Lupus Nephritis – Clinical Research

Approach to Lupus Patients With Advanced Renal Failure

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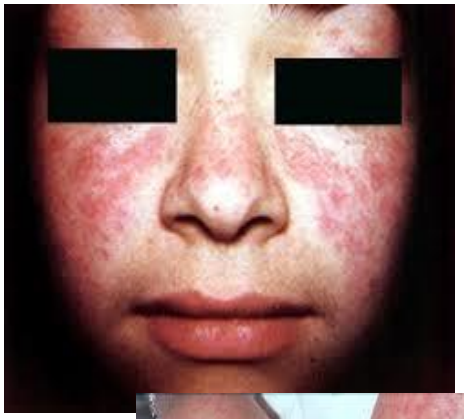
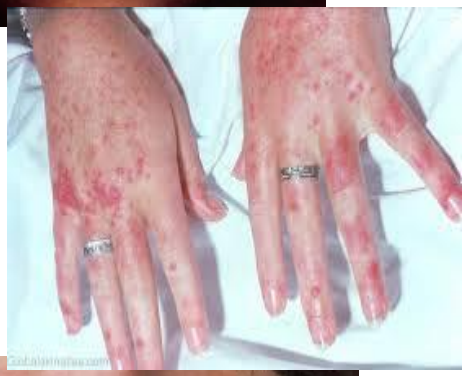
Outline

- Lupus and kidney involvement
- Unmet need for lupus nephritis treatment
- Disease activity in SLE ESRD patients
- Choosing the most appropriate renal replacement modality
- Renal transplant in SLE

Systemic Lupus Erythematosus

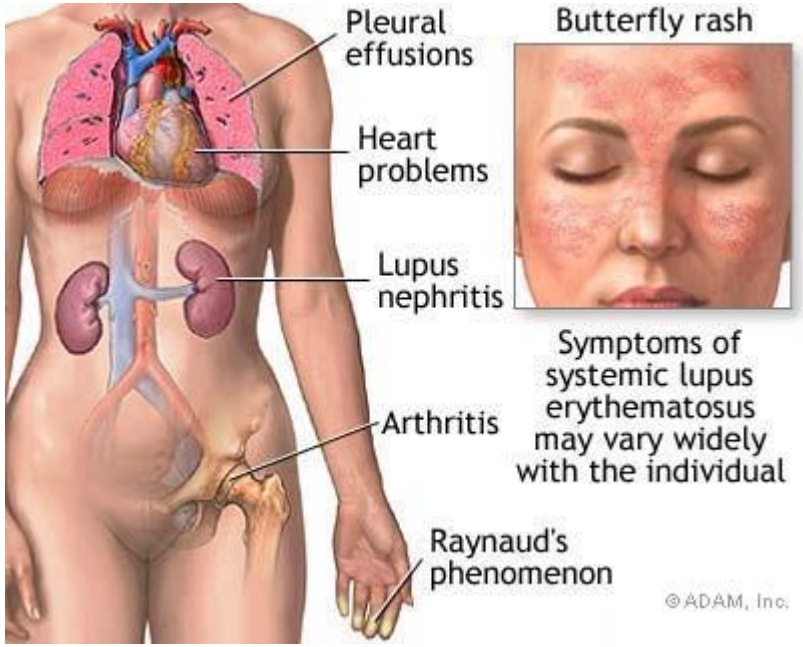
- "Lupus Erythematosus" was introduced in 19th century to describe skin lesions.
- 100 years later, a systemic disease with aberrant autoimmunity
- Prevalence- 1 case per 2000 population; 322,000 cases in the US
- Incidence higher in African Americans, Hispanics, and Asian ancestry.
- 4 year survival rate- 50% in 1950s
- 15 year survival rate- 80% in 2012





Lupus Nephritis 狼疮肾炎

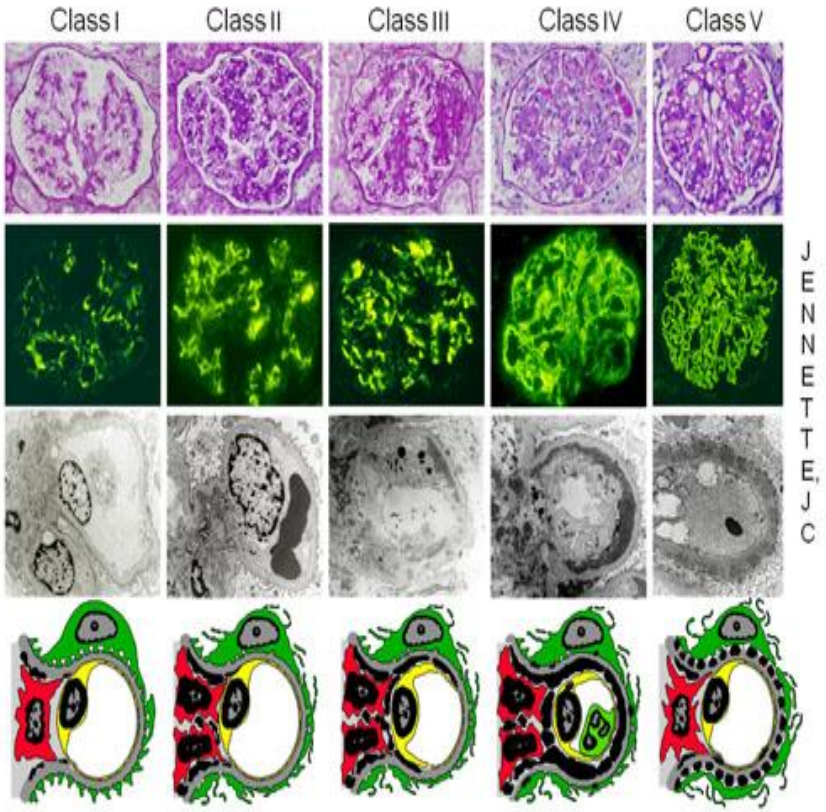
- Kidney involvement occurs in up to 50% of patients with SLE.
- It usually occurs within first 5 years of diagnosis of SLE.
- Renal involvement can occur before ACR criterion for SLE is made.



Lupus Nephritis

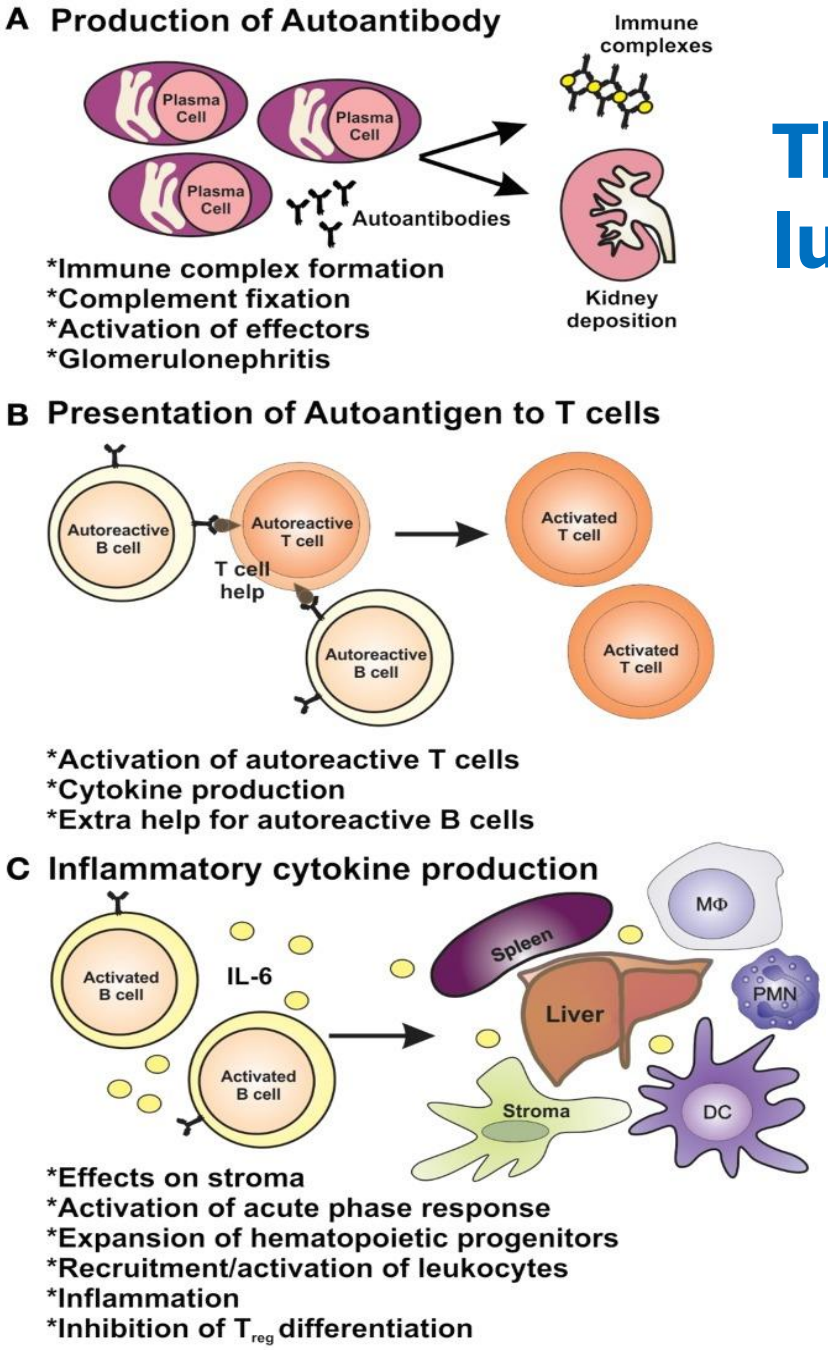
Clinical feature of patients with lupus nephritis

Feature	%
Proteinuria	100
Nephrotic syndrome	45 to 65
Granular casts	30
Red cell casts	10
Microscopic hematuria	80
Macroscopic hematuria	1 to 2
Reduced renal function	40 to 80
Rapid declining renal function	30
Acute renal failure	1 to 2
Hypertension	15 to 50
Hyperkalemia	15
Tubular abnormalities	60 to 80



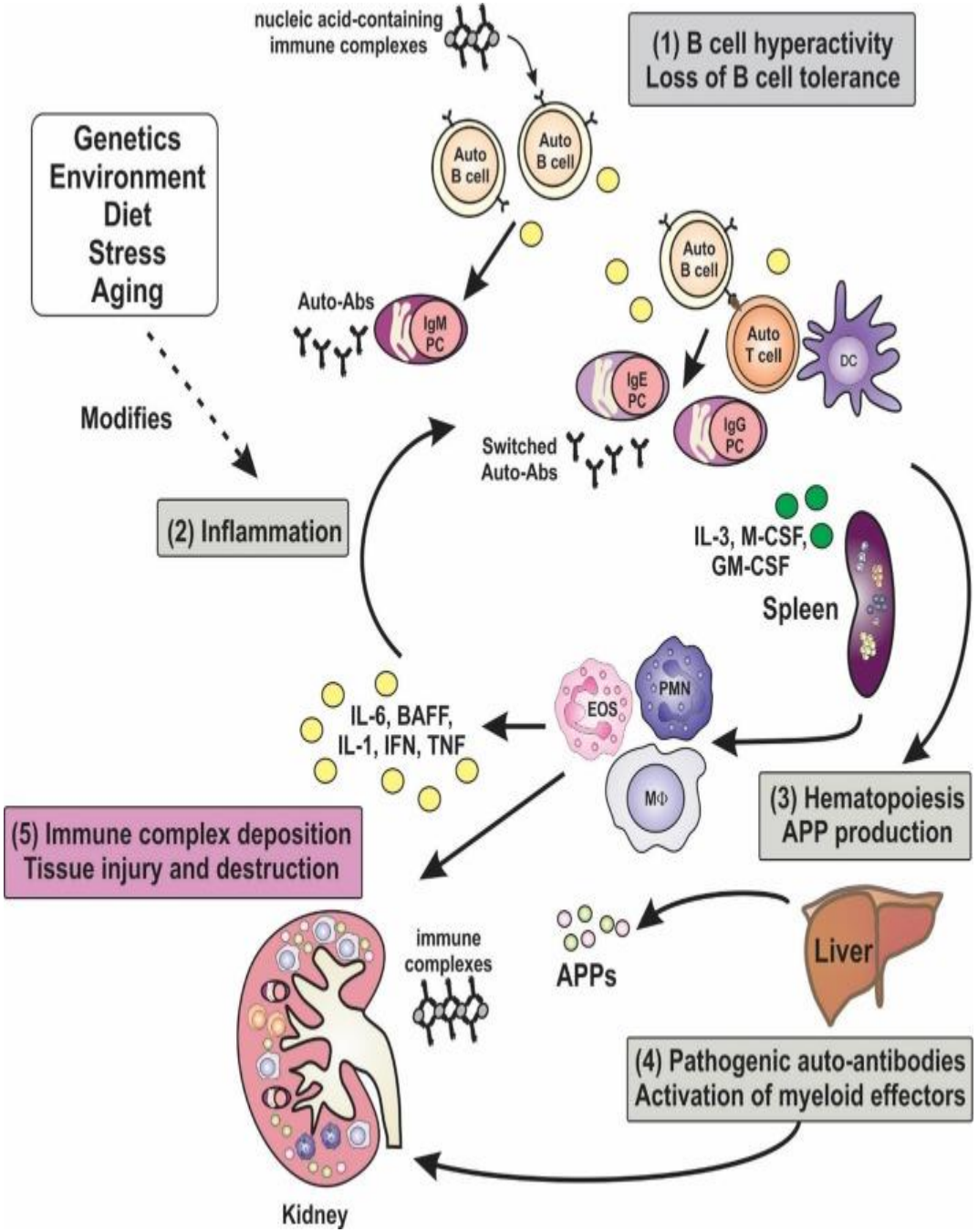
Cameron et al:JASN 1999

The roles of B cells in lupus pathogenesis.



B cells have multiple roles in autoimmunity through
(A) ability to produce autoantibodies and
(B) via their role as antigen-presenting cells and
(C) as producers of inflammatory cytokines.

