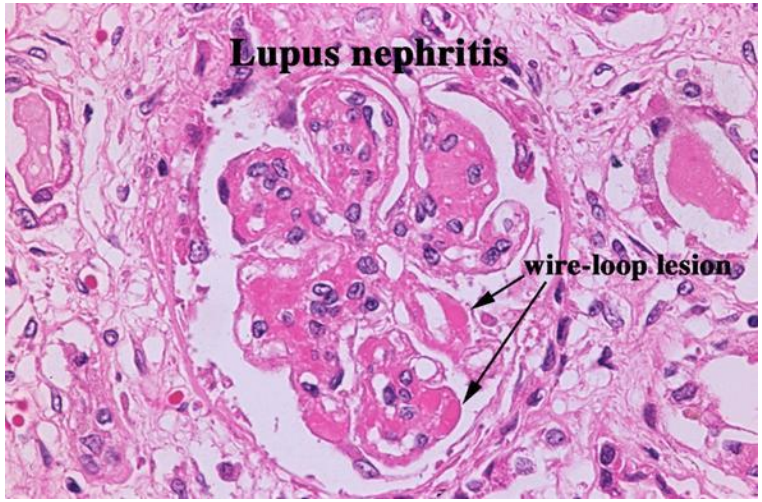
Lupus Nephritis

An Update



Introduction

- Systemic lupus erythematosus (SLE), a disease of unknown etiology, is characterized by
  - excessive immune complex formation,
  - autoantibody production,
  - complement activation and
  - immunologically-mediated tissue injury

- SLE in Asians has higher rates of renal involvement in compared with Caucasians.

- Renal involvement affects ≈60% of patients with SLE

Mok CC *et al.* Nephrology (Carlton). 2014 Jan;19(1):11-20

Lupus Nephritis- Definition

ACR* definition:

- Persistent proteinuria >0.5 g/d or >3+ by dipstick, and/or
- Cellular casts including RBCs, Hb, granular, tubular, or mixed.

Additional recommendations by ACR:

- Spot urine protein/creatinine ratio of >0.5

Active Urinary Sediment:

- >5 RBCs/hpf
- >5WBCs/hpf in the absence of infection
- cellular casts limited to RBC or WBC casts

*WHO and ACR (American College of Rheumatology guidelines)

Hahn BH, et al. Arthritis care & research. 2012 Jun 1;64(6):797-808.

Lupus Nephritis

- Lupus nephritis is an immune complex glomerulonephritis that develops as a frequent complication of SLE.
- Lupus nephritis (LN) remains a major cause of ESRD.
- Associated with a >4-fold increase in mortality and significant morbidity in patients with lupus.
- Asians having the greatest risk.
- The first case of SLE was reported from India in 1965.

Shobha V et al. Int J Rheumat Clin Immunol 2014 Jul 23;2(1): 1-9
Mok CC *et al.* Nephrology (Carlton). 2014 Jan;19(1):11-20

Epidemiology

- SLE is predominantly a disease of women, Women to men ratio being 8: 1.
- Pediatric patients and > 45 years of age: M:F ratio- 2:1
- Men are more likely to be having LN at diagnosis of SLE.
- Significantly reduces survival, to ≈88% at 10 years
- Women have better survival than men.
- The reported prevalence in India ranges from 14 to 60 per 100,000.

Rajadhyaksha AG. Lupus Nephritis (LN). *Medicine Update* 2011; 277-292

Hahn BH, et al American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis care & research. 2012 Jun 1;64(6):797-808.

