C3/C4 levels.
 - Elevated dsDNA
 - Low complements (low C3 and C4 levels)

GBM



When to Refer to Nephrology?

- Anyone with SLE and abnormal creatinine and urinalysis.
- Determine if need kidney biopsy
 - Lupus nephritis versus other causes of kidney disease (examples diabetes, hypertension)

When to Biopsy?

- No need to biopsy
 - Less than 500 mg/day proteinuria
 - Bland urine sediment <5 rbc/hpf
 - Normal creatinine
- Biopsy anyone else
- Guide clinical treatment
 - Labs can't reflect pathology
 - Can be done as outpatient
 - Relapses
 - Protocol biopsy?

Diagnosis of Lupus Nephritis

- Better outcomes when diagnosed/treated promptly!
- SLE patients with renal disease 6 or more months prior to biopsy with increased rates of end-stage renal disease.
 - 47 vs. 14 per 1000 patients HR 9.3 (CI 1.8-47)
 - Faurschou M et al. J Rheumatology 2006;33:1563-69.

ISN/RPS Classification

- Class 1 - Minimal mesangial lupus nephritis
- Class 2 - Mesangial proliferative lupus nephritis
- Class 3 - Focal proliferative lupus nephritis
- Class 4 - Diffuse proliferative lupus nephritis
- Class 5 - Membranous lupus nephritis
- Class 6 - Advanced sclerosing lupus nephritis

Mesangial Lupus Nephritis

- Class I: Minimal mesangial lupus nephritis
 - Earliest and mildest
 - Usually normal urinalysis, minimal proteinuria, normal blood pressure, and normal creatinine.
- Class II: Mesangial proliferative lupus nephritis
 - Hematuria
 - Minimal proteinuria
 - Normal creatinine
 - Normal blood pressure

