

Management of Lupus nephritis

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MD, DM (Pediatric Nephrology, AIIMS)

Childhood SLE

Onset < 16 years: **20%**

Onset < 10 years: **3-5%**

F:M (prepubertal) **2:1**

F:M (adolescence) **4.5:1**

More severe disease

4 criteria
(1 clinical and 1 immunological)

OR

Biopsy proven lupus nephritis with
ANA or anti-dsDNA antibodies

SLICC (Systemic Lupus Erythematosus Collaborating Clinics) criteria-2012

Clinical criteria	Immunological criteria
Acute cutaneous lupus	ANA
Chronic cutaneous lupus	Anti dsDNA
Oral or nasal ulcers	Anti Sm
Non-scarring alopecia	Antiphospholipid antibody
Synovitis	Low complement
Serositis	Direct coomb's test
Renal involvement	
Neurological involvement	
Hemolytic anemia	
Leucopenia	
Thrombocytopenia	

2019 European League Against Rheumatism/American College of Rheumatology

Entry criteria + score of 10 or more

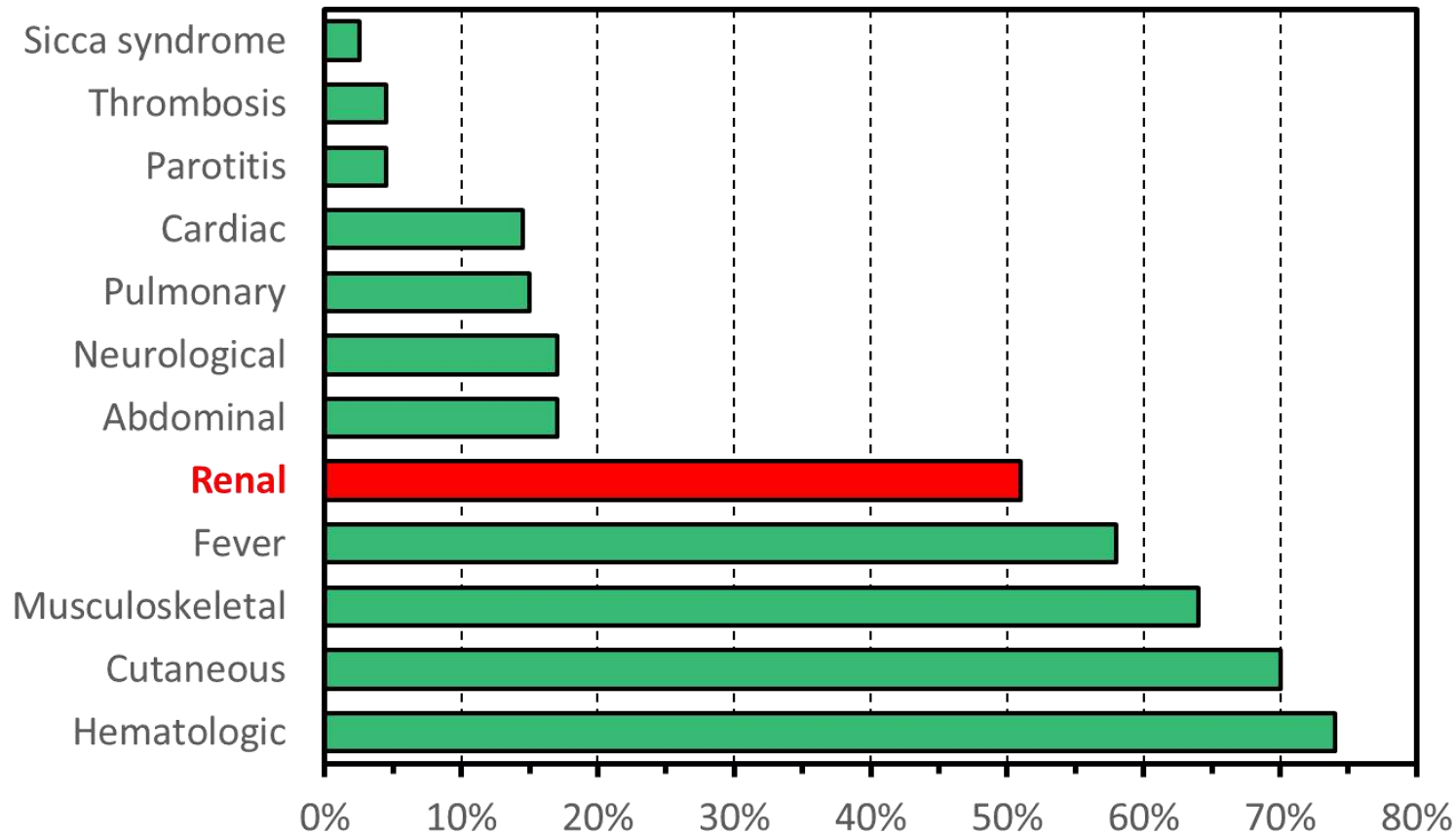
<i>EULAR/</i>	Sensitivity	98.2 %
<i>ACR Criteria</i>	Specificity	93.2 %
<i>SLICC criteria</i>	Sensitivity	94.6 %
	Specificity	98.6 %