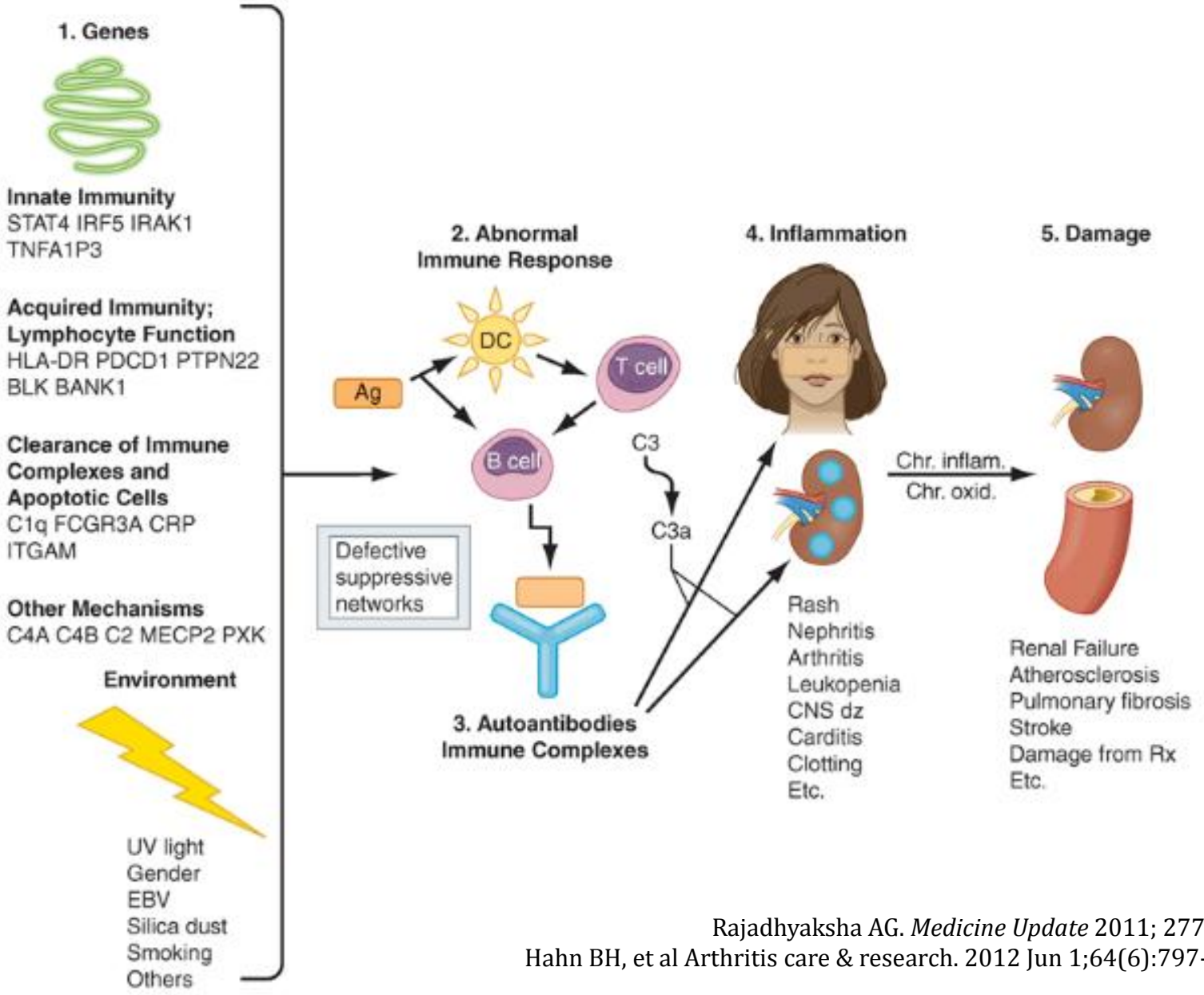
ISN/RPS 2003 Classification of LN

Class I	Minimal mesangial LN
Class II	Mesangial proliferative LN
Class III	Focal LN* (<50%) of glomeruli)
	III (A): active lesions
	III (A/C): active and chronic lesions
	III (C): chronic lesions
Class IV	Diffuse LN* (≥50% glomeruli)
	Diffuse segemental (IV-S) or global (IV-G) LN*
	IV (A): active lesions
	IV (A/C): active and chronic lesions
	IV (C): chronic lesions
Class V	Membranous LN
Class VI	Advanced sclerosing LN
	(>=90% globally sclerosed glomeruli without residual activity)

*LN, Lupus nephritis

KDIGO Clinical Practice Guidelines. Kidney Int. Suppl. 2012; 2: 139–274

Pathogenesis



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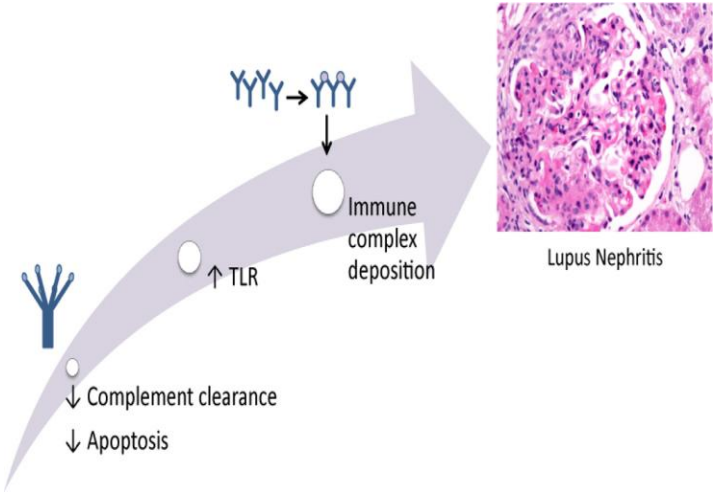
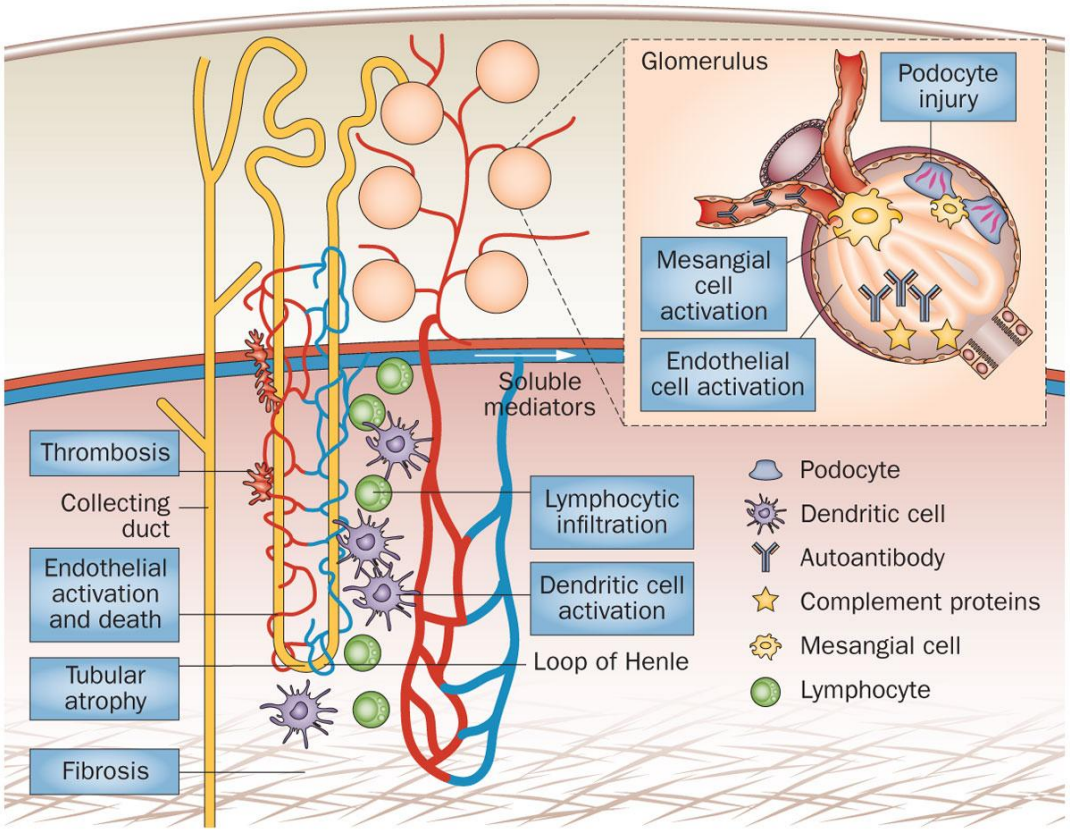


- Factors: Genetic predisposition, Environmental and hormonal factors
- Pathogenic auto-antibodies leads to persistent inflammation and various organ damage
- These preformed immune complexes and locally formed immune deposits are deposited in kidneys.
- Autoantigens interact with circulating autoantibodies leading to in situ formation of immune complexes.

Sterner RM *et al.* J Clin Cell Immunol. 2014 Apr;5(2). pii: 205.

Pathogenesis

In situ formation of immune complexes with complement activation and induction of inflammatory mediators results in chemotaxis and activation of inflammatory cells within the kidney and further release of proinflammatory signals



Chan TM et al. *Nat Rev Nephrol*. 2015 Jan;11(1):46-61.