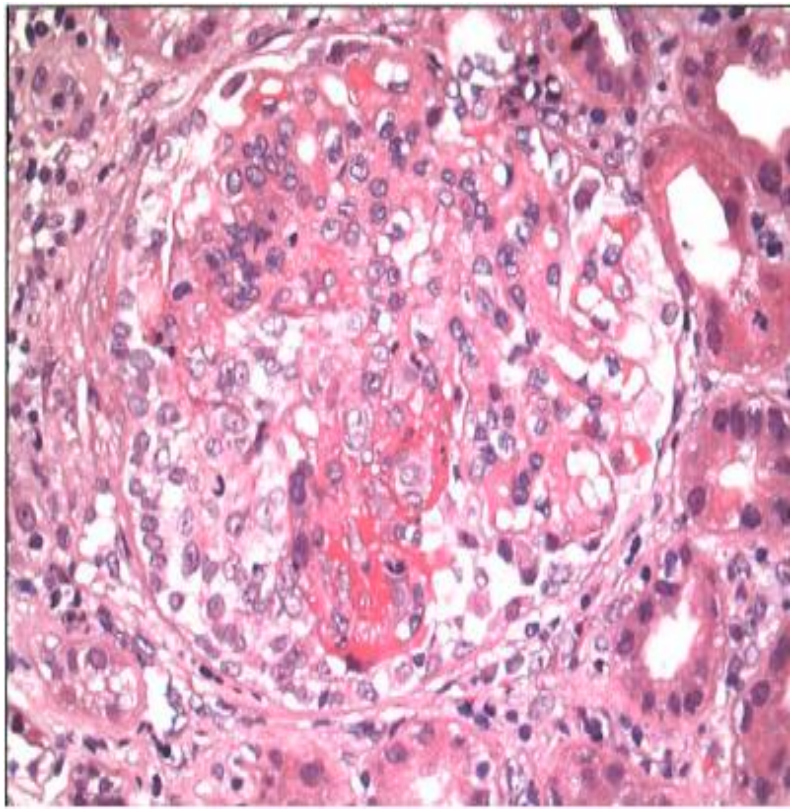
Timothy A. Gottschalk, Front Immunol. 2015; 6: 550.



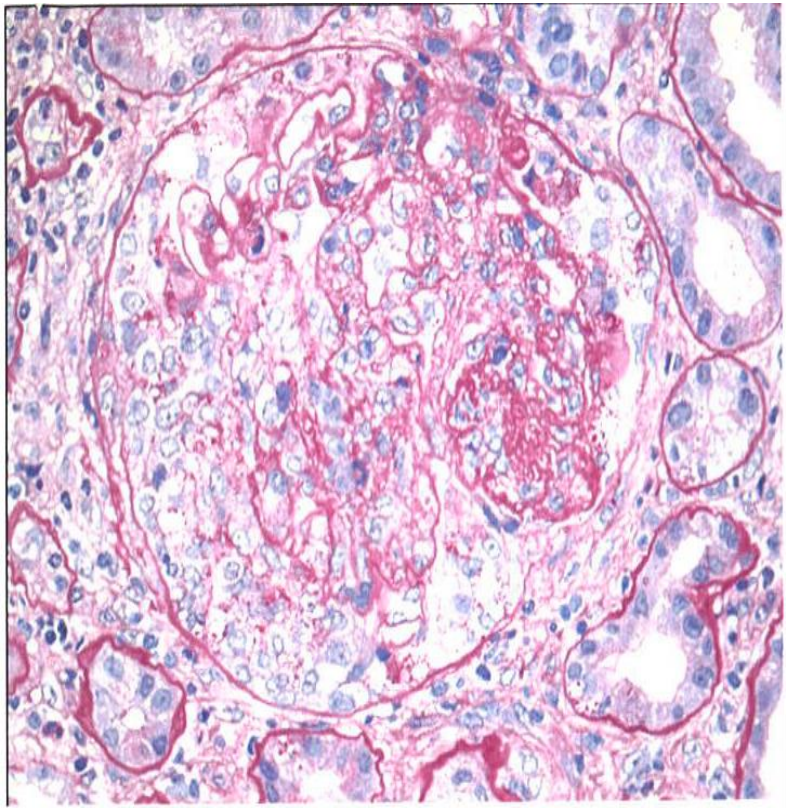
Timothy A. Gottschalk, Front Immunol. 2015; 6: 550.

Lupus Nephritis Predicting Outcome

Proliferative GN with necrosis



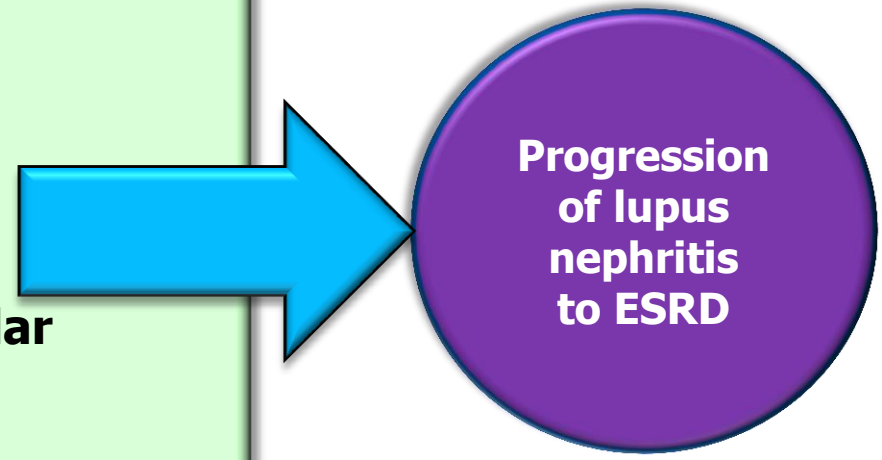
Cellular Crescent



Tubulo-Interstitial Fibrosis

Progression of Lupus Nephritis to ESRD -Risk Factors and Associations

African American, Asian and Hispanic ethnicity
Creatinine > 140µmol/L or >1.83 mg/dL
Nephrotic range proteinuria
Delayed kidney biopsy
Younger age
Male gender
Anti-Ro antibodies
Pathology: MPGN (WHO Class IV, tubular atrophy)
Lack of access to medical care
Poor response to immunosuppressive therapy
Comorbidities: hypertension, diabetes mellitus, high body mass index



Maroz N, American Journal of the Medical Sciences. 346(4):319-323, 2013.

Lupus Nephritis and ESRD

- Approximately 10 to 30 percent of patients with proliferative lupus nephritis progress to ESRD (Appel GB Am J Med. 1987;83(5):877).
- Mean age at ESRD onset was 41 years; 81.6% of the patients were women and 49.5% were African American. (Costenbader KH, Arthritis Rheum. 2011;63(6):1681.)

Lupus Nephritis
High Risk for Mortality

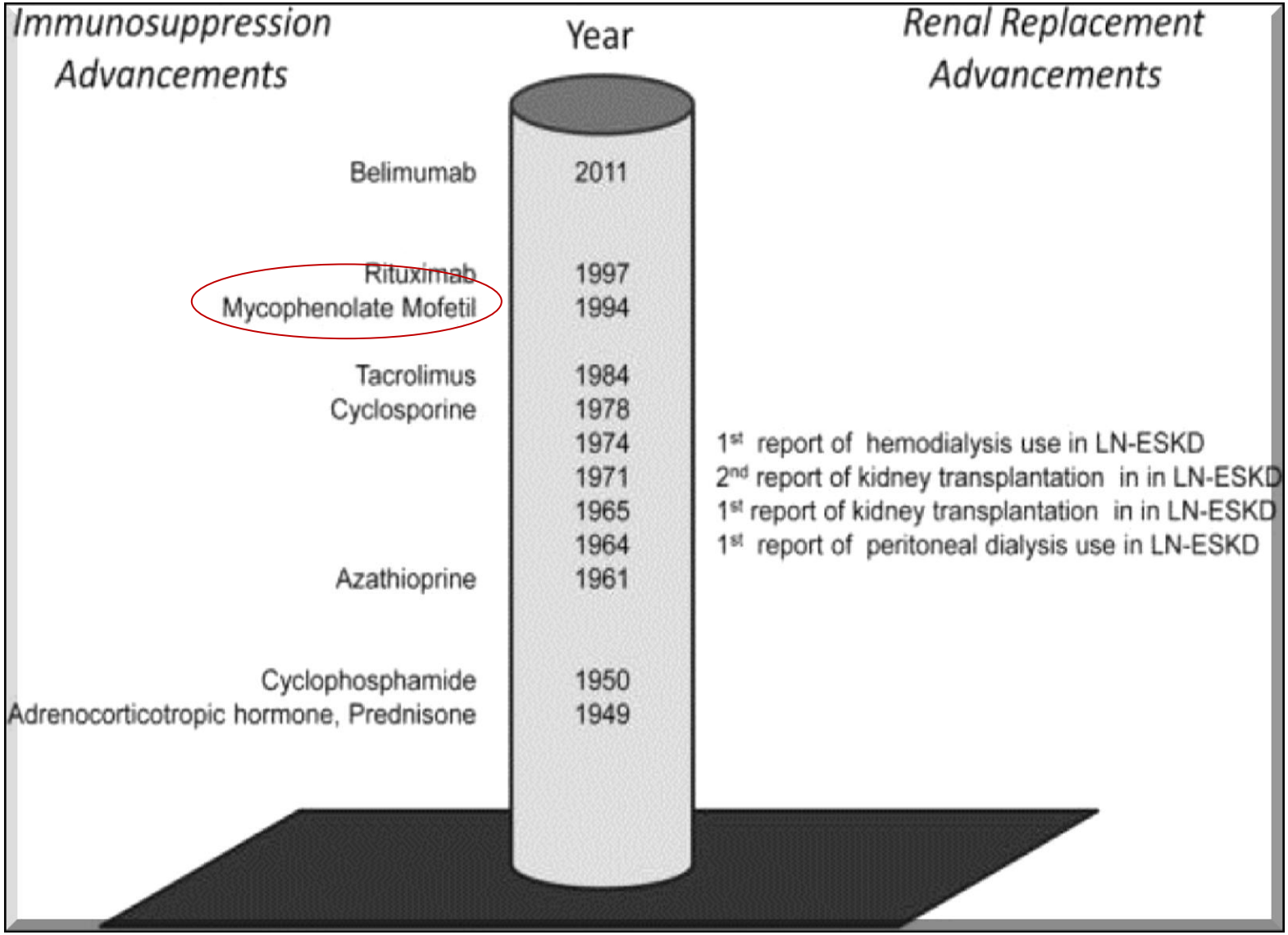
- **Hong Kong:**
  - Lupus nephritis: 6-fold increase in mortality compared with the general population.
  - Lupus ESRD: 26-fold excess in the risk of death, which is more than twice the risk associated with malignancy or cardiovascular disease in these patients.

Yap DY, Nephrol Dial Transplant. 2012 Aug;27(8):3248-54

- **USA:**
  - In 12,344 individuals with incident Lupus ESRD in USRDS data (1995 – 2006) - not reduced in Standardized Mortality Ratio during this 12-year study period.

Costenbader KH, Arthritis Rheum. 2011; 63:1681–1688.

Evolution of Accepted Immunosuppressive Therapies For Treatment of Lupus Nephritis



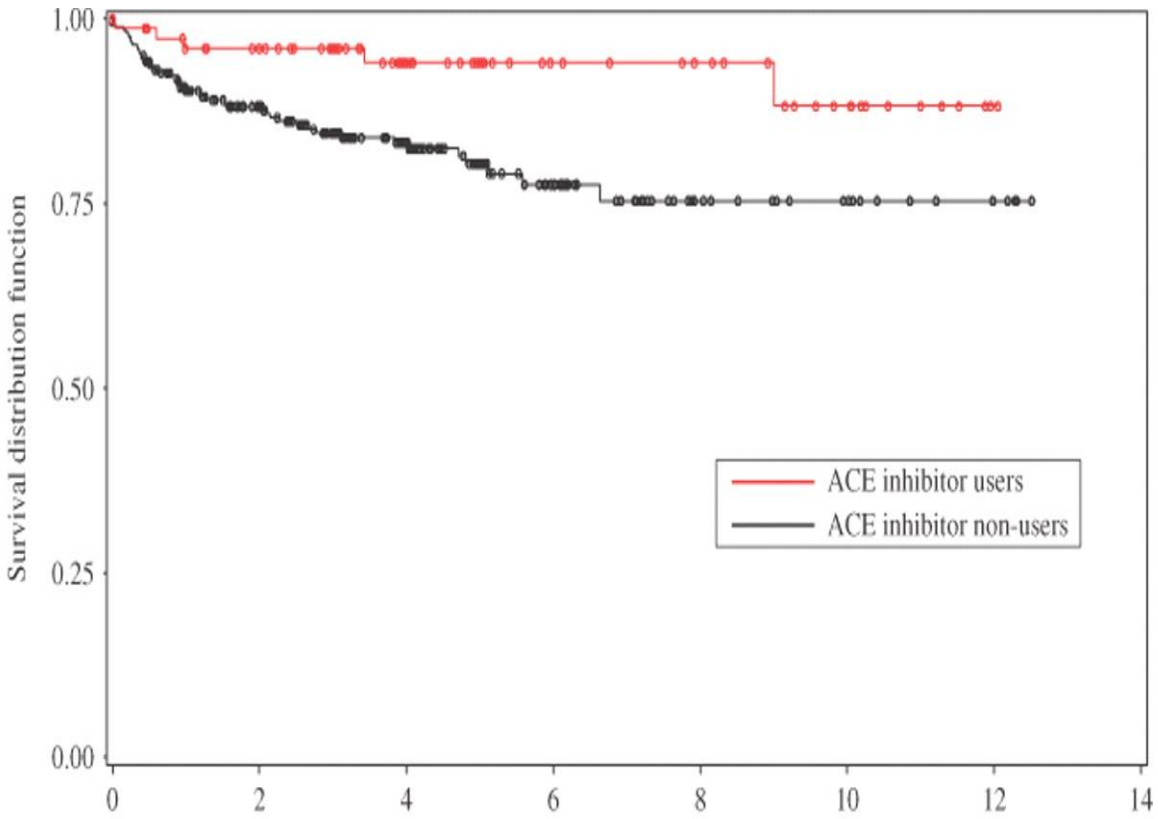
Maroz N, American Journal of the Medical Sciences. 346(4):319-323, 2013.