Earlier recognition of patients with single or major organ involvement

Cheng 2022

Entry criterion			
Antinuclear antibodies (ANA) at a titer of $\geq 1:80$ on HEp-2 cells or an equivalent positive test (ever)			
↓			
If absent, do not classify as SLE If present, apply additive criteria			
↓			
Additive criteria			
Do not count a criterion if there is a more likely explanation than SLE.			
Occurrence of a criterion on at least one occasion is sufficient.			
SLE classification requires at least one clinical criterion and ≥ 10 points.			
Criteria need not occur simultaneously.			
Within each domain, only the highest weighted criterion is counted toward the total score.			
Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
<i>Constitutional</i>		<i>Antiphospholipid antibodies</i>	
Fever	2	Anti-cardiolipin antibodies OR	
<i>Hematologic</i>		Anti- $\beta 2$ GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	<i>Complement proteins</i>	
Autoimmune hemolysis	4	Low C3 OR low C4	3
<i>Neuropsychiatric</i>		Low C3 AND low C4	4
Delirium	2	<i>SLE-specific antibodies</i>	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
<i>Mucocutaneous</i>			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
<i>Serosal</i>			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
<i>Musculoskeletal</i>			
Joint involvement	6		
<i>Renal</i>			
Proteinuria $>0.5\text{g}/24\text{h}$	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Lupus nephritis is observed in 40-80% of children with SLE



High prevalence in Asian children

East and South-East Asian 34-86%

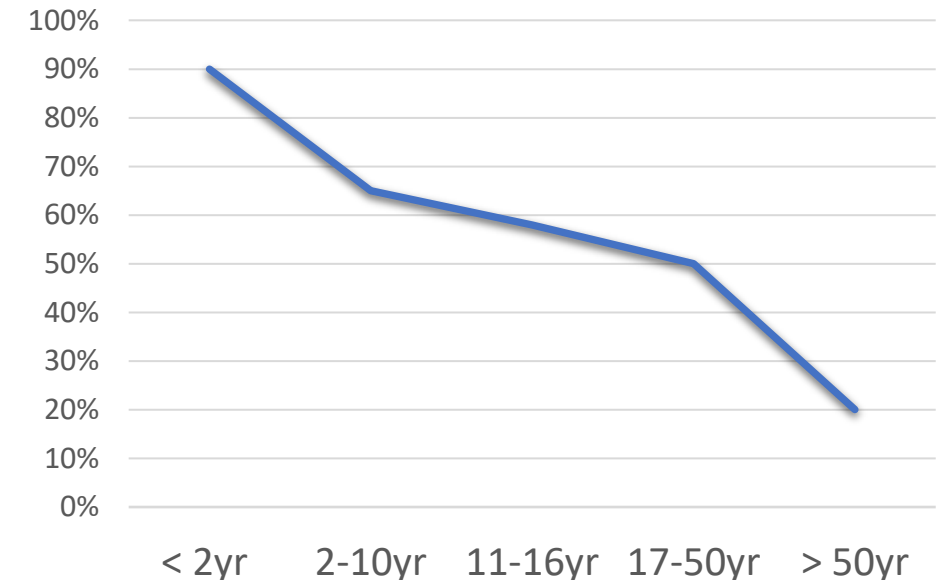
Indian 61%

Egyptian 83%

Renal involvement more common in childhood

Metanalysis of 16 studies

OR 1.62 (1.2-2.2)



Bader-Meunier et al, J Pediatr 2005

Pluchinotta et al, Lupus 2007

Livingston et al, Lupus 2011

Abbreviated ISN/RPS classification of Lupus Nephritis

Class	Description
Class I	Minimal mesangial lupus nephritis
Class II	Mesangial proliferative lupus nephritis
Class III	Focal lupus nephritis ^{a,b}
Class IV	Diffuse lupus nephritis ^{a,b}
Class IV-S	Diffuse segmental proliferative lupus nephritis
Class IV-G	Diffuse global proliferative lupus nephritis
Class V	Membranous lupus nephritis
Class VI	Advanced sclerosing lupus nephritis

65%



Class I



Class II



Class III/IV



Class V

a. Indicate the proportion of glomeruli with active and with sclerotic lesions.

b. Indicate the proportion of glomeruli with fibrinoid necrosis and/or cellular crescents.