Clinical Features

- Renal disease can be asymptomatic especially in patients with class I and II.
- Renal symptoms appear when patients are in nephritic stage or develop nephrotic syndrome.
- Clinical features generally correlate with disease activity and class of LN

Mok CC *et al.* Nephrology (Carlton). 2014 Jan;19(1):11-20
Rajadhyaksha AG. Lupus Nephritis (LN). *Medicine Update* 2011; 277-292

Clinical Features

Class	Anti-dsDNA	Complement	Urinary Sediments	24 hrs. proteinuria	HT	Creatinine	GFR
Class I	Increased +/-	Reduced -	Inactive	< 1gm	N	N	N
Class II	Increased +/-	Reduced -	Inactive	< 1gm	Infrequent	N	N
Class III	Increased +	Reduced -	Common	>1gm	+ / -	+/-	N
Class IV	Increased ++	Reduced - -	Active (RBC+ casts)	>1gm	+	+	Reduced -
Class V	Increased	Reduced -	Active	Nephrotic syndrome	+	+	Reduced -
Class VI	Usually N	Usually N	Minimal	+	+	++	Reduced --

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Diagnosis - Urinalysis

- Most important test for detection as well as monitoring of LN.
- An early morning, midstream, clean catch and non refrigerated specimen is analysed for evidence of proteinuria and active urinary sediments.
- "Telescopic urine sediments" i.e. all types of cells and casts in urine are found in severe proliferative glomerular and tubular disease.

Disorder	Observation
Inflammatory Glomerular and tubulo- interstitial disorder	Hematuria (Usually microscopic)
Proteinuric State	Granular and fatty casts
Nephritic State	RBC, WBC or mixed casts
Chronic Renal Failure	Broad and waxy casts

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Diagnosis- Renal biopsy

- Atleast 8- 10 glomeruli should be examined for conclusive results.
- Indications of renal biopsy:

A. Nephritic urinary sediments

B. Glomerular hematuria with > 0.5 gm/ day proteinuria

C. Glomerular hematuria with < 0.5 gm/ day proteinuria with reduced C3

D. positive Anti-dsDNA

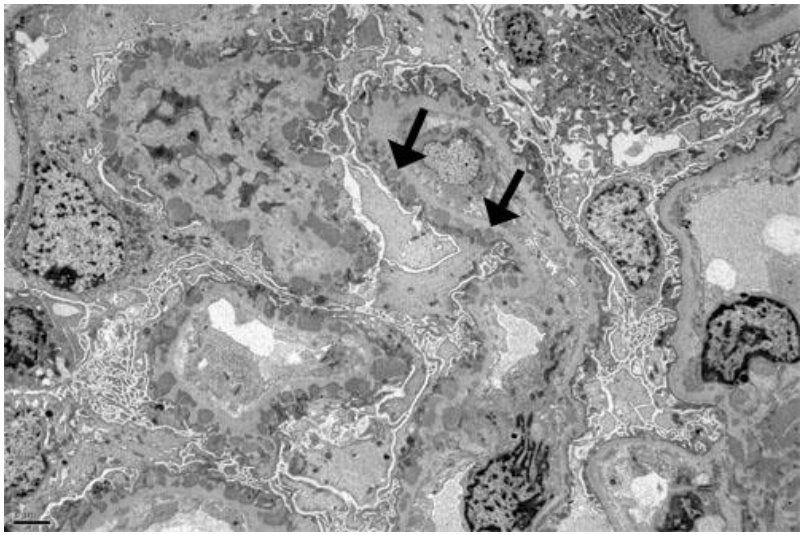
E. Proteinuria > 1 gm/day.

Hahn BH, et al American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis care & research. 2012 Jun 1;64(6):797-808.

Diagnosis- Renal biopsy

Repeat Biopsy Indications:

A. Unexplained worsening proteinuria
B. Unexplained worsening renal function (> 30% rise in creatinine)
C. Persistent glomerular hematuria with > 2g/day proteinuria
D. Proteinuria >3gm/day
E. Nephritic or Nephrotic flare.



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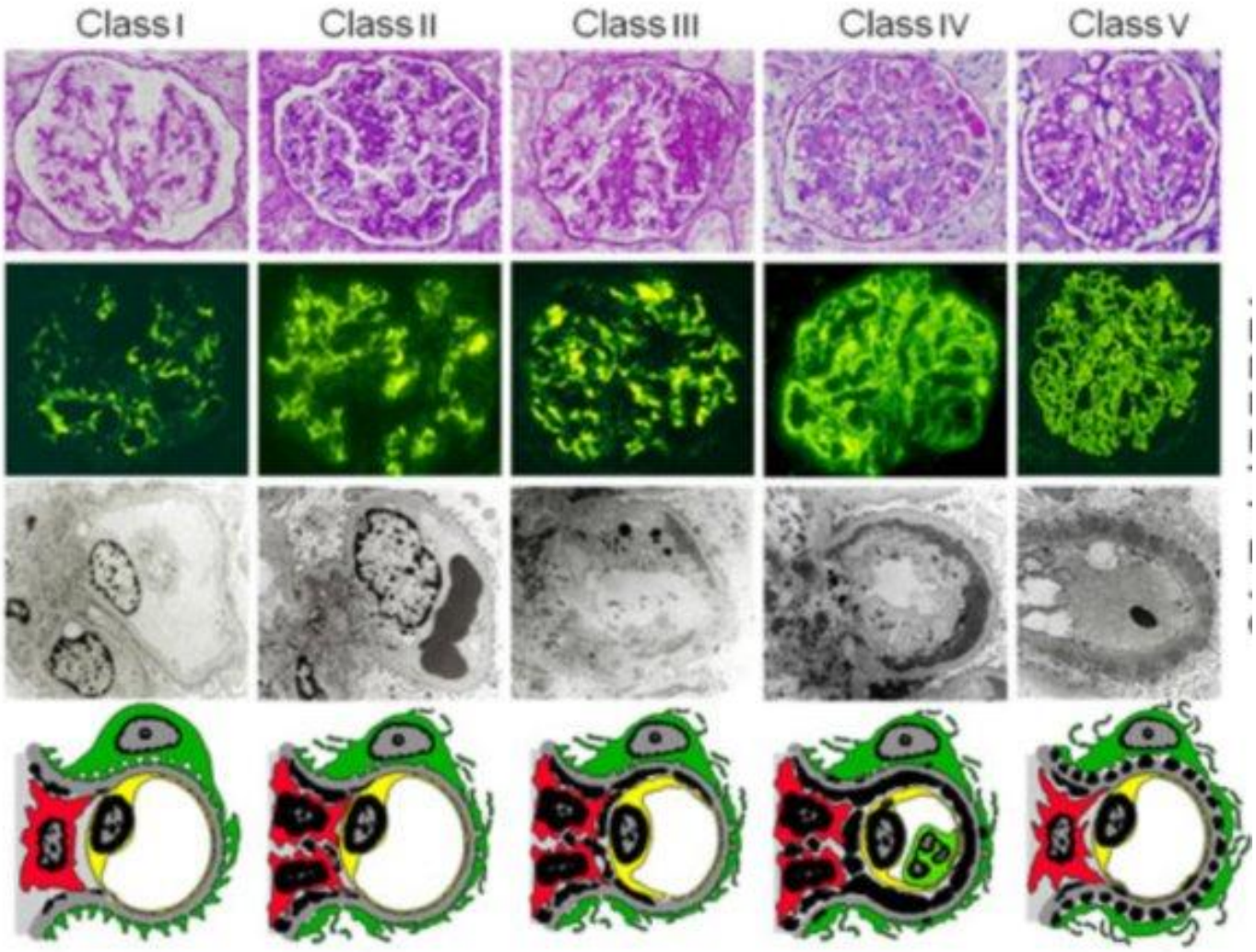
Diagnosis- Renal biopsy