Treatment for Lupus Nephritis

- **Non-immunosuprressive therapy**
  - Angiotension inhibition: ACEi, ARB for Proteinuria
  - BP control
  - Lipid Lowering
- **Immunosuppressive therapy**
  - Patients with proliferative classes of lupus nephritis need immunomodulatory treatment to turn off the immune system.

induction	maintaince
cyclophosphamide	cyclophosphamide
Mycophenolate mofetil	Mycophenolate mofetil
Rituximab	Rituximab
Steroids	Steroids
	Cyclosporine
	Azathioprine

Kaplan–Meier survival curve for the development of renal involvement as a function of the use of ACE inhibitors.



Numbers of patients at risk							
Users	80	75	54	32	21	16	6
Non-users	298	257	151	79	33	16	8

Durán-Barragán S et al. Rheumatology 2008;47:1093-1096

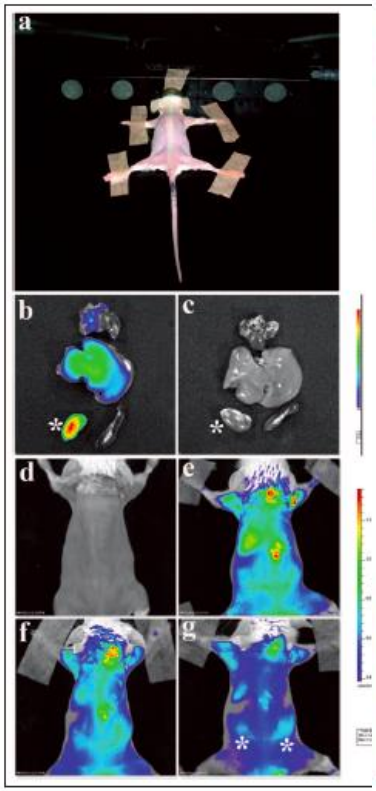
RHEUMATOLOGY

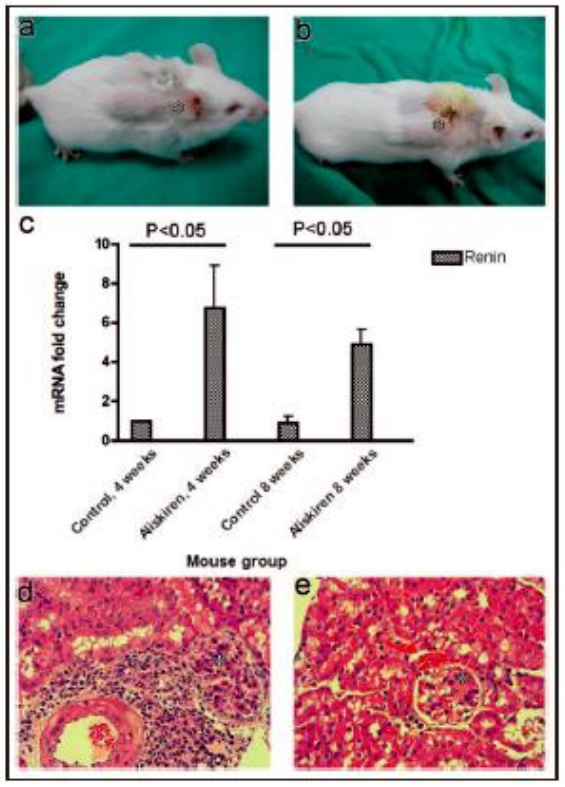
Aliskiren attenuates proteinuria in mice with lupus nephritis by a blood pressure-independent mechanism

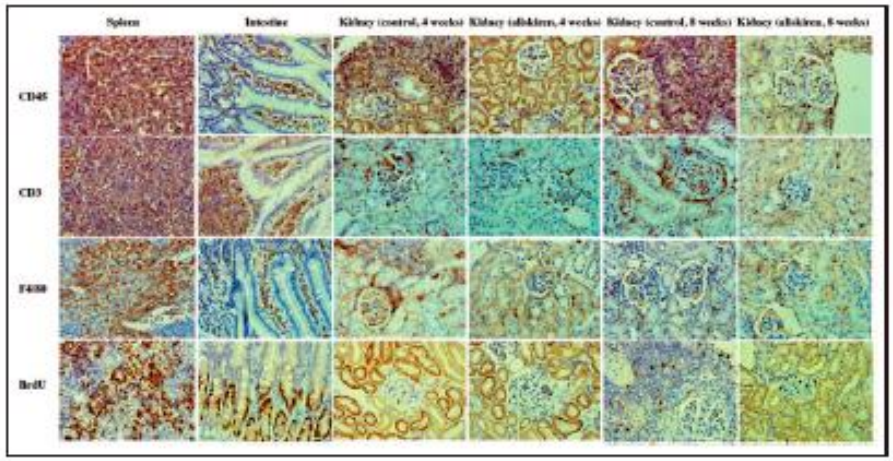
T-H Yen[1], H-Y Yang[1], Y-H Yeh[2], P-H Chu[2], C-J Wen[3], J-F Fu[4], I-K Wang[5], C-C Liang[5], C-T Chang[5], K-H Chen[1], Y-C Tian[1], C-C Hung[1], J-L Lin[1] and C-W Yang[1]

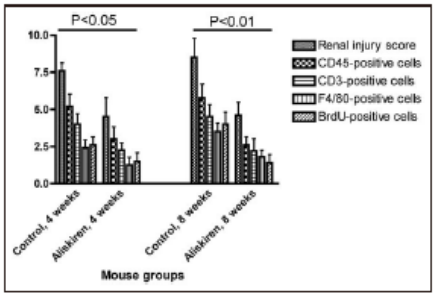
[1]Kidney Research Center, Department of Nephrology, Chang Gung Memorial Hospital and College of Medicine, Chang Gung University, Taiwan; [2]First Cardiovascular Division, Chang Gung Memorial Hospital and College of Medicine, Chang Gung University, Taiwan; [3]Molecular Imaging Center, Chang Gung Memorial Hospital, Taiwan; [4]Department of Medical Research, Chang Gung Memorial Hospital, Taiwan; and [5]Department of Nephrology, China Medical University Hospital and College of Medicine, China Medical University, Taiwan

Lupus (2013) 22, 180–189

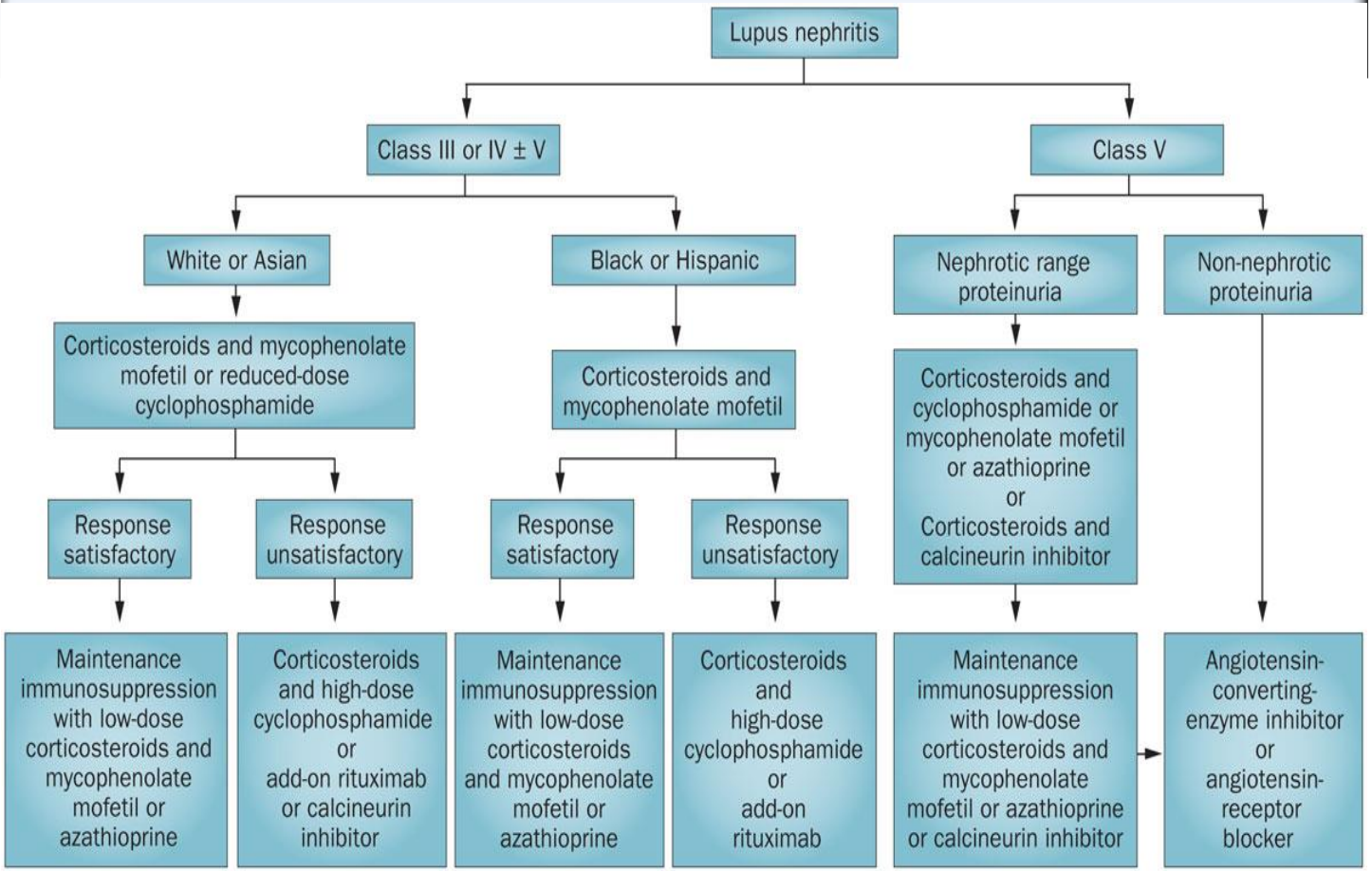








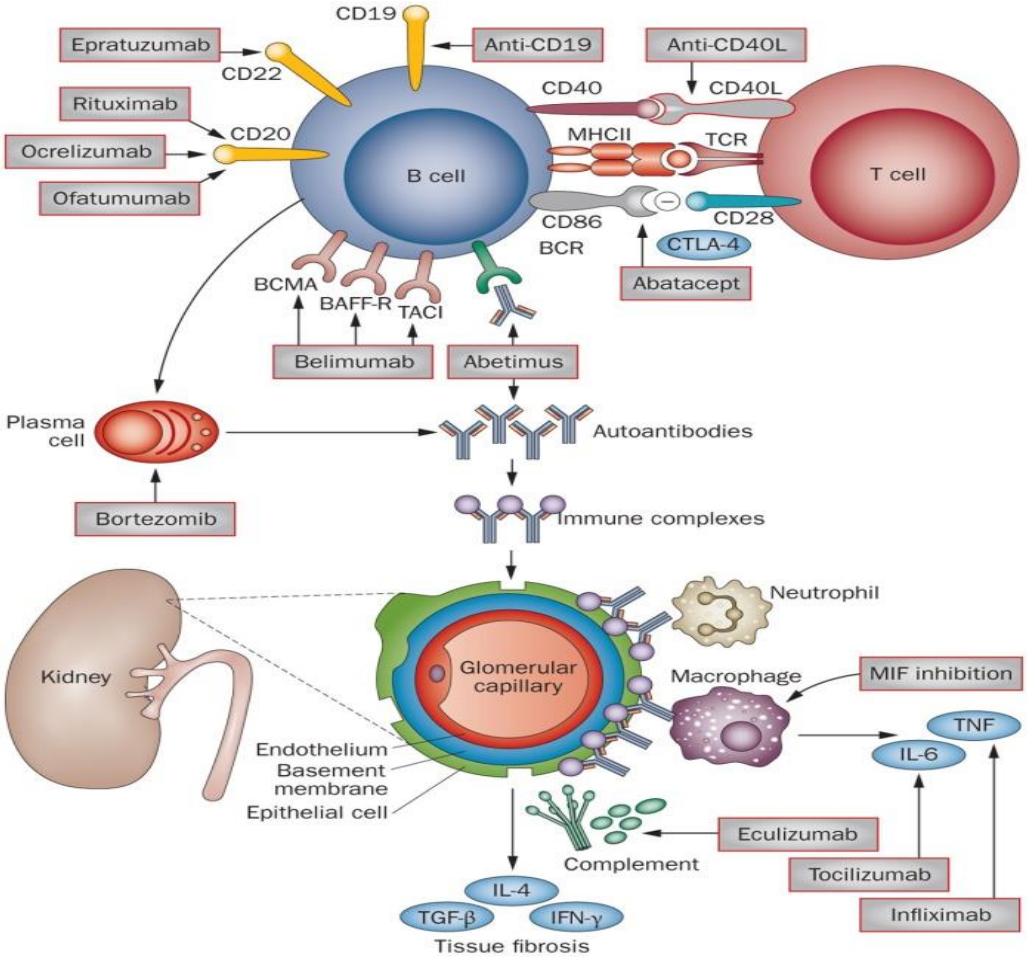
Treatment algorithm for severe (class III–V) lupus