(A): Active lesions - (A/C): Active and chronic lesions - (C): Chronic inactive lesions.

Revised ISN/RPS classification: 2018

Minimal mesangial lupus nephritis

Mesangial proliferative lupus nephritis: hypercellularity ≥ 4 cells in mesangial area

Class III and IV: **elimination of S/G and A/C**

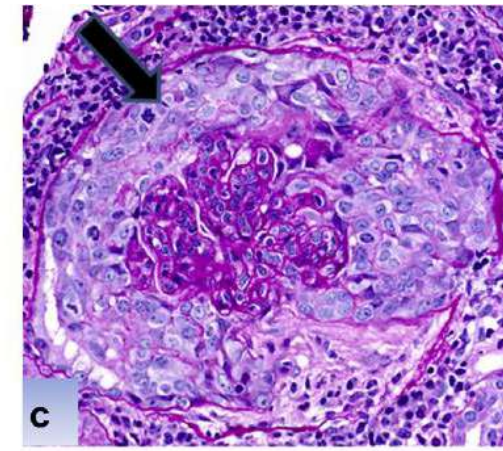
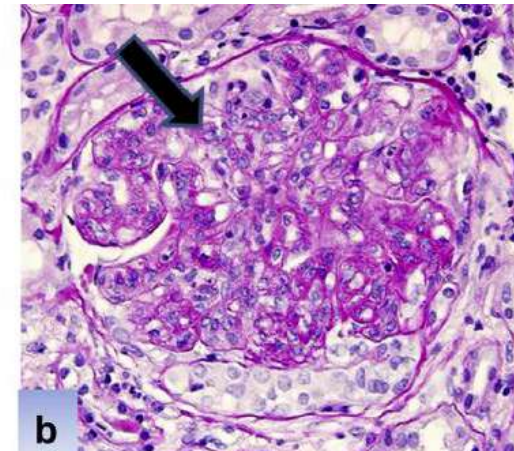
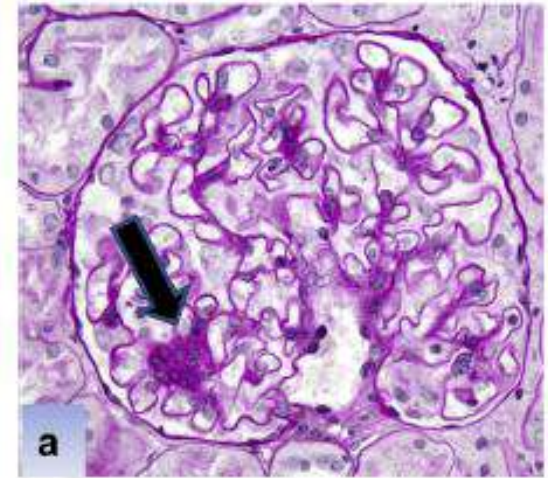
- **Crescents:** 10% of glomerular capsular circumference
- **Fibrinoid necrosis**
- **Adhesions**

Modified NIH activity index

Endocapillary hypercellularity
Neutrophils/karyorrhexis
Fibrinoid necrosis
Hyaline deposits
Cellular/fibrocellular crescents
Interstitial Inflammation