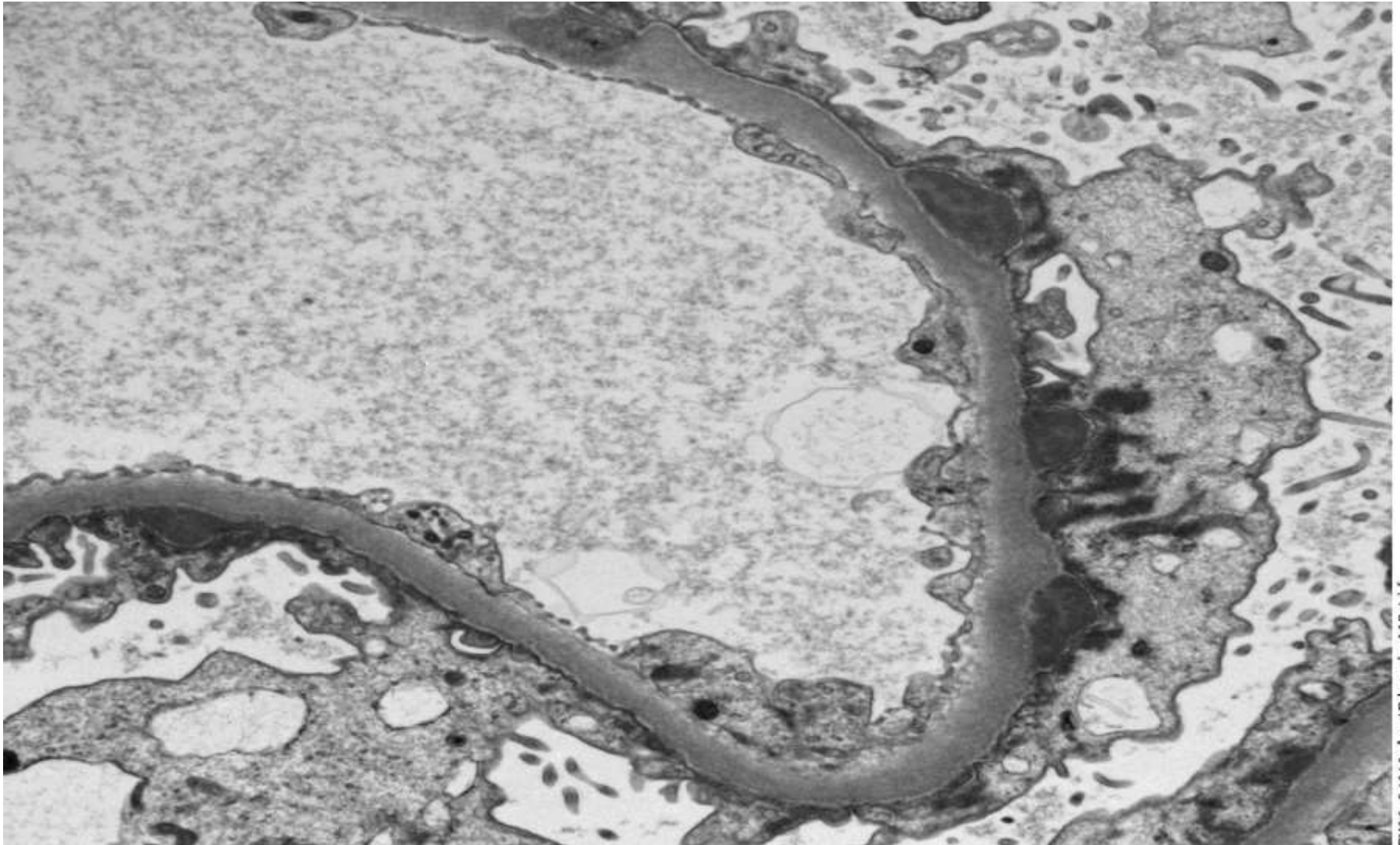
Proliferative Lupus Nephritis

- Class III: Focal proliferative lupus nephritis
 - Glomeruli affected <50%
 - Subendothelial deposits
- Class IV: Diffuse proliferative lupus nephritis
 - Glomeruli affected >50%
 - Subendothelial deposits
- Sub-divided
 - Active
 - Active/Chronic
 - Chronic

Proliferative LN cont.

- Clinical Characteristics
 - Hematuria
 - Proteinuria
 - Abnormal creatinine
 - Hypertension
 - Rapidly progressive glomerulonephritis (especially class IV)
 - Decreased complement levels (C3/C4)
 - Elevated dsDNA

Electron Microscopy



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Class V - Membranous

- Clinically
 - Nephrotic syndrome (lot of protein in urine)
 - Hematuria
 - Hypertension
 - Creatinine normal or slightly abnormal

Class VI - Advanced Sclerosing Lupus Nephritis

- >90% glomeruli with scarring/sclerosis
- Clinical characteristics
 - Bland urine sediment
 - Some proteinuria

Lupus Nephritis

TREATMENT

Mesangial Lupus Nephritis

- Class 1 - Minimal mesangial lupus nephritis
- Class 2 - Mesangial proliferative lupus nephritis
 - Treat other signs/symptoms of lupus
 - No renal specific treatment needed for lupus nephritis

Proliferative LN Treatment (Class III/IV)

- We get excited!!!!
- Needs renal specific treatment!!!!
- High rates of needing dialysis if failure to treatment
- Treatment
 - Induction (usually 6 months)
 - Maintenance 1.5 – 3 years - lifetime

Proliferative LN Treatment (Class III/IV)

- Cyclophosphamide

- NIH Trial 1992 and 1996

- Combo treatment – cyclophosphamide (Cytoxan) plus steroids is best at that time!

- Boumpas DT et al. Controlled trial of pulse methylprednisolone versus 2 regimens of pulse cyclophosphamide in severe lupus nephritis. *Lancet* 1992;340:741-745

- Gourley MF et. Al. Methylprednisolone and cyclophosphamide alone or in combination in patients with lupus nephritis. A randomized controlled trial. *Ann Intern Med* 1996;125:549-557.