Chan, T. M. (2014) Treatment of severe lupus nephritis: the new horizon
***Nat. Rev. Nephrol.* doi:10.1038/nrneph.2014.215**

nature REVIEWS NEPHROLOGY

Biologic therapies for lupus nephritis

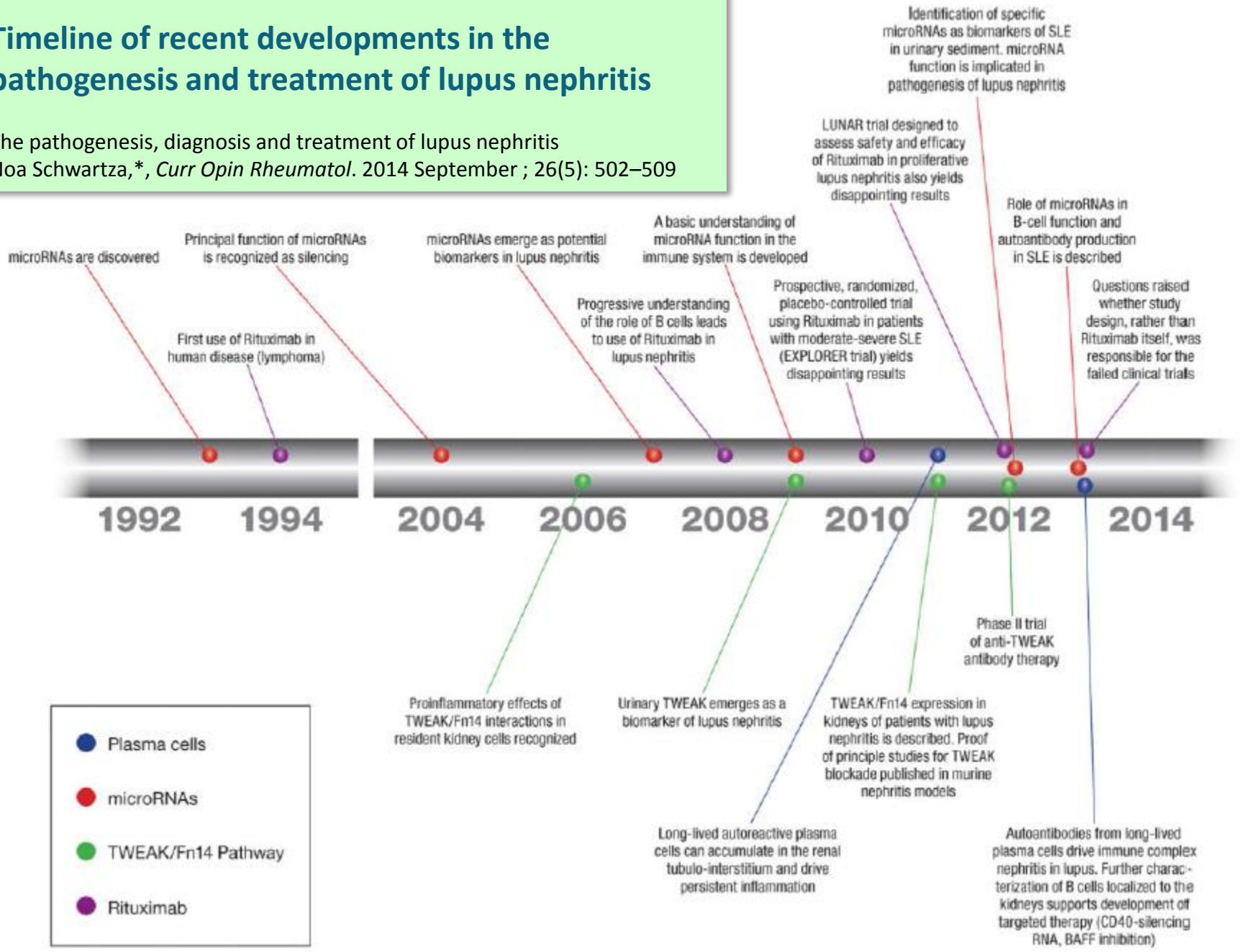


Chan, T. M. (2014) Treatment of severe lupus nephritis: the new horizon
***Nat. Rev. Nephrol.* doi:10.1038/nrneph.2014.215**

nature REVIEWS NEPHROLOGY

Timeline of recent developments in the pathogenesis and treatment of lupus nephritis

The pathogenesis, diagnosis and treatment of lupus nephritis
Noa Schwartza,*, *Curr Opin Rheumatol*. 2014 September ; 26(5): 502–509



An Era of MicroRNA as Biomarker and Target for Treatment

Review Article

MicroRNAs Implicated in the Immunopathogenesis of Lupus Nephritis

Cristen B. Chafin

REVIEWS

MicroRNAs in kidney physiology and disease

Piera Trionfini, Ariela Benigni and Giuseppe Remuzzi

Abstract | MicroRNAs (miRNAs) are small non-coding RNA molecules that regulate gene expression. They have important roles during kidney development, homeostasis and disease. In particular, miRNAs participate in the onset and progression of tubulointerstitial sclerosis and end-stage glomerular lesions that occur in various forms of chronic kidney disease (CKD). Therefore, miRNAs represent potential new therapeutic targets for a debilitating disease that continues to increase in prevalence worldwide and for which fully effective therapies are lacking. Several lines of research aimed at improving common CKD diagnostic tools and avoiding invasive kidney biopsies have also identified circulating miRNAs as possible diagnostic and even prognostic biomarkers of kidney disease. This Review discusses current understanding of the function of miRNAs in CKD, focusing on functions specifically involved in the transforming growth factor β1 pathway, which is activated in CKD. miRNAs that, according to available evidence, seem to be involved in diabetic nephropathy, IgA nephropathy, lupus nephritis, polycystic kidney disease and graft rejection, are also discussed

Trionfini, P. *et al. Nat. Rev. Nephrol.* **11**, 23–33 (2015);

Curr Opin Rheumatol. 2014 September ; 26(5): 502–509. doi:10.1097/BOR.0000000000000089.

The pathogenesis, diagnosis and treatment of lupus nephritis

Noa Schwartz[a,*], **Beatrice Goilav**[b,*], and **Chaim Putterman**[c,d]

SCIENTIFIC REPORTS

OPEN

Human embryonic stem cell-derived mesenchymal cells preserve kidney function and extend lifespan in NZB/W F1 mouse model of lupus nephritis

Received: 18 August 2015
Accepted: 03 November 2015
Published: 02 December 2015

Austin Thiel*, Gregory Yavanian*, Maria-Dorothea Nastke, Peter Morales, Nicholas A. Kouris, Erin A. Kimbrel & Robert Lanza

Stem Cell Reports
Article
OPEN ACCESS

ISSCR

Interleukin-25 Mediates Transcriptional Control of PD-L1 via STAT3 in Multipotent Human Mesenchymal Stromal Cells (hMSCs) to Suppress Th17 Responses

Wei-Bei Wang,[1,8] Men-Luh Yen,[2,8] Ko-Jiunn Liu,[3,4,*] Pei-Ju Hsu,[1] Ming-Hong Lin,[5] Pei-Min Chen,[2] Putty-Reddy Sudhir,[6] Chein-Hung Chen,[6] Chung-Hsuan Chen,[6] Huei-Kang Sytwu,[5] and B. Linju Yen[1,7,*]

Treatment Goal
治療目標

- Long term preservation of renal function
  - 長期保護腎臟功能
- Prevention of flares
  - 避免紅斑狼瘡發作
- Avoidance of treatment-related harms
  - 避免治療相關傷害
- Improve quality of life and survival
  - 提高存活及生活品質

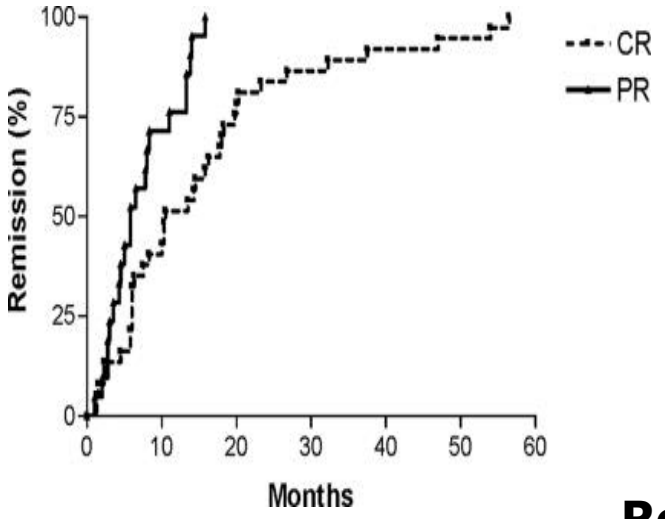
Value of a Complete or Partial Remission in Severe Lupus Nephritis

- A complete remission was attained in 37 (43%) patients, a partial remission in 21 (24%) patients, and no remission in 28 (32%) patients.
- Patients with a complete remission had a lower serum creatinine and chronicity index compared with patients with partial or no remission.

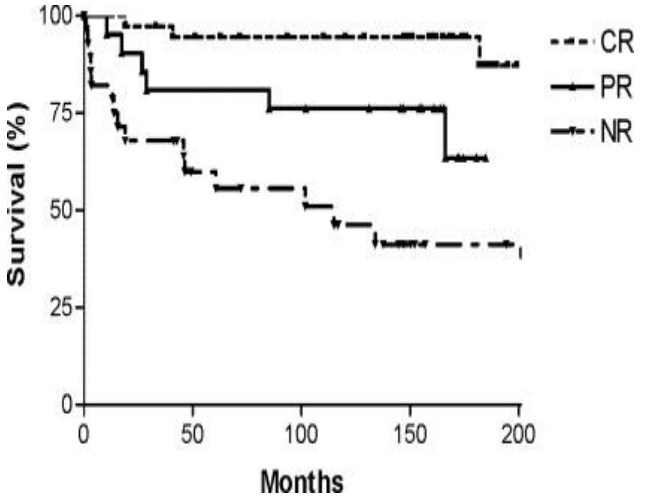
- **The patient survival at 10 yr was 95% for complete remission, 76% for partial remission, and 46% for no remission.**
- **The renal survival at 10 yr was 94% for complete remission, 45% for partial remission, and 19% for no remission,**
- **The patient survival without end-stage renal disease at 10 yr was 92% for complete remission, 43% for partial remission, and 13% for no remission.**

Yiann E. Chen et al. CJASN 2008;3:46-53

Patients With Severe Lupus Nephritis Based on Remission Status

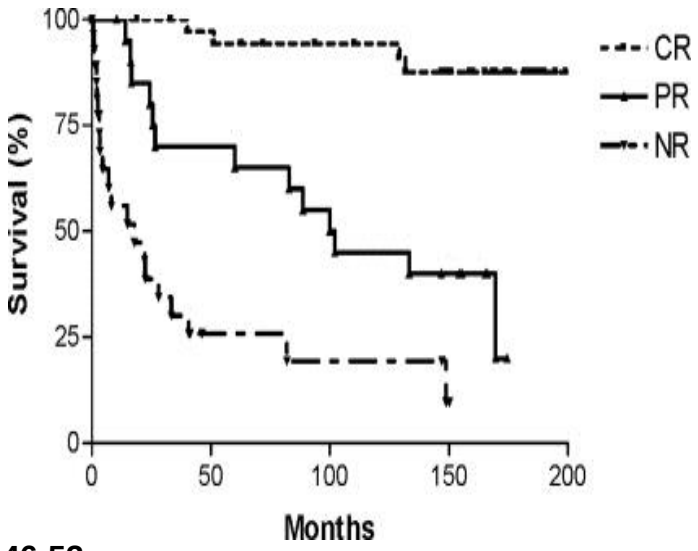


Renal remission



Patient survival

Renal survival.



CJASN

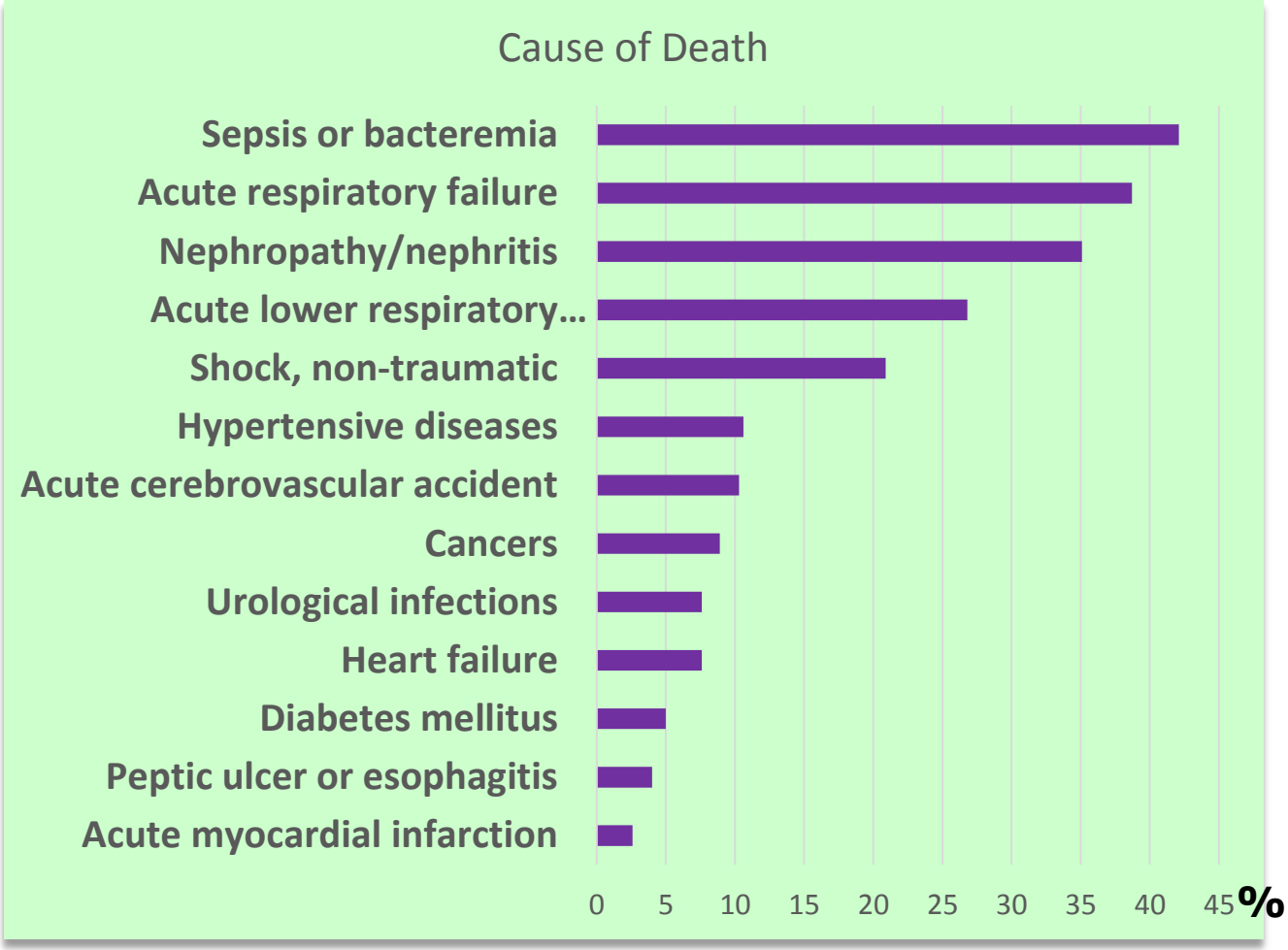
Yiann E. Chen et al. CJASN 2008;3:46-53

Treating Patients with Lupus Nephritis

To Cure, not to Kill.