Hongyan L *et al.* Clin Dev Immunol. 2013; 2013: 289316

Diagnosis- Serological tests

- **Anti Nuclear Antibody (ANA)** useful screening test with sensitivity > 90 % in patients with SLE.
- **Anti-dsDNA Antibody -** These are more specific with SLE and high titers correlate with disease activity, IgG antibodies of high avidity in fixing complement correlate with renal involvement .
- **Anti-Sm Antibodies -** Correlate with increased incidence of renal lupus and indicate worse prognosis.
- **C3 and C4 -** Reduction in levels of C3 and C4 on serial monitoring predict flare.

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Assessment of disease activity

- Treatment of LN depends upon the severity of disease

Proliferative disease

Mild	Moderately Severe	Severe
1. Class III without severe histological features 2. Chronicity Index < or = 3 3. Normal renal function 4. Non nephritic range proteinuria	1. Mild disease with partial or no response after initial induction or delayed remission > 12 months. 2. Focal proliferative nephritis with adverse histological features or reproducible increase of at least 30% in creatinine 3. Class IV without adverse histological features	1. Moderately severe with no remission at 6 to 12 months therapy 2. Proliferative disease with impaired renal function + fibrinoid necrosis or crescents in > 25% glomeruli 3. Mixed membranous and proliferative nephritis 4. Proliferative nephritis with CI > 4 or AI > 10 + CI >3 4. RPGN with doubling of creatinine in 2-3 months

Membranous Disease

Mild	Moderate	Severe
Non Nephrotic range proteinuria with normal renal function	Nephrotic range proteinuria with normal renal function	Nephrotic range proteinuria with impaired renal function

Indicators of poor prognosis

- Asian, African American race
- Azotemia (sr. creat. >2.4 mg/dl)
- Anemia (hematocrit < 26%)
- Antiphospholipid antibody syndrome
- Diffuse proliferative disease
- Poor response to initial immunosuppressive therapy.
- Flares with worsening renal function.
- High activity and chronicity index.
- Lower education level and low socio economic status

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Management Class I and II LN

- **Class I LN :**

  Treatment as dictated by the extrarenal clinical manifestations of lupus

- **Class II LN:**

  Treat patients with class II LN and proteinuria <1 g/d as dictated by the extrarenal clinical manifestations of lupus.

- Class II LN with proteinuria >3 g/d be treated with corticosteroids or CNIs as described for MCD.

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Hahn BH, et al Arthritis care & research. 2012 Jun 1;64(6):797-808.

Class III LN (focal LN) and class IV LN (diffuse LN)

- Initial therapy with corticosteroids , combined with either cyclophosphamide or MMF
- If patients have worsening LN (rising SCr, worsening proteinuria) during the first 3 months of treatment,
  - A change be made to an alternative recommended initial therapy, or
  - A repeat kidney biopsy be performed to guide further treatment

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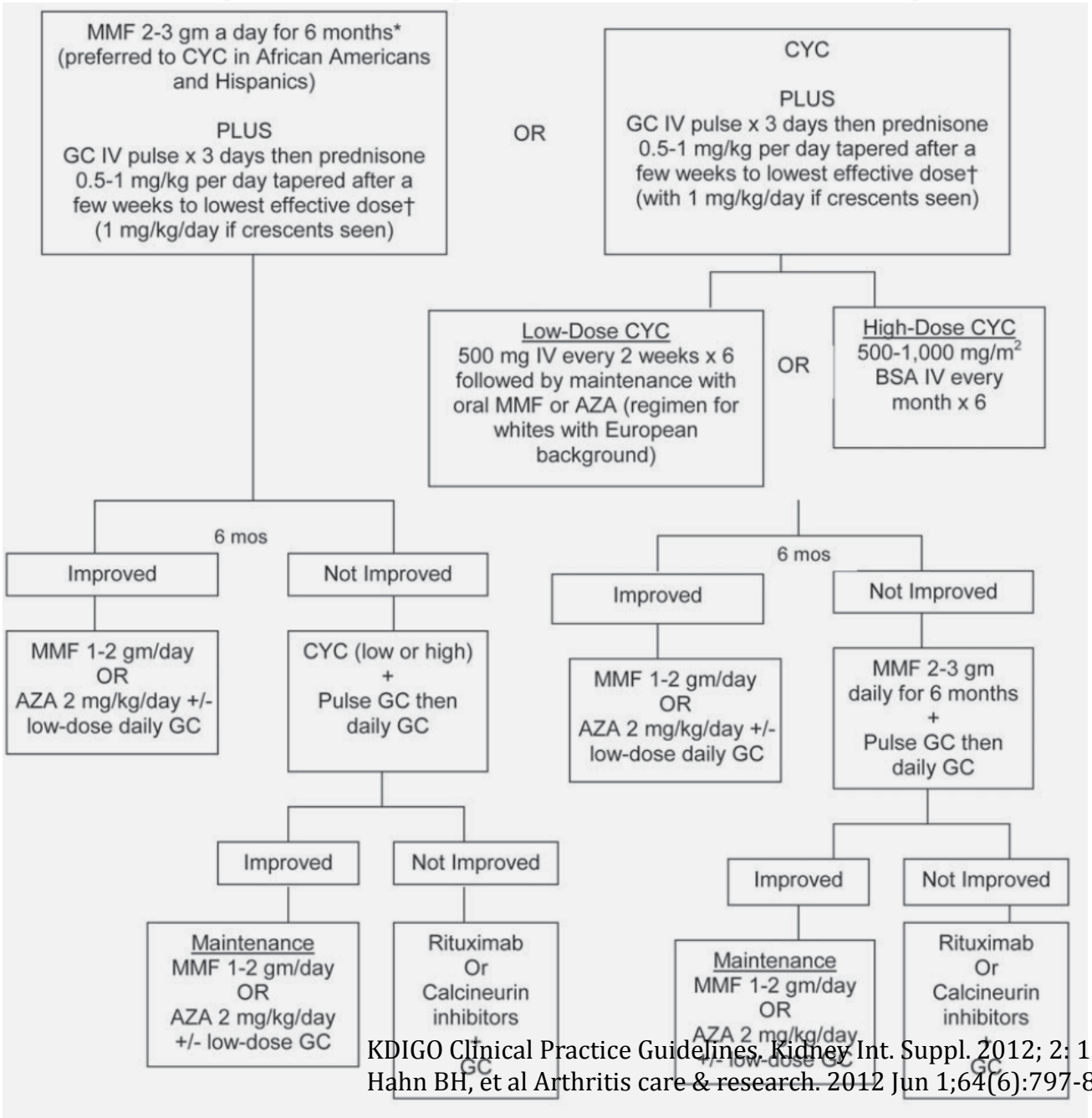