Toxicity

- Cyclophosphamide (Cytosan)
 - Best treatment at that time
 - Toxicities
 - **Infertility**
 - Hemorrhagic cystitis
 - Anemia
 - Leukopenia
 - Thrombocytopenia
 - **Infections**
 - Alopecia
- We do use lower doses in kidney diseases on average in comparison to cancer treatment doses.

Proliferative LN Treatment (Class III/IV)

- Lower Doses of Cyclophosphamide
 - Euro-Lupus Nephritis Trial
 - 90 patients with proliferative GN
 - 6 doses of 500 mg IV cyclophosphamide qweeks for total 3 grams vs. 6 doses of higher dose IV cyclophosphamide. With steroids. With azathioprine as maintenance drug.
 - Similar results between groups
 - 16% vs. 20% renal failure
 - 71% vs. 54% remission
 - 27% vs. 29% renal flares
 - Careful with patient population

Mycophenolate Mofetil vs. Cyclophosphamide for **Induction**
Treatment of Lupus Nephritis. **ALMS** Investigators, Gerald
Appel et al. JASN 2009: 20; 1103-12.

- 370 patients w/ Class III, IV, V Lupus nephritis
 - MMF (Cellcept) goal 3g/day (1500 mg bid) x 6 mos
 - Cyclophosphamide (Cytoxan) 0.5-1g/m² in monthly doses x 6 mos
 - Both received prednisone, starting 60 mg/day
 - End points
 - Decrease in urine protein/creatinine ratio
 - Stabilization or improvement in serum Cr
 - Cellcept 56% (104 of 185 pts) responded
 - Cyclophosphamide 53% (98 of 185 pts) responded
 - **Cellcept (mycophenolate) as good, but not superior to cyclophosphamide (Cytoxan) (p=0.58).**

Lupus Nephritis Review

- Class III and IV treatment (below + steroids)
 - Induction therapy
 - 6 months
 - Cyclophosphamide IV vs. Cellcept (MMF) oral
 - Cyclophosphamide monthly or lower dose every 2 weeks for 6 doses
 - Side effect profile
 - » Aggressive vs. less aggressive disease
 - Maintenance therapy
 - 18-24 months or longer (possibly lifetime) if partial remission/relapse
 - MMF oral vs. azathioprine oral vs. cyclophosphamide IV (q 3-4 mos)
 - Mainly MMF or azathioprine now

Mycophenolate vs. Azathioprine as **Maintenance** Therapy for Lupus Nephritis. Mary Dooley et al. NEJM 2011: 365;1886-95

- **ALMs maintenance Trial** 36 month, RCT, 227 patients
 - MMF 2g/day
 - Azathioprine 2mg/kg/day
 - Up to 10 mg/day of prednisone allowed
 - Primary end point (time to tx failure: death, esrd, doubling of Cr, rescue therapy needed)
 - MMF 16.4% failure, Azathioprine 32.4%, p=.003
 - Adverse events same
 - Withdrawal due to adverse events (Azathioprine 39.6% and 25.2% MMF, p=.02)
 - **MMF was superior to azathioprine** in maintaining a renal response and preventing relapse in lupus nephritis.

Maintenance Treatment for Proliferative Lupus Nephritis

- Our patient population
 - Cellcept/Mycophenolate is preferred
 - ALMS Maintenance trial with more patients like our patient population.
 - Some use of azathioprine due to costs

Newer Therapies

- Possible benefit in combo or for resistant lupus nephritis. Recent trials!
 - Ocrelizumab
 - Abatacept
 - Rituximab (Rituxan)
 - Belimumab (Benlysta)

Rituximab

- Efficacy and Safety of Rituximab in Patients with Active Proliferative Lupus Nephritis (LUNAR group) Rovin RH, Appel GB et al. Arthritis and Rheumatism 2012; 64(4):1215-1226.
 - 144 patients
 - MMF and steroids
 - MMF, steroids, and rituximab (day 1,15, 168, 182)
 - Rituximab group with better complement levels and greater reduction in dsDNA but no difference in clinical outcomes.
- Still might be role in resistant or relapsing patients

Abatacept

- 24 weeks of abatacept vs. placebo
- Both groups received Euro-lupus protocol induction plus maintenance with AZA.
- N=134
- No difference in complete remission at 24 to 52 weeks.
- Seems to be safe drug.