Sepsis is the Leading Cause of Death of Systemic Lupus Erythematosus Patients in Taiwan

Beware of Sepsis as a cause of death before entering ESRD. (N=302, 2005-2007)



Characteristics of Comorbidities and Costs Among Patients Who Died from Systemic Lupus Erythematosus in Taiwan

Shih-Chao Kang Arch Med Sci. 2012 Sep 8; 8(4): 690–696.

Unmet Medical Needs In Lupus Nephritis:
Solutions Through Evidence-based, Personalized Medicine

(i) **How to better predict the individual risk** for LN in a SLE patient, or for CKD/ESRD in a LN patient. 預測個別風險

(ii) **How to better identify optimal therapeutic options** for an individual patient. 確認適當治療

(iii) **How to better monitor disease activity** of SLE and LN separately to better define response to treatment, and to dissect ongoing immunologic activity from persistent kidney damage. 監測疾病活動性

(iv) **How to develop efficient treatments** with acceptable or no side effects. 發展有效治療

(v) **How to improve the design of randomized clinical trials** so that drugs have a chance to show efficacy. 改進隨機臨床試驗

Hans-Joachim Anders, Clinical Kidney Journal, 2015, vol. 8, no. 5, 492–502

Unmet need	Current strategies	Possible future strategies	EBM	PM
Predict LN in SLE	Urine screening	**Genetic risk stratification**		+
Predict CKD/ESRD in LN	LN class in biopsy SCr, proteinuria, BMI	**Genetic risk stratification** (APOL1 in African ancestry)		+
	Response to treatment, blood pressure, race	Re-biopsy, urine **proteomics**		+
Assess treatment response on activity	SCr, proteinuria, urinary sediment	SLE/autoimmunity biomarkers	+	+
		Re-biopsy, kidney injury markers	+	+
		Renal inflammation **biomarkers**	+	+
Dissect LN activity from irreversible kidney damage	SCr, proteinuria	Re-biopsy, urine proteomics, more	+	
		sensitive biomarkers on nephron	+	
		number, renal reserve,	+	
		non-invasive GFR assay	+	
Avoid drug resistance	-	Genetic/metabolic risk stratification		+
Avoid drug toxicity, especially steroids	Adjust dose if needed	Genetic/metabolic risk		+
		stratification, combination of low-dose immunosuppressants with anti-inflammatory drugs, favor	+	
		specific drugs over unselective immunosuppressants	+	

Unmet need	Current strategies	Possible future strategies	EBM	PM
Improve response rates	Increase dose of unspecific drugs	Individualize treatment with specific drugs		+
Avoid disease flares	Maintenance therapy with unspecific drugs	Preemptive flare prophylaxis based on **biomarkers** with drugs of low toxicity, individualize treatment with specific drugs		+
Control smoldering disease	Symptom-based treatment with toxic drugs	Biomarker-based treatment with drugs of low toxicity	+	
Normalize cardiovascular risk	Lifestyle modifications, statins, aspirin	Efficient control of systemic autoimmunity and inflammation	+	
Avoid pregnancy risks	Avoid teratogenic drugs (CYC, MMF, ACEI/ARB, OAK)	Develop more non-teratogenic drug options	+	
Trials that demonstrate efficacy for efficacious drugs	-	Solve problem of poor recruitment,	+	
		Biomarker-driven patient selection		
		Use endpoints that address drug MoA, avoid add-on design, use steroid sparing as end point, include re-biopsy as end point		

紅斑性狼瘡
腎病及替代治療選擇

Early CKD → Late CKD → Pre-dialysis

末期腎病 ESRD

腹透
Peritoneal Dialysis

血透
Hemodialysis

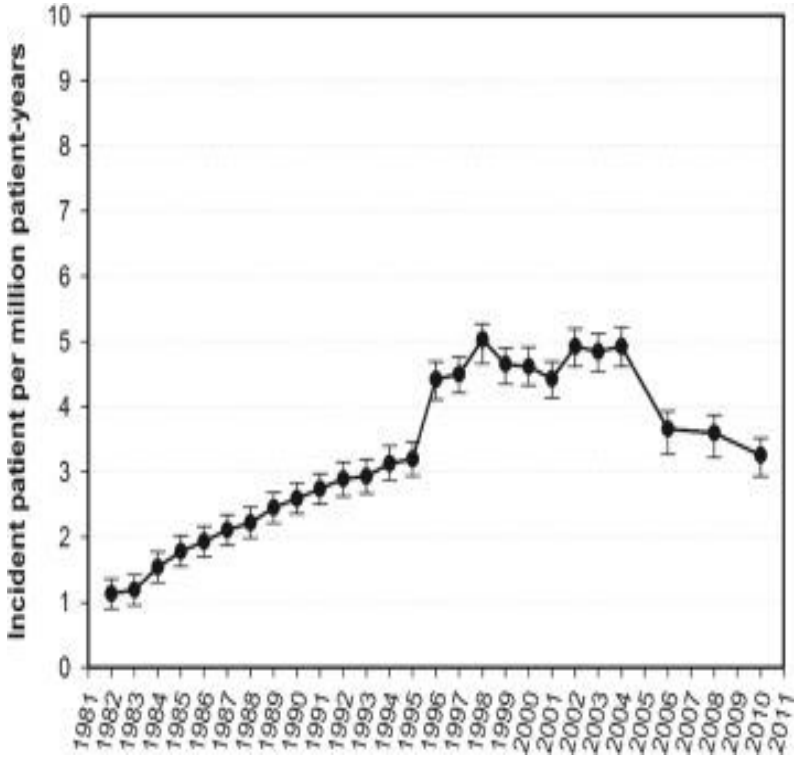
移植
Transplantation

Dialysis Modalities in Patients with SLE

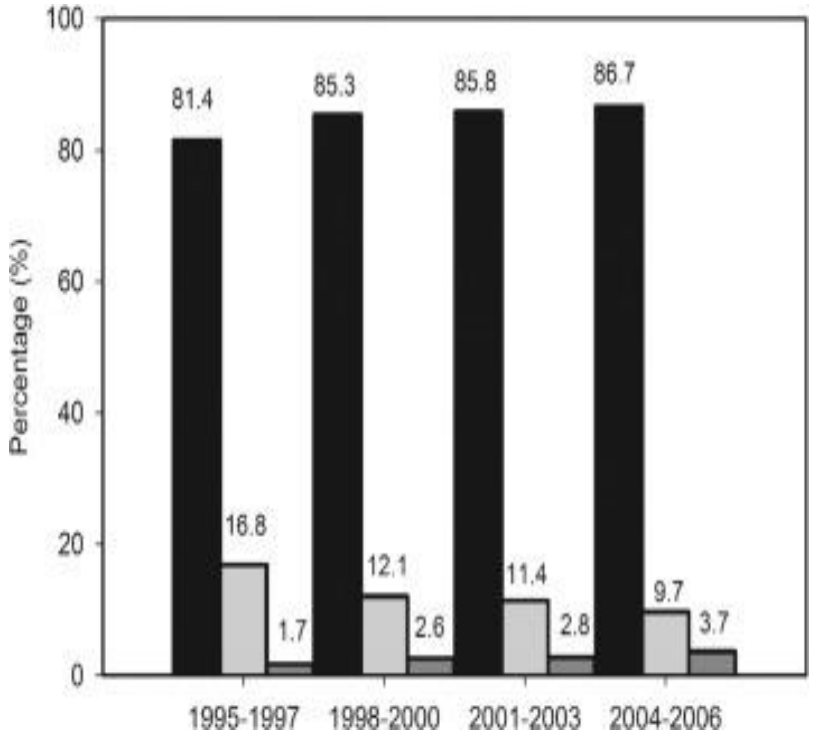
- Analysis of the U.S. Renal Data System data from 1995 to 2006 indicated LN progression to ESRD in 11,317 patients;
- 85% of these patients were initiated on HD, 12.2% were started on PD and 2.8% underwent preemptive kidney transplantation at the onset of ESRD.

ESRD, Transplantation, and Dialysis in Lupus Nephritis

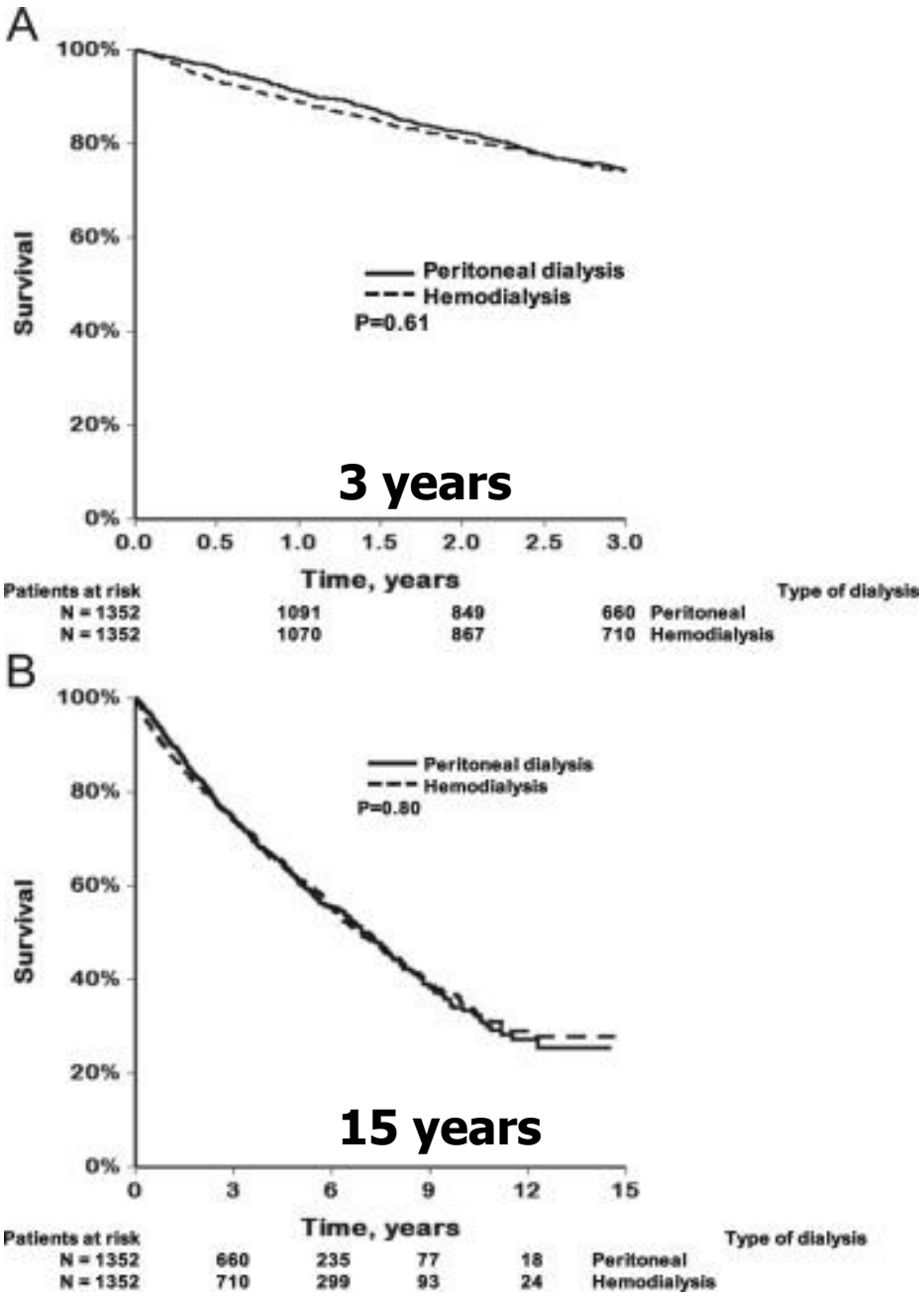
Alberto J. Sabucedo and Gabriel Contreras, Seminars in Nephrology, 2015, 35(5), 500-508



The change in the standardized incidence rate of ESRD in patients with lupus nephritis



The trend of initial RRT for LN patients with ESRD from 1995 to 2006. Black bar shows hemodialysis, light gray bar shows peritoneal dialysis, and dark gray bar shows pre-emptive kidney transplantation



Equal (A) Short-term and (B) long-term overall survival of ESRD patients with lupus initiating with peritoneal dialysis versus hemodialysis in the matched cohort.

ESRD, Transplantation, and Dialysis in Lupus Nephritis

Alberto J. Sabucedo and Gabriel Contreras, Seminars in Nephrology, 2015, 35(5), 500-508

Assessment of Lupus Activity in ESRD

- In Lupus ESRD population, serologic markers (Complement and anti-dsDNA) cannot reliably assess disease activity.
- Clinical alertness to the potential development of extrarenal manifestations of SLE in ESRD patients is important.
- Extrarenal manifestation of SLE: **alopecia, arthritis, myositis, pleuritis, pericarditis, fever, and vasculitis.**
- non-renal (nr) SLE disease activity index (SLEDAI).