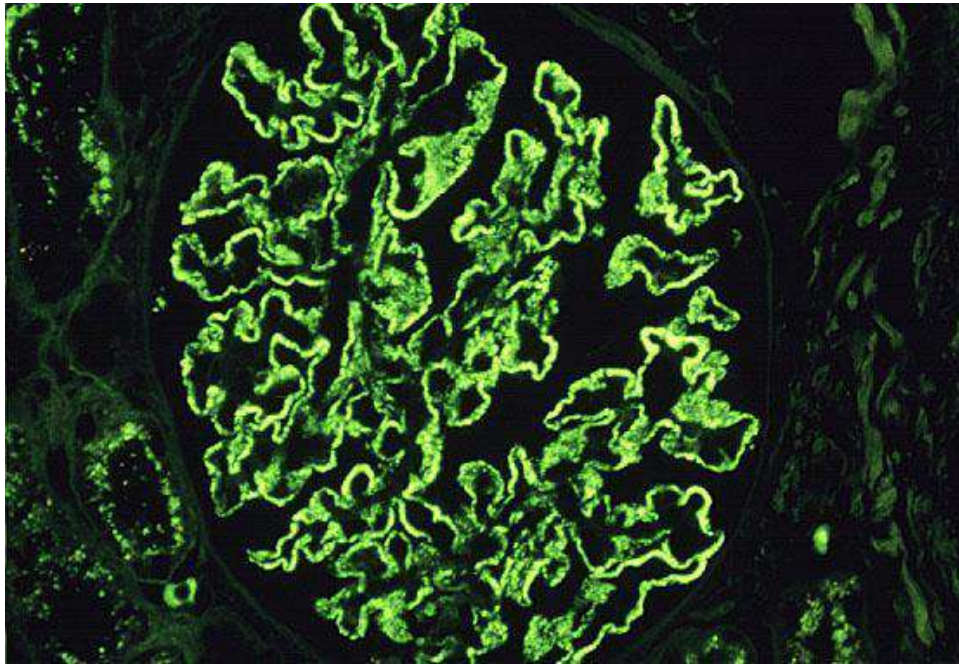
Modified NIH chronicity index

Total glomerulosclerosis score
Fibrous crescents
Tubular atrophy
Interstitial fibrosis

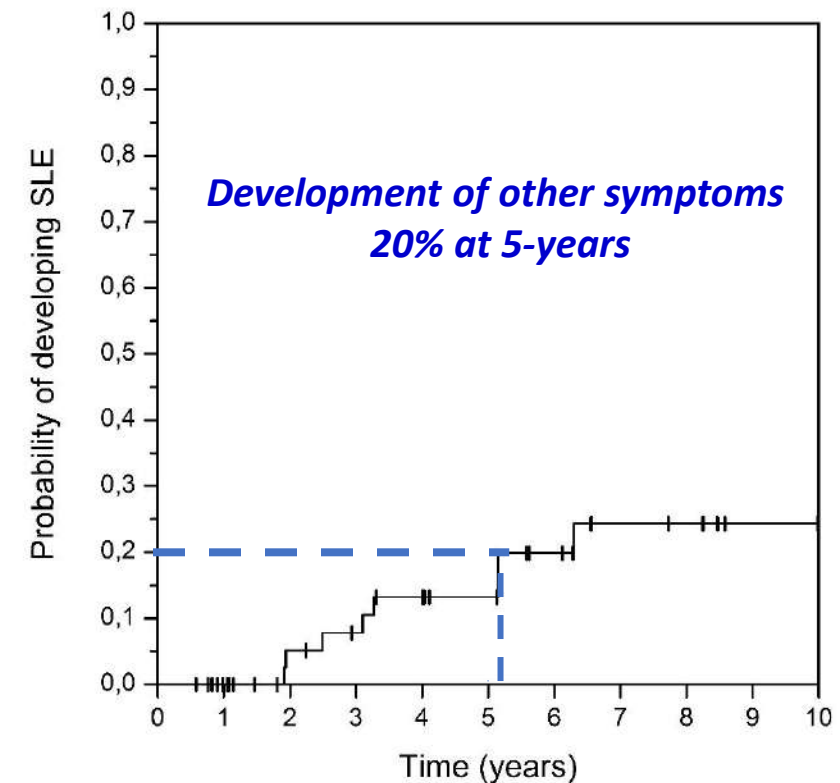


Immunofluorescence: “Full house” staining (C3, C1q, IgA, IgM, IgG)

Approximately 40% of children present with a “lupus-like nephritis”
but lack other diagnostic criteria for the diagnosis of SLE



Development of SLE in patients with FHN



Can clinical features predict extent of renal involvement?

N=244	Class II	Class III	Class IV	Class V
Hypertension	43%	47%	78%	56%
Microscopic hematuria	57%	63%	74%	33%
Nephrotic range proteinuria	-	37%	38%	59%
Acute Renal failure	2%	13%	37%	16%

N=22	Class II	Class III	Class IV	Class V
Isolated hematuria	56%	18%	18%	5%
Isolated pyuria	50%	33%	17%	0%

Rahman Lupus 2001

EULAR/EDTA recommendation 2012:

Any sign of renal involvement should be an indication for renal biopsy.

Renal biopsy is indispensable since in most cases, clinical, serological or laboratory, tests cannot accurately predict renal biopsy findings

Indication of renal biopsy

Suspected lupus AND

Proteinuria 1+ or more or up/uc $\geq 0.2\text{mg/mg}$

OR

microscopic hematuria (confirmed on 2 occasions, one week apart)

OR

deranged renal function tests

Low threshold for biopsy

What is remission?