Lupus Nephritis

- Class V

- Membranous lupus nephritis
 - Need renal specific treatment but course usually not as severe as proliferative lupus nephritis.
- Subepithelial immune deposits
- Pure class V treatment
 - Cyclophosphamide vs. Cyclosporine vs. Cellcept(newer)
- Can be mixed with Class III/V, IV/V
 - Treat disease like you would treat proliferative component (Class III or IV)

Lupus Nephritis

- Class V LN (membranous) Induction therapy
- ALMS
 - 370 patients w/ Class III, IV, V LN – 60 patients Class V
- US Study
 - 140 patients w/ Class III, IV, V LN – 24 pts Class V
- Between two studies 52 patients Class V LN with nephrotic syndrome and 40 patients completed study.
- Across all groups Cellcept (mycophenolate) as good as cyclophosphamide.

Lupus Nephritis

- Class VI
 - Advanced sclerosing lupus nephritis
 - >90% scarring on biopsy
 - Progressive Chronic Kidney Disease
 - Monitor closely
 - Prepare for hemodialysis when necessary
 - No special immunosuppressive therapy for renal disease

Lupus Nephritis in Pregnancy

- It happens too often!
- Lupus nephritis patient becomes pregnant or flare of lupus nephritis during pregnancy.
 - Talk about birth control and check for pregnancy at each visit during treatment.
 - Stop ACEI and ARB
 - Stop cyclophosphamide and MMF
 - When needed use azathioprine and prednisone for renal specific treatment.

Other Renal Disease in SLE

- Lupus podocytopathy
 - Glomerular podocytopathy with diffuse epithelial foot process effacement
 - SLE with
 - Minimal change disease
 - FSGS
 - Glomerular Podocytopathy in Patients with SLE Kraft SW et al. JASN 2005;16:175
 - 1 in 10,000 chance SLE and MCD
 - 7 of 470 patients with lupus nephritis
 - Most responded to steroids like MCD or FSGS patients without SLE

Steroids alone is main treatment for lupus podocytopathy

Review

- Indication for kidney biopsy?
 - A. 2 rbc per high-powered field (hpf) and normal shaped rbc
 - B. Bland urine sediment and 100 mg per day proteinuria
 - C. 2 gram proteinuria per day and 10 rbc/hpf with dysmorphic rbc
 - D. Bland urine sediment and 100 mg per day proteinuria

Review

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Review

- Clinical Characteristics of proliferative lupus nephritis (Class III and IV) includes all of the below except?
 - A. Hematuria
 - B. Proteinuria
 - C. Abnormal creatinine
 - D. Hypertension
 - E. Rapidly progressive glomerulonephritis
 - F. Elevated complement levels
 - G. Elevated dsDNA

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Review

- Which class of lupus nephritis does not need renal specific immunosuppressive therapy?
 - A. Class II lupus nephritis
 - B. Class III lupus nephritis
 - C. Class IV lupus nephritis
 - D. Class V lupus nephritis
 - E. Mixed class III/V lupus nephritis
 - F. Class VI lupus nephritis

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Another View

- Which classes of lupus nephritis need renal specific immunosuppressive therapy?
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Treatment of Lupus Nephritis

- How long is induction therapy for lupus nephritis?
 - A. 1 month
 - B. 6 months
 - C. 9 months
 - D. 1 year
 - E. Lifetime

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- Which is not a proven therapy for Class IV lupus nephritis induction therapy?
 - A. Cyclophosphamide (Cytosan)
 - B. Cellcept (mycophenolate mofetil)
 - C. Azathioprine (Imuran)
 - D. Prednisone

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The End

- Thanks for your time and attention!