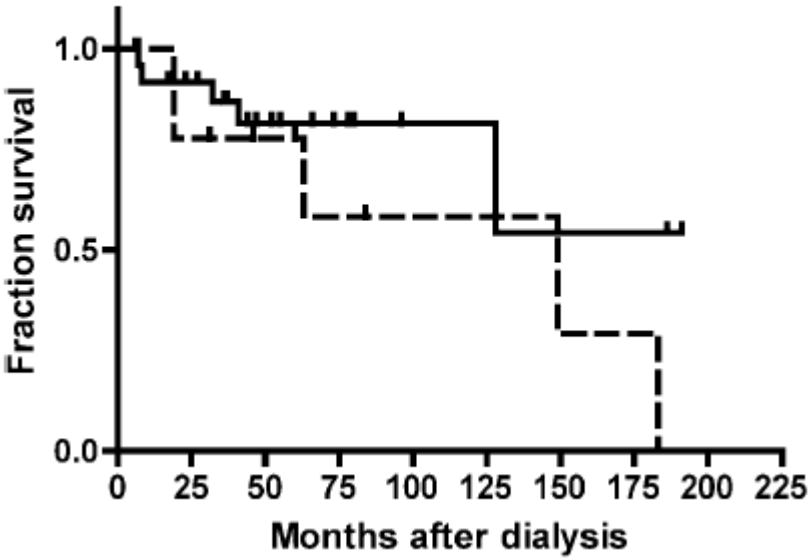
Lupus Activity In End-stage Renal Disease Patients - Reduced

- Gradual complete or partial resolution of the extrarenal manifestations of lupus.
- Active clinical lupus (eg, arthritis/arthralgias, rash, and serositis) fell from 55 % at the onset of dialysis to 6.5 % in the 5th year and, in a small number of patients, to 0 percent in the 10th year.
- Serologic activity (defined as the percentage of patients with two or more abnormal studies for ANA, anti-dsDNA, CH50, or C3) fell from 80 to 22 % (Mojcik CF, Am J Med. 1996;101(1):100).
- The number of patients with severe extrarenal disease activity [SLE-DAI] >10 declined from 17 to 3 after the initiation of dialysis and to 0 after transplantation (Nossent HC, Ann Intern Med. 1991;114(3):183.)

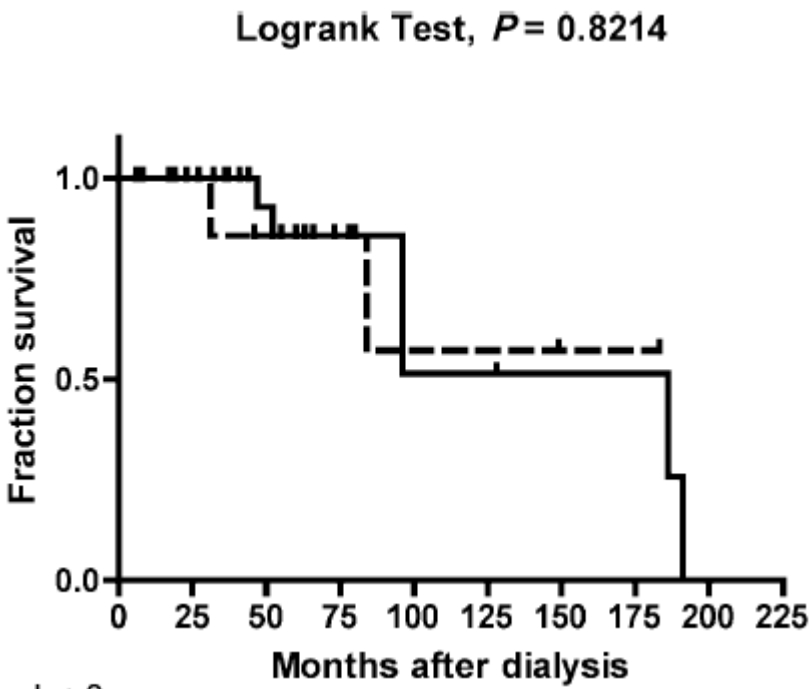
Impact of Renal Survival on the Course and Outcome of Systemic Lupus Erythematosus Patients Treated With Chronic Peritoneal Dialysis

Chih-Chia Liang & Chih-Wei Yang, *Therapeutic Apheresis and Dialysis* 14(1):35–42, 2009

patient survival



technical survival



Short renal survival group at pre-dialysis has lower C3, C4 level and higher peritoneal transport post-dialysis than long renal survival SLE patients, however, similar patient and technical survival after dialysis in both group.

ESRD-associated Immune Alterations May Modulate Disease Activity in SLE by Several Mechanisms

1. B cell survival is reduced in ESRD.

An increased resistance to B-cell activating factor (BAFF), down-regulation of BAFF receptors, and increased B-cell apoptosis. BAFF is a member of the tumor necrosis factor family of cytokines that drives B cell differentiation, proliferation and survival.

2. Decreased T-cell production in ESRD.

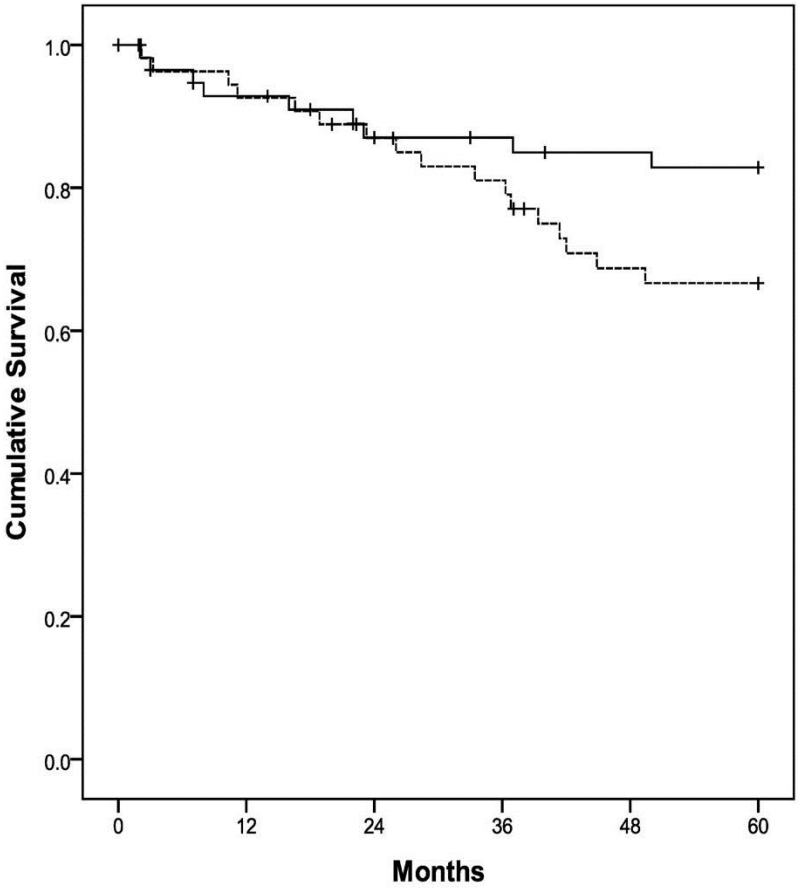
A shift from Th2 toward Th1 responses, lead to immunosuppression and decreased autoantibody production in SLE patients.

Antonio Inda-Filho, *Semin Dial*. 2013 ; 26(5): 590–596

Lupus Activity In End-stage Renal Disease Patients - Not Reduced

- Lupus dialysis patients continue to have extrarenal manifestations. **(African American)**
- Varying patient population and the clinical specialty of physician (ie, **nephrology** versus **rheumatology** versus **dermatology**).

Kaplan–Meyer cumulative survival comparing SLE (dashed lined) with the control group (continuous line) over 60 months (P = 0.096).

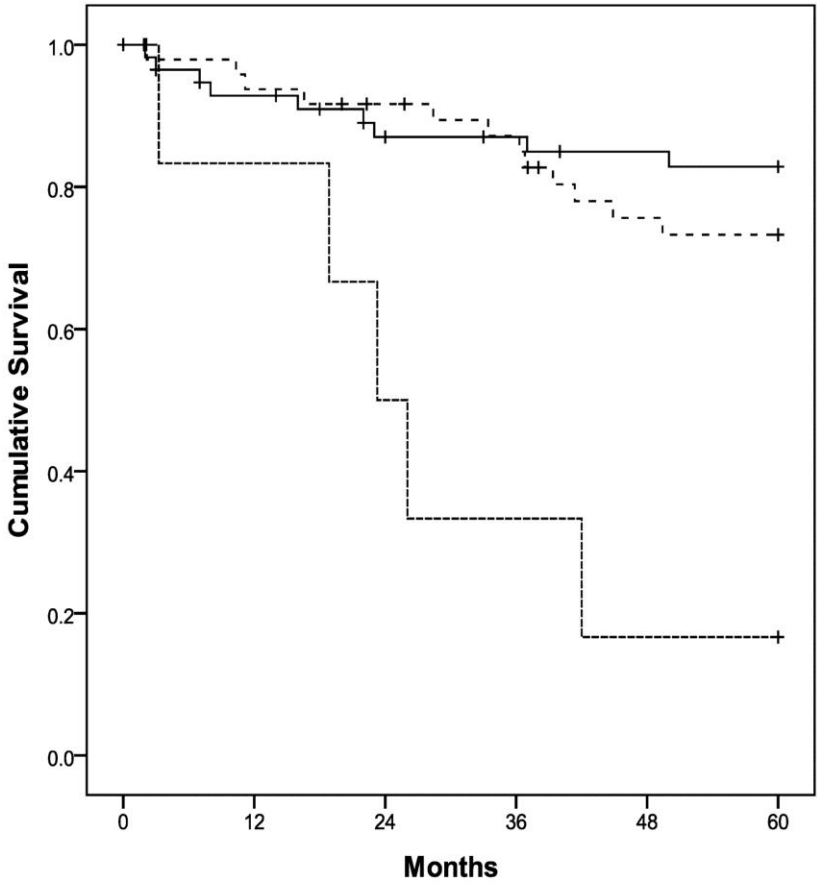


	Months					
	0	12	24	36	48	60
Controls	57[a]	50	44	42	40	39
SLE patients	57	50	45	41	33	32

Francinne Machado Ribeiro et al.
Rheumatology 2012;rheumatology.kes298

RHEUMATOLOGY

Kaplan–Meyer cumulative survival comparing SLE with nrSLEDAI > 8 (refined dashed line) and nrSLEDAI ≤ 8 (coarse dashed line) with the control group (continuous line) over 60 months.



Control

nrSLEDAI ≤ 8

nrSLEDAI > 8

	Months					
	0	12	24	36	48	60
Controls	57[a]	50	44	42	40	39
nrSLEDAI ≤8	51	45	42	39	32	31
nrSLEDAI >8	6	5	3	2	1	1

Francinne Machado Ribeiro et al.
Rheumatology 2012;rheumatology.kes298

RHEUMATOLOGY

Non-renal (nr) SLE disease activity index (SLEDAI)

- The 5-year survival rate of the control group and the one from SLE patients with nrSLEDAI ≤ 8 (n = 51) were similar (83% and 73%, respectively) but significantly better than the one for SLE patients with nrSLEDAI > 8 (n = 6, 17%), $P < 0.001$.
- **Conclusion.** A high nrSLEDAI was strongly associated with 5-year mortality in lupus patients on dialysis.

Survival of lupus patients on dialysis: a Brazilian cohort
Francinne Machado Ribeiro et al. Rheumatology 2012;rheumatology.kes298

Role of Rheumatologist in ESRD SLE Patients

- SLE patients on dialysis who continued to have regular follow-up visits with their rheumatologist (2 or more per year) had improved longevity and were more likely to receive effective immunosuppressive therapy.
- Aggressive immunosuppressive therapy was found to correlate with a better 10-year survival rate than prednisone and hydroxychloroquine, prednisone alone or no immunosuppressive medication. In addition, the combined use of prednisone and hydroxychloroquine was associated with better survival than prednisone alone.

Choosing the most appropriate renal replacement modality

- To Choose PD or HD ?

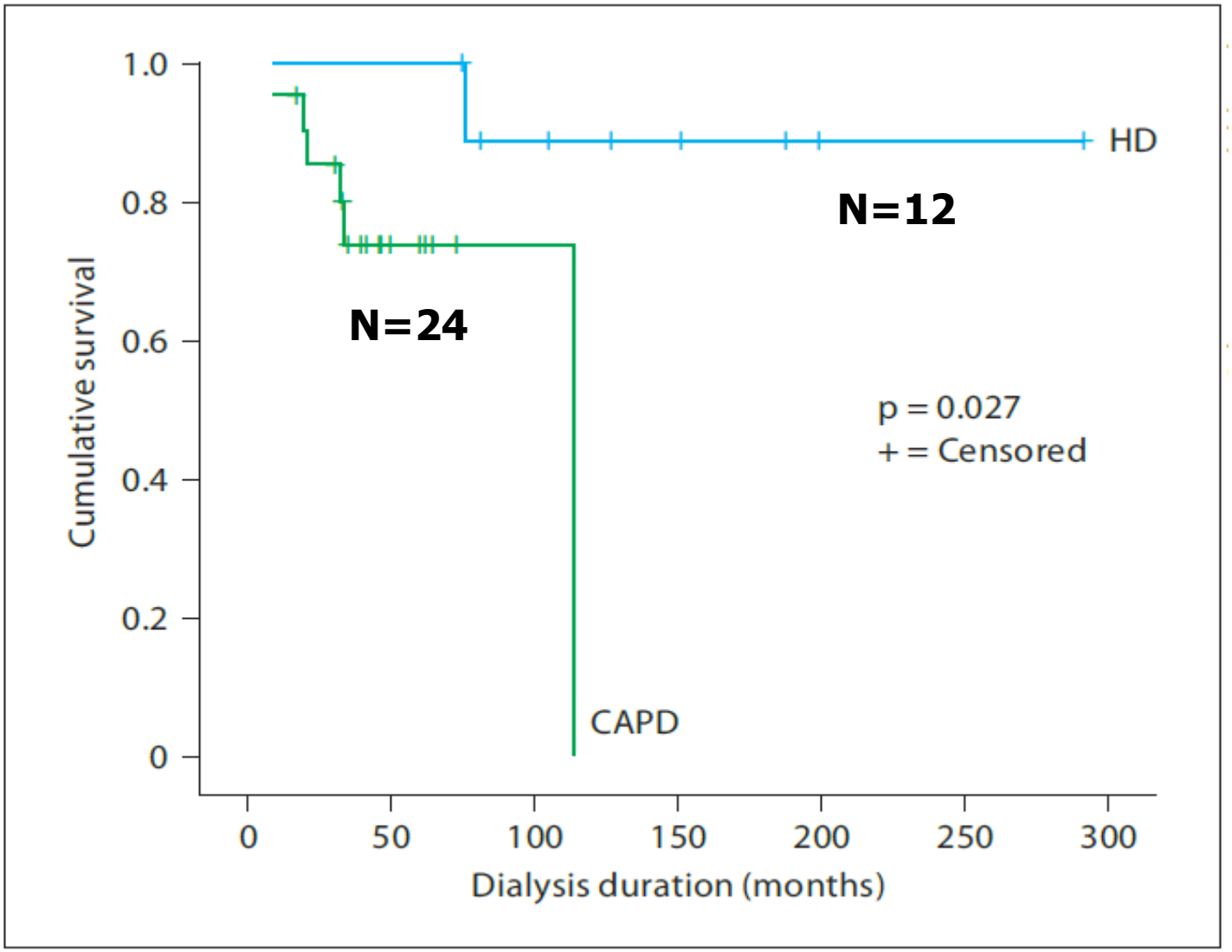


Fig. 1. Kaplan-Meier survival curve of SLE PD and HD patients.