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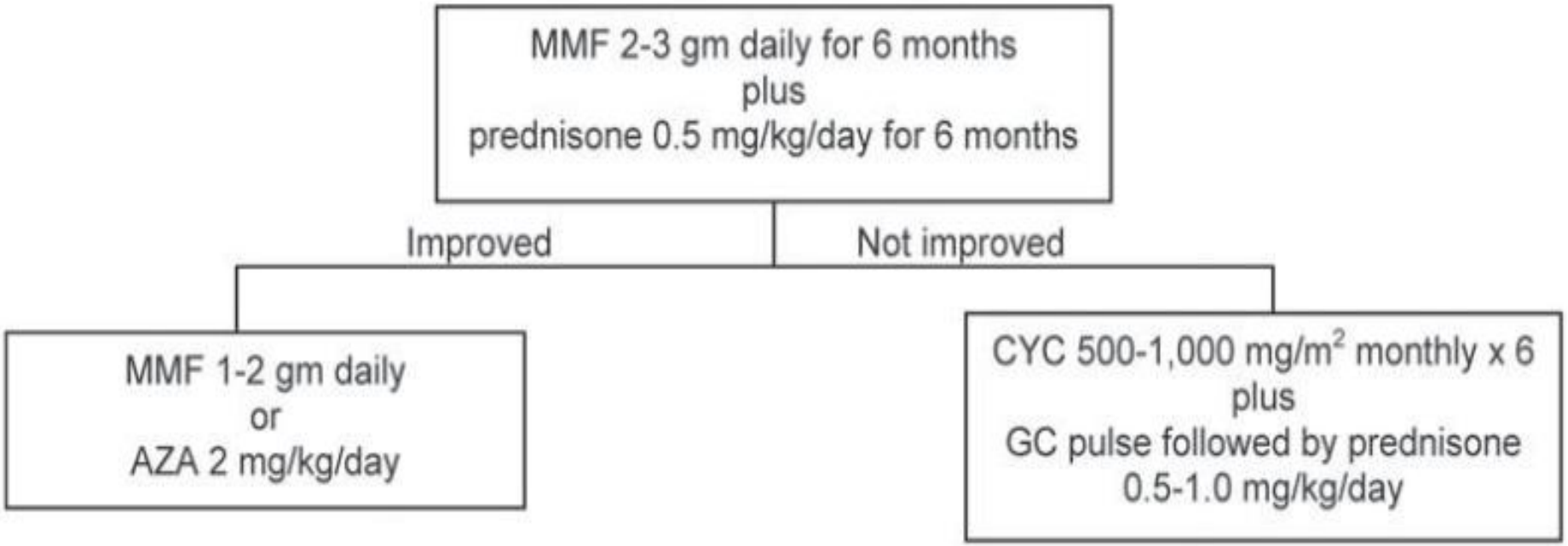
Class V LN (membranous LN)

- Treatment of class V without proliferative changes and with nephrotic range proteinuria (3 gm/24 hours).



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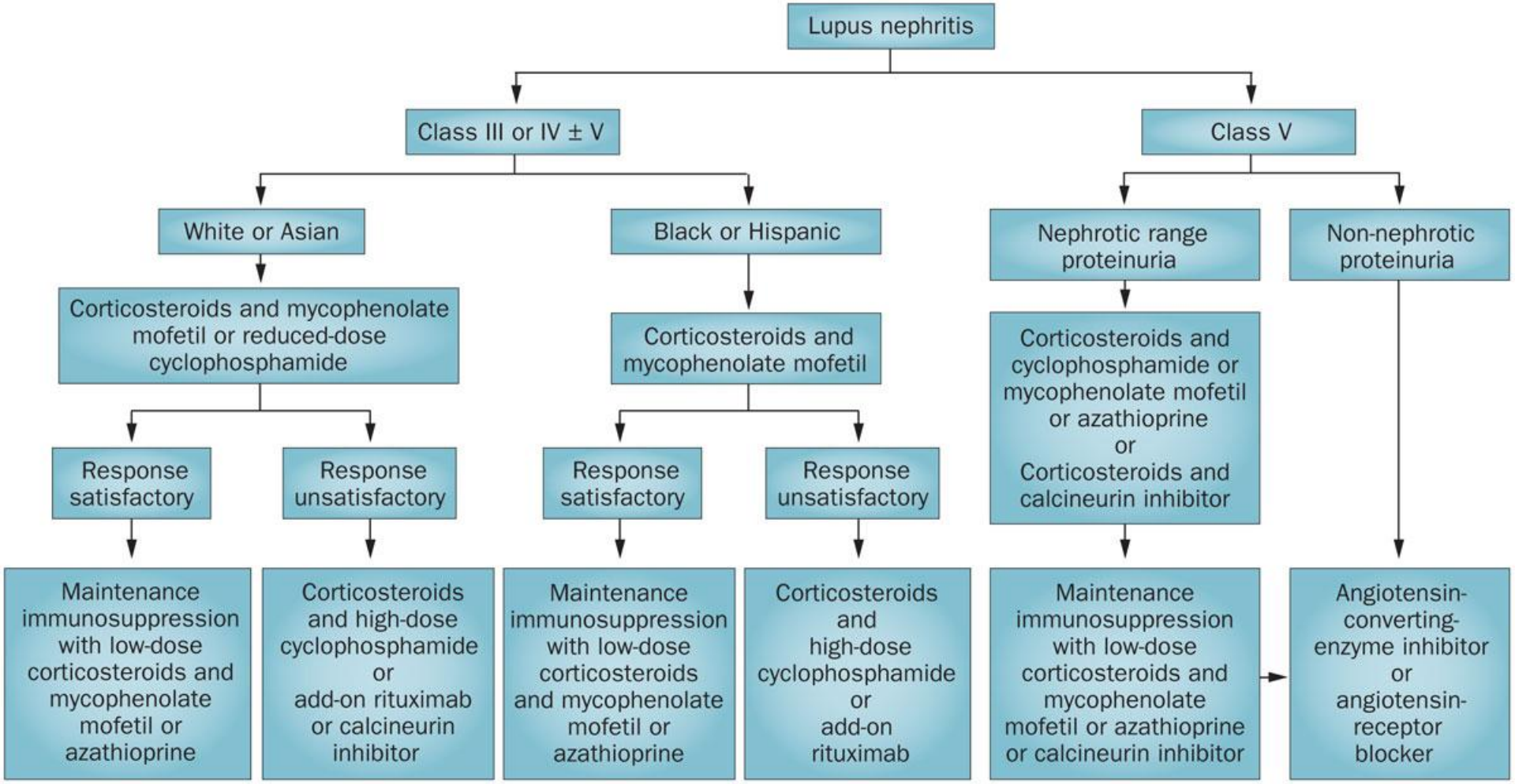
Treatment Algorithm



Chan TM et al. *Nat Rev Nephrol*. 2015 Jan;11(1):46-61.

Indicators of remission

- Inactive urinary sediments in the absence of extrarenal disease
- Normalization of complement levels for at least 6 months when patients are off immunosuppressive therapy except low dose CS.
- Therapy to be continued for at least 1 year beyond remission

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Treatment of Renal Flare

- **Mild to moderate nephritic flare-**

  High dose CS if no remission treat as severe or CS +AZA/MMF

- **Severe nephritic –**
  Monthly CY pulses plus MP or CS + AZA/ MMF

- **Nephrotic- < 3 gram proteinuria moderate dose**

  CS > 3 gram proteinuria high dose CS (Or)

  AZA/ CsA or CS+ AZA or bimonthly CY/ MMF

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Treatment – Summary

Histology/severity	Induction	Maintenance
Proliferative-mild	Prednisolone 0.5-1 mg/kg 4-6 weeks gradually taper +/- AZA if no response in 3 months consider treatment for moderately severe disease	Low dose CS < 0.125mg/Kg/day +/- AZA further tapering at the end of each year of remission.
Moderately severe	MMF 2gm/day or AZA + high dose CS, if no remission 6-12 months pulse IV CY+/- pulse MP for 7 pulses + 0.5mg/Kg/per day CS for 4 weeks and then taper	If remission in 6-12 months taper MMF to 1.5 gm/day for 6-12 months then 1gm per day, further tapering at the end of each year in remission or quarterly pulses of CY or AZA 1-2mg /kg/day
Severe	Monthly pulses of CY+ MP for 6-12 months, if no response add Rituximab or switch to MMF.	Quarterly pulse of CY for at least one year after remission or AZA 1-2mg /KG/Day or MMF 1-2gm.day
Membranous- mild	High dose CS +/- AZA	Lose dose CS +/- AZA
Moderate/severe	By monthly pulse CY for 6 pulses or CsA+/- AZA or high dose CS +MMF	Low dose CS+/-AZA or AZA
Mesangial	Low dose CS	Low dose CS

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Novel immunosuppressive/modulatory therapies for SLE

- **B-cell targeted therapies**
  - B-cell depletion
    - Anti-CD20 mAb
    - Anti-CD22 mAb
  - B-cell survival factors
    - Anti-BLyS mAb
    - TACI Ig
- **Toleragen**
  - LJP-394
- **Co-stimulatory blockade**
  - CTLA4-Ig
  - Anti-CD40 ligand mAb
- **Anti-cytokine therapies**
  - Anti-IL-10 mAb
  - Anti-TNF-
- **Anti-complement therapy**
  - Anti-C5b-9 mAb
- **Non-specific immunotherapy**
  - IV immunoglobulin
  - Bone marrow transplantation

Chan TM et al. *Nat Rev Nephrol*. 2015 Jan;11(1):46-61.

Novel Targeted Therapies

Agent	Type of Therapy	Class of Molecule	Molecular Binding	Biological Action
Rituximab	Anti-CD20	Chimeric monoclonal antibody	B-cell-specific surface antigen CD20	B-cell apoptosis/lysis
Ocrelizumab	Anti-CD20	Humanized monoclonal antibody	B-cell-specific surface antigen CD20	B-cell apoptosis/lysis
Ofatumumab	Anti-CD20	Fully human monoclonal antibody	B-cell-specific surface antigen CD20	B-cell apoptosis/lysis
Epratuzumab	Anti-CD22	Fully human monoclonal antibody	B-cell-specific surface antigen CD22	B cell apoptosis
MEDI-551	Anti-CD19	Afucosylated human monoclonal antibody	B-cell-specific surface antigen CD19	B cell apoptosis
Belimumab	BLyS inhibition	Fully human monoclonal antibody	B-cell activating factor BLyS	Blocks soluble BLyS and prevent its binding on B-cell receptors
BR3-Fc	BLyS inhibition	Recombinant fusion protein	B-cell activating factor BLyS	Blocks soluble BLyS and prevent its binding on B-cell receptors
AMG-623	BLyS inhibition	Peptide-Fc fusion protein	B-cell activating factor BLyS	Blocks soluble BLyS and prevent its binding on B-cell receptors
Atacicept	BLyS/APRIL inhibition	Recombinant fusion protein (TACI-Ig)	B-cell activating factors BLyS and APRIL	Binds both BLyS and APRIL
Anti-BR3	Anti-BR3	Mouse monoclonal antibody	BLyS receptor 3	Blocks BLyS receptor 3

Ramos-Casals M et al. *Am J Med*. 2012 Apr;125(4):327-36.

Novel Therapies

- **Rituximab**

  B-lymphocyte–depleting therapy, appears to be effective in SLE and lupus nephritis.

- **Belimumab**
  - an anti–B-lymphocyte stimulator [BLyS] monoclonal antibody).
  - It has been found to have beneficial effects on clinical and laboratory parameters in patients with active SLE.
  - In addition, the number of B cells and serum IgM were reduced over time.

Chan TM et al. *Nat Rev Nephrol*. 2015 Jan;11(1):46-61.

Novel Therapies

- **Atacicept**

  Atacicept is a TACI-Ig fusion protein that inhibits BLyS and a proliferation-inducing ligand.

  Atacicept has demonstrated to have biologic effects in patients with SLE, resulting in a dose-dependent reduction in B cells and immunoglobulin levels.

- **Abetimus**

  Abetimus is a B-lymphocyte tolerogen.

  Administration of abetimus to patients with SLE has uniformly been associated with reductions in circulating anti-dsDNA antibodies.

Chan TM et al. *Nat Rev Nephrol*. 2015 Jan;11(1):46-61.

Novel Therapies

- **Anticytokine therapies**

  Various anticytokine therapies have been proposed, including monoclonal antibodies directed against interferon-α, interleukin (IL)-1, IL-6, IL-10, and tumor necrosis factor alpha (TNF-α), among others.

  Infliximab

  A chimeric tumor necrosis factor-alpha (TNF-α) monoclonal antibody

  Improves urinary protein levels and SLE activity

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Effectors – Complement Proteins

- C5a, a potent neutrophil and monocyte chemotactic factor, is generated by enzymatic cleavage of complement component C5.

- **Eculizumab**

  A humanized antibody that blocks C5 cleavage and thereby prevents the generation of the proinflammatory complement components C5a and C5b-9

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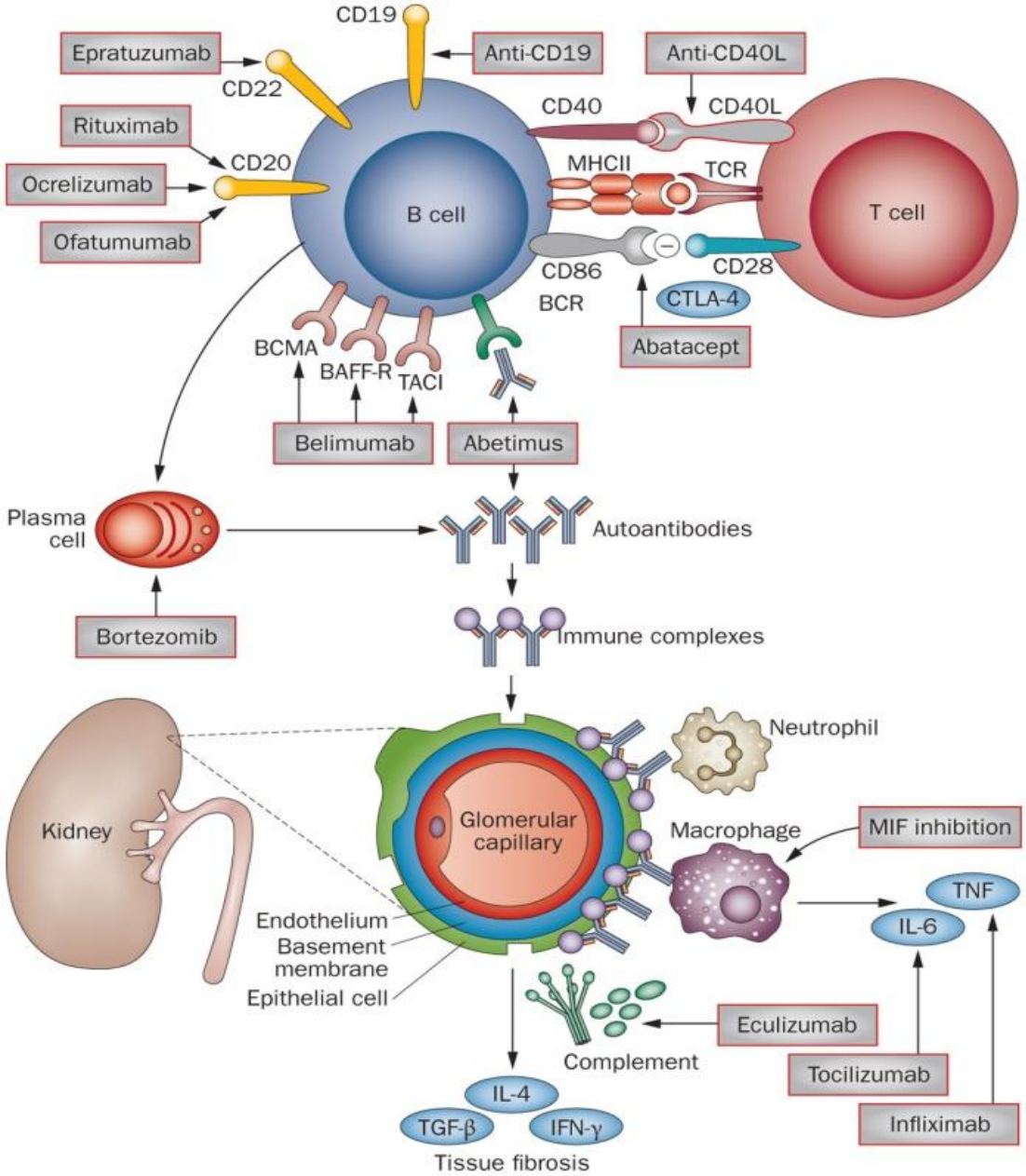
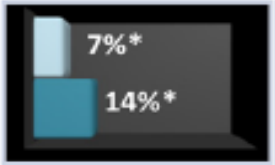
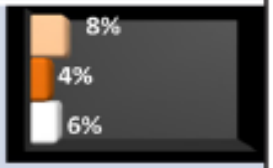
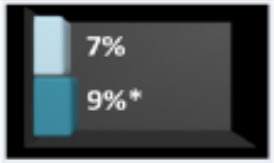
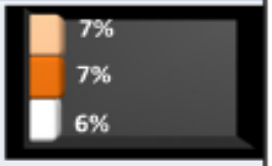
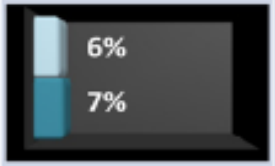
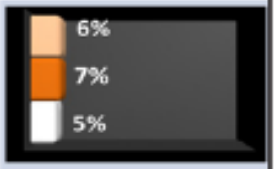
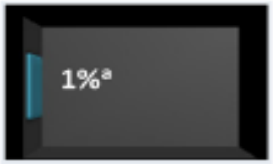
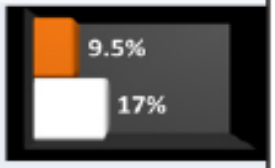
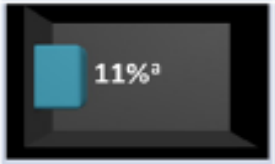
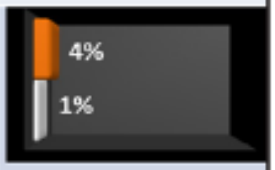
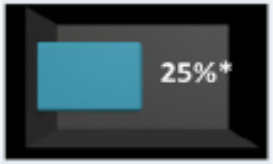
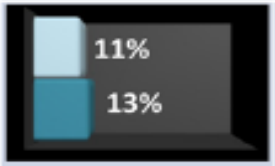
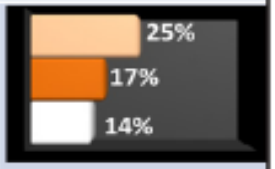
NOVEL THERAPIES IN LUPUS NEPHRITIS



Biological response modifiers like anti CD 40 ligand antibodies, CTLA 4 Ig, anti-TNF-α chimeric monoclonal antibodies are the newer agents

Chan TM et al. *Nat Rev Nephrol*. 2015 Jan;11(1):46-61.

Summary of Few Clinical Trials

Agent	Name of trial	SLE activity criteria for inclusion	Response measurement instrument	Follow-up	% of benefit over placebo	% of severe infection
Belimumab	BLISS-52	SELENA-SLEDAI ≥ 6	SRI	52 weeks		
Belimumab	BLISS-76	SELENA-SLEDAI ≥ 6	SRI	52 weeks		
Belimumab	BLISS-76	SELENA-SLEDAI ≥ 6	SRI	76 weeks		
Rituximab	EXPLORER	BILAG A ≥ 1 or BILAG B ≥ 2	BILAG	52 weeks		
Rituximab	LUNAR	LN class III/IV	Renal response	52 weeks		
Epratuzumab	EMBLEM	BILAG 2004 A ≥ 1 or BILAG 2004 B ≥ 2	CRI	12 weeks		*Not detailed*
Ocrelizumab	BELONG	LN class III/IV	Renal response	48 weeks		

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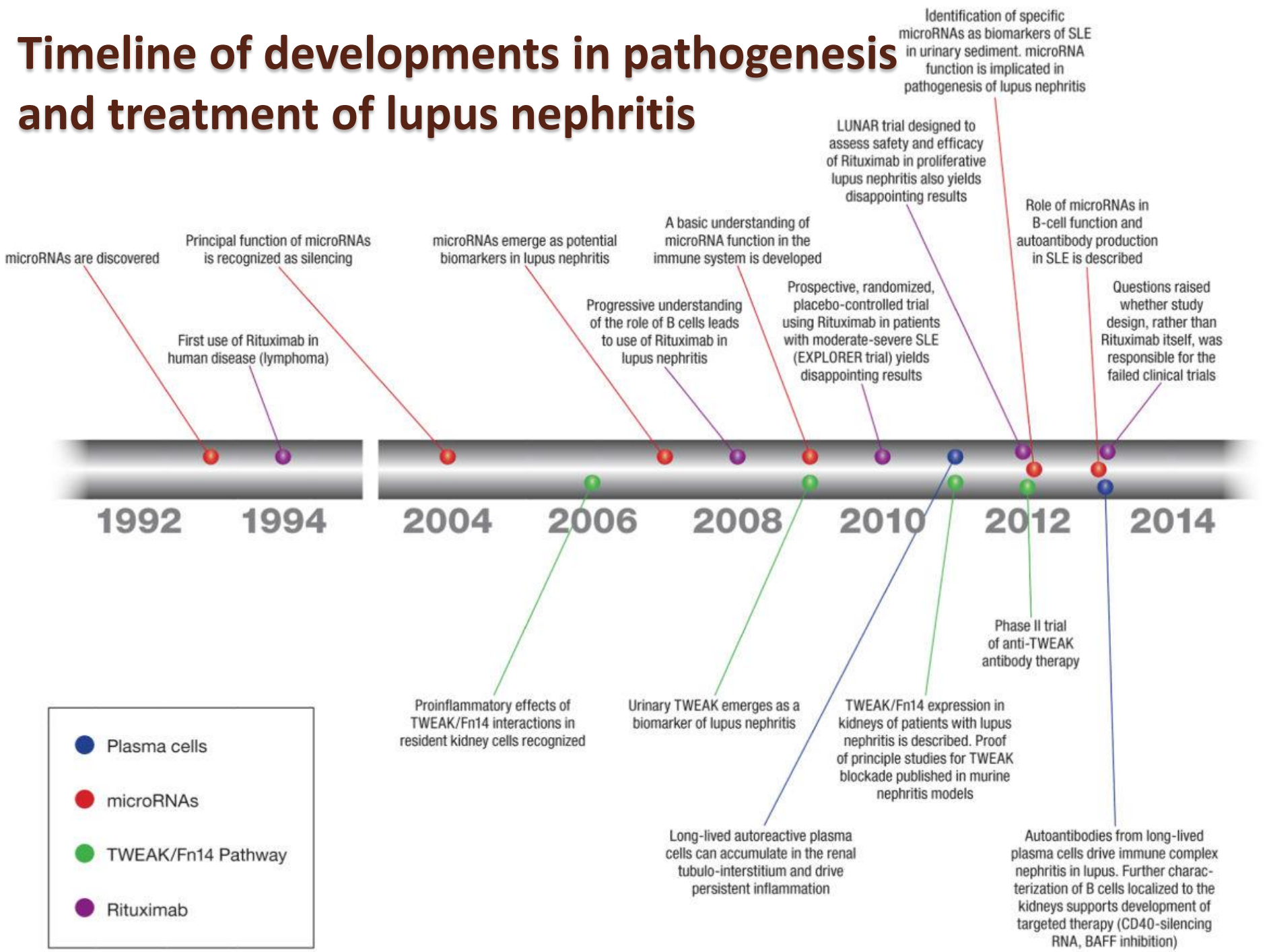
Timeline of developments in pathogenesis and treatment of lupus nephritis



Conclusion

- Lupus nephritis is a common and severe manifestation of systemic lupus erythematosus.
- An important cause of both acute kidney injury and end-stage renal disease.
- Despite its aggressive course, lupus nephritis is amenable to treatment in the majority of patients.
- The paradigm of immunosuppressive treatment for lupus nephritis has evolved over the past few decades from corticosteroids alone to corticosteroids combined with cyclophosphamide.

Conclusion

- Sequential treatment regimens for induction and long-term maintenance therapy are effective
- Mycophenolate mofetil has emerged as a standard of care option for both induction and maintenance immunosuppressive treatment.
- The current era has witnessed the emergence of multiple novel therapeutic options, such as calcineurin inhibitors and biologic agents that target key pathogenetic mechanisms of lupus nephritis.
- Clinical outcomes have improved in parallel with these therapeutic advances.

Thank You