Kidney Blood Press Res 2009;32:451–456

Table 4. Comparison of lupus activity before the end of the observation period

	CAPD group	HD group	p value
C3, mg/dl	87.30 ± 20.24	76.64 ± 20.31	0.18
C4, mg/dl	23.97 ± 9.97	18.94 ± 5.70	0.128
CRP, mg/l	37.1 ± 41.4	6.7 ± 9.5	0.037
Anti-dsDNA, U/ml	155.33 ± 374.82	48.67 ± 55.75	0.34

Table 5. Causes of death

	PD (n = 22)		HD (n = 14)	
	count	%	count	%
AMI	1	4.5	0	0
IE	1	4.5	0	0
Mycotic aneurysm	0	0	1	7.1
PD peritonitis	2	9.1	0	0
Pulmonary edema	1	4.5	0	0
Sepsis	2	9.1	0	0

Kidney Blood Press Res 2009;32:451–456

Peritoneal Dialysis and Hemodialysis in Systemic Lupus Erythematosus Patients: Comparison of Clinical Outcomes

Table 1. Comparison of baseline demographic data between CAPD group and HD group before dialysis

		CAPD group	HD group	p value
Patients, n		24	12	
Age, years		37.59 ± 10.19	48.71 ± 9.54	0.002
Duration of dialysis, months		43.17 ± 68.64	142.08 ± 24.07	0.001
Duration between diagnosis of SLE to the start of dialysis, months		87.36 ± 69.35	121.33 ± 60.67	0.874
Follow-up duration, months	Median	37.00	126.83	
	IQR	27.88 – 60.46	79.88 – 190.67	
Patients on immunosuppressive drugs at the initiation of dialysis, n (%)		17 (70.83)	10 (83.33)	>0.05
Albumin, g/dl		3.12 ± 0.90	3.85 ± 0.26	0.018
Total cholesterol, mg/dl		243.23 ± 58.27	177.00 ± 35.24	0.012
Triglyceride, mg/dl		239.73 ± 116.55	155.08 ± 73.54	0.053
Calcium, mg/dl		8.42 ± 1.34	10.25 ± 1.23	0.001
Phosphate		5.09 ± 2.28	4.98 ± 1.78	0.890
iPTH, pg/ml		369.65 ± 463.55	141.03 ± 87.55	0.136
Ferritin		338.90 ± 240.32	400.39 ± 315.61	0.620
Hb, g/dl		8.10 ± 2.51	10.01 ± 1.20	0.03
WBC/μl		6,345.45 ± 2,845.47	5,253.85 ± 1,387.21	0.265
PLT, 1,000/μl		178.25 ± 75.81	175.40 ± 78.55	0.932
C3, mg/dl		59.09 ± 28.77	74.3 ± 29.33	0.174
C4, mg/dl		20.50 ± 9.46	17.28 ± 6.61	0.295
Anti-dsDNA, U/ml		140.36 ± 368.19	353.18 ± 573.24	0.300

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Kidney Blood Press Res 2009;32:451–456

Influence of predialysis comorbidity and damage accrual on mortality in lupus patients treated with peritoneal dialysis

C-C Liang et al

Lupus (2010) 19, 1210–1218

Improved C3, nr SLEDAI score after PD

Table 1 Clinical characteristics of study patients ($n = 38$)

Characteristics	*Value*
Age at PD entry, years	32.2 ± 10.4
Gender	
Female	33 (86.8)
Male	5 (13.2)
Renal survival, months	78.6 ± 64.3
Duration of PD, months	39.7 ± 22.4
Renal pathology ($n = 14$)	
Class I/II/III/V	4 (28.5)
Class IV	8 (57.1)
Class VI	2 (14.4)
Number of patients on immunosuppressive drugs	
Predialysis[a]	33 (86.8)
Dialysis[b]	22 (57.9)
GFR, ml/min[c]	5.81 ± 4.60
PET[d]	
Kt/V	2.12 ± 0.37
D/P Cr	0.64 ± 0.12
NUF, ml	391.62 ± 187.09

Table 2 Comparisons of laboratory data and disease activity before and during peritoneal dialysis

Variable	*Predialysis*[a]	*Dialysis*[b]	p-*value*
Hemoglobin, g/dl	8.00 ± 2.03	8.94 ± 1.62	0.02
White blood cell count, /μl	6552 ± 2362	7546 ± 2305	NS
Platelet count, 1000/μl	170.22 ± 67.64	242.47 ± 85.12	<0.001
Creatinine, mg/dl	9.06 ± 4.21	11.63 ± 3.21	<0.01
Albumin, g/dl	3.12 ± 0.85	3.44 ± 0.60	0.04
Fasting glucose, mg/dl	100.74 ± 37.91	97.31 ± 21.64	NS
Corrected calcium, mg/dl	8.76 ± 1.03	9.46 ± 0.85	<0.01
Phosphate, mg/dl	5.78 ± 2.26	5.41 ± 1.25	NS
Cholesterol, mg/dl	229.25 ± 57.63	202.17 ± 50.82	NS
Triglyceride, mg/dl	206.34 ± 136.96	227.50 ± 164.14	NS
C3, mg/dl	67.06 ± 23.44	84.75 ± 28.32	<0.01
C4, mg/dl	20.35 ± 7.83	22.98 ± 10.54	NS
Dosage of prednisolone, mg/day	13.42 ± 10.01	5.01 ± 5.17	<0.001
Non-renal SLEDAI score	4.00 ± 3.08	2.13 ± 2.09	<0.001

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			1.62 0.02
			2305 NS
			85.12 <0.001
			3.21 <0.01
			0.60 0.04
			21.64 NS
			0.85 <0.01
			1.25 NS
			50.82 NS
			164.14 NS
C3, mg/dl	67.06 ± 23.44	84.75 ± 28.32	<0.01
C4, mg/dl	20.35 ± 7.83	22.98 ± 10.54	NS
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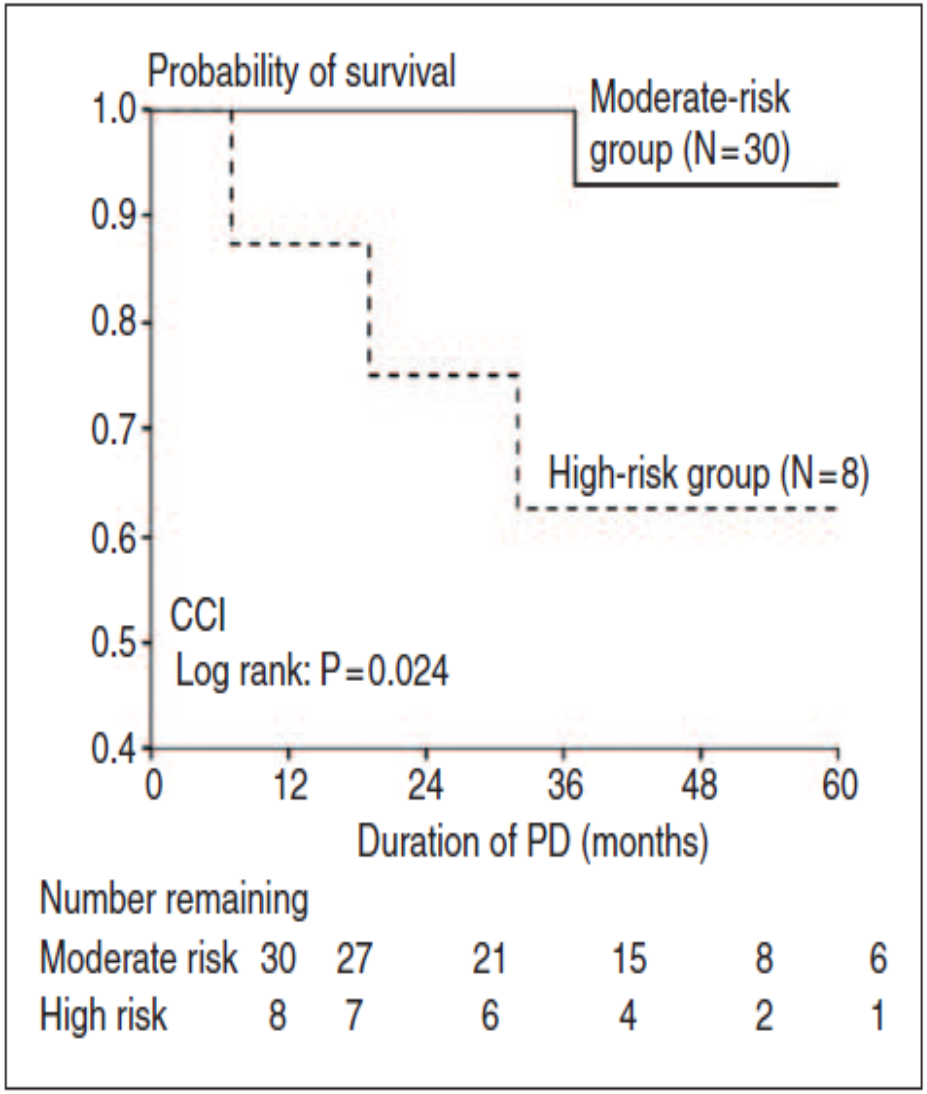
Higher SLE Activity Imposes High-Risk for mortalitv

Table 4 Univariate analysis for determinants of risk factors associated with mortality in lupus patients treated with chronic peritoneal dialysis

Variable	*RR*	*95% CI*	p-*value*
Age at PD entry, years	1.03	0.95–1.11	0.515
Female sex	0.41	0.04–3.72	0.507
GFR, ml/min	1.12	0.97–1.30	0.118
Dosage of prednisolone, mg/day	0.99	0.92–1.07	0.816
Serum albumin level, mg/dl	0.91	0.34–2.47	0.855
Serum creatinine level, mg/dl	0.65	0.45–0.92	0.014
Non-renal SLEDAI score, per point	1.10	0.88–1.36	0.413
Kt/V, per unit	0.30	0.03–3.48	0.338
Date at PD entry			
1997–2008 ($n=31$)	1.00	–	–
1990–1996 ($n=7$)	10.25	1.86–56.42	0.007
PSTR			
L/LA (N=23)	1.00	–	–
H/HA (N=15)	1.43	–0.32–6.47	0.643
nrSDI score			
Score 3 ($n=17$)	1.00	–	–
Score 4–6 ($n=17$)	1.37	0.12–15.18	0.800
Score >6 ($n=4$)	2.16	0.13–35.01	0.587
Khan Index			
Low-risk group ($n=31$)	1.00	–	–
Moderate-risk group ($n=7$)	3.04	0.43–21.72	0.267
Davies Index			
Low-risk group ($n=27$)	1.00	–	–
Moderate-risk group ($n=11$)	4.80	0.49–46.30	0.175



Liang CC et al, Lupus (2010) 19, 1210–1218

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Serum albumin l			
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Score 3 (n = 17)	**1.00**	**-**	**-**
Score 4-6 (n = 17)	**1.37**	**0.12-15.18**	**0.800**
Score >6(n = 4)	**2.16**	**0.13-35.01**	**0.587**
Khan Index			
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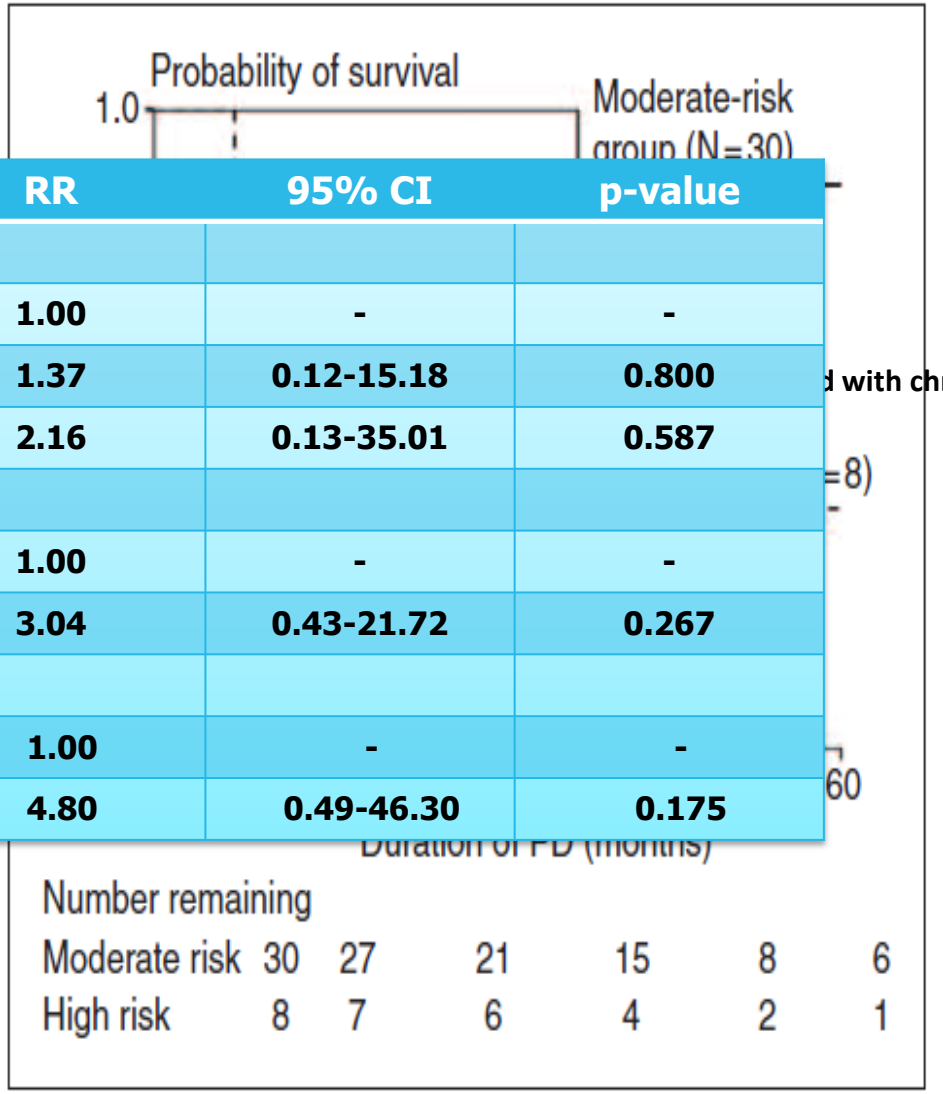

Liang CC et al, Lupus (2010) 19, 1210–1218

Outcome of Lupus Nephritis After Entering Into End-Stage Renal Disease and Comparison Between Different Treatment Modalities: A Nationwide Population-Based Cohort Study in Taiwan

M.-J. Wu, Y.-C. Lo, J.-L. Lan, T.-M. Yu, K.-H. Shu, D.-Y. Chen, H.-C. Ho, C.-H. Lin, and S.-N. Chang

- 1998-2009, n=1998 SLE patients with ESRD
- Hemodialysis, 82.1%, peritoneal dialysis, 9.8%, and KT 8.1%
- The 1-year, 5-year, 10-year patient survival rates were best for those who underwent KT (100%, 98.1%, and 94.4%, respectively), followed by peritoneal dialysis (88.3%, 79.1%,and 76%, respectively), and hemodialysis (53.6%, 46.0%, and 41.6%, respectively).
- Conclusion. KT provides a better survival benefit for SLE patients with ESRD than hemodialysis and peritoneal dialysis.

Table 1. Patient Characteristics in All 1998 Lupus Patient With End-Stage Renal Failure

	KT n = 161	Peritoneal Dialysis n = 196	Hemodialysis n = 1641
	n (%)	n (%)	n (%)
Gender			
Women	125 (77.6)	174 (88.8)	1385 (84.4)
Men	36 (22.4)	22 (11.2)	256 (15.6)
Age, y			
<20	18 (11.2)	18 (9.2)	150 (9.1)
20–29	65 (40.4)	60 (30.6)	403 (24.6)
30–39	45 (28.0)	44 (22.5)	395 (24.1)
40–49	24 (14.9)	45 (23.0)	301 (18.3)
50–59	9 (5.6)	13 (6.6)	175 (10.7)
≧60	0 (0.0)	16 (8.2)	217 (13.2)
Mean ± SD	30.9 ± 10.7	36.2 ± 14.1	39.3 ± 16.4
Comorbidities			
Hepatitis B	1 (0.6)	3 (1.5)	23 (1.4)
Hepatitis C	0 (0.0)	3 (1.5)	29 (1.8)
Chronic liver disease	12 (7.5)	17 (8.7)	218 (13.3)
Diabetes mellitus	7 (4.4)	16 (8.2)	178 (10.9)
Hypertension	123 (76.4)	150 (76.5)	1036 (63.1)
Hyperlipidemia	32 (19.9)	45 (23.0)	337 (20.5)
Malignancy	0 (0.0)	5 (2.6)	45 (2.7)
Coronary artery disease	23 (14.3)	19 (9.7)	218 (13.3)
Follow-up time, y	10.1 ± 3.34	4.34 ± 3.05	3.31 ± 3.87

Transplantation Proceedings, 46, 339e341 (2014) 339

Survival analysis in systemic lupus erythematosus patients on maintenance dialysis

One of the largest and most recent retrospective studies collected data from 1073 SLE ESRD patients in Taiwan who started maintenance dialysis between March 1997 and December 2006. While men had poorer outcomes on HD than on PD, outcomes in women did not differ based on dialysis mortality.

Rheumatology key messages

- Older age and a higher daily steroid dose predict mortality in Taiwanese SLE ESRD patients.
- Different dialysis modalities exerted no effect on the survival of female SLE ESRD patients in Taiwan.
- Taiwanese male SLE ESRD patients on HD had a poorer adjusted survival than those on PD.

Chang YS, et al. Rheumatology. 2013; 52:166–172

To Choose PD or HD ?

- In the absence of large RCTs demonstrating a clear benefit of a dialysis modality, the decision to choose a dialysis modality should be personalized for each patient - Observation for SLE activity is cirtical.

- PD may be preferable in patients with a history of antiphospholipid antibodies syndrome (APLS) because of the possibility of access failure with HD.

Antiphospholipid antibodies and thrombosis in ESRD – Vascular access failure

- Retrospective study compared rates of vascular access thrombosis in 36 SLE patients and 36 non-SLE controls, matched for age, sex, race and vascular access and found a 66.6% rate in SLE compared with 38.9% in non-SLE patients (OR 3.1,95%CI 1.2–8.2).

Hydroxychloroquine – prevent thrombosis

- Is associated with the lower rates of SLE flares, may be beneficial in decreasing thrombosis risk in anti-phospholipid positive patients.

Antonio Inda-Filhoa*Semin Dial*. 2013 ; 26(5): 590–596

Immunosuppressive Treatments To Reduce Corticosteroid Use and Treat Extra-renal Manifestations of SLE in ESRD

- **Hydroxychloroquine** may improve outcomes in lupus patients with ESRD by decreasing risk of flares and thrombotic complications – *retinal toxicity*
- **Rituximab** can be used in HD patients with no dosage adjustment - *not eliminated by HD*.
- **Cyclosporine** and low-dose **azathioprine** may be used to manage extra-renal manifestations - *hematologic and liver toxicity*.
- **Cyclophosphamide** is used to treat life-threatening severe manifestations of SLE, including neuropsychiatric lupus - *prolonged half-life.*
- **MMF** metabolism is impaired in dialysis patients - poor gastrointestinal tolerance.

Antonio Inda-Filho *Semin Dial*. 2013 ; 26(5): 590–596

Immunosuppressives Use in ESRD SLE Patients: Clearance of Azathioprine and Cyclophosphamide by HD

TABLE 1. Clearance of immunosuppressive agents with high-permeability hemodialysis (HD) and peritoneal dialysis (PD)

Immunosuppressive agent	Molecular weight (dalton)	Clearance with high-permeability HD	Clearance with PD
Azathioprine	277.26	Likely	No data
Basilixumab	144,000.0	No data	No data
Cyclophosphamide	279.1	Likely	No data
Cyclosporine	1202.61	Unlikely	No
Mycophenolate mofetil	433.50	Unlikely	No
Prednisone	358.43	No data	No
Rituximab	145,000.0	Unlikely	Unlikely
Sirolimus	914.2	Unlikely	Unlikely
Tacrolimus	804.02	Unlikely	Unlikely
Thymoglobulin	669,000.0	Unlikely	No data

Timing of Transplantation

- **Rapid Progression to ESRD- Wait 3-6 moth of dialysis**
- It has been recommended that all patients with ESRD due to lupus nephritis be dialyzed for at least three to six months and be on less than 10 mg of prednisone per day before renal transplantation is performed, particularly among those with relatively rapid progression to ESRD.

- **Slow progression to ERSD- pre-emptive living transplantation**

Better Survival by Renal Transplantation

Allograft survival — similar to other diseases

- Most studies found that overall 5- and 10-year graft survival rates are similar among patients with lupus, compared with those in patients with other diseases.
- The 1-, 5-, and 10-year death-censored graft survival was similar between groups (88, 81, and 71 percent in lupus patients and 91, 83 and 74 percent in control patients, respectively).

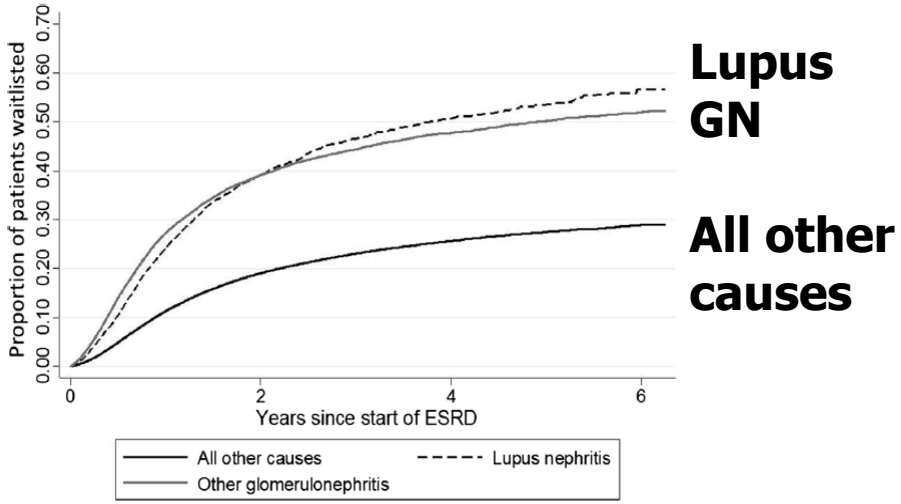

Figure 2 Cumulative incidence of placement on the deceased donor kidney transplant waitlist among U.S. ESRD patients initiating treatment 7/05–9/11, by attributed cause of ESRD. $P < 0.001$ by log-rank.

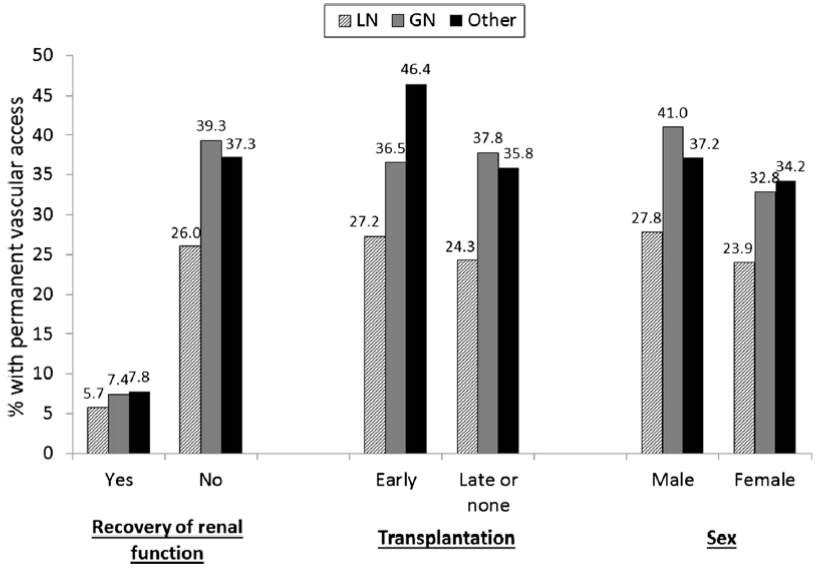

Figure 3 Permanent vascular access placement by patient characteristics, among U.S. ESRD patients initiating treatment 7/05–9/11, by attributed cause of ESRD. Recovery of renal function is defined as recovery occurring at any time during treatment, regardless of whether patient returned to dialysis; early transplant is defined as a transplant within 1 year of ESRD start.

US ESRD due to Lupus (n = 6,594) vs. other causes (n = 617,758)

Patients with Lupus Nephritis-ESRD are

1. more likely to receive pre-ESRD care
2. have better access to transplant than patients with ESRD due to other causes,
3. are far less likely to have a permanent vascular access in place for dialysis.

Plantinga et al. BMC Nephrology (2015) 16:39

Evaluation and Treatment for Transplantation

- **Evaluation for antiphospholipid antibodies prior to transplantation —**
  - Should be screened for the presence of **antiphospholipid antibodies** for increased risk for thrombotic events.
- **Immunosuppressive therapy for antirejection —**
  - Induction and maintenance immunosuppressive regimens to prevent rejection are the same among patients with ESRD from lupus nephritis as among patients with other forms of renal disease.
  - The use of **steroid-free regimens** among patients with ESRD due to lupus nephritis is not standard practice.

Recurrent Lupus Nephritis

- 2-11 %
- **Clinical presentation**
  - An increased serum creatinine, new-onset proteinuria of a variable degree, and new-onset hematuria on routine screening.
- **Serologic testing** — not helpful for diagnosis
  - Serologic tests including complement levels and titers of anti-double-stranded DNA antibodies are not helpful in establishing the diagnosis.
- **Biopsy findings**
  - The histologic lesion may be different and is often less severe from that observed in the native kidney.

Treatment for Recurrent Lupus Nephritis

- **Non-immunosuppressive treatment of recurrent nephritis**
  - renin-angiotensin system blockade (RAS).
- **Immunosuppressive treatment of recurrent nephritis**
  - Treatment options include mycophenolate mofetil and cyclophosphamide.

SUMMARY AND RECOMMENDATIONS

- 10至30%左右增生性狼瘡性腎炎會進展到終末期腎病。總體預後近幾十年來有所改善，可能是由於使用免疫抑制劑。
- 狼瘡性腎炎血液透析或腹膜透析患者的存活是相似的。
- 狼瘡患者應進行篩檢是否有抗磷脂抗體的存在以評估血栓的風險。
- 透析後應該觀察狼瘡腎外全身性症狀表現，並會影響存活。

SUMMARY AND RECOMMENDATIONS

- 狼瘡腎衰竭患者腎移植是一個最佳治療的選擇。與其他疾病相比，5年和10年的移植存活率相似。
- 狼瘡性腎炎在腎移植後2％至11％患者會復發。
- 新出現蛋白尿，血尿，或血清肌酐增加之患者應懷疑復發性狼瘡性腎炎。
- 狼瘡腎炎治療亟需進行廣泛性新階段之實證醫學和個體化醫療研究以提升精確治療效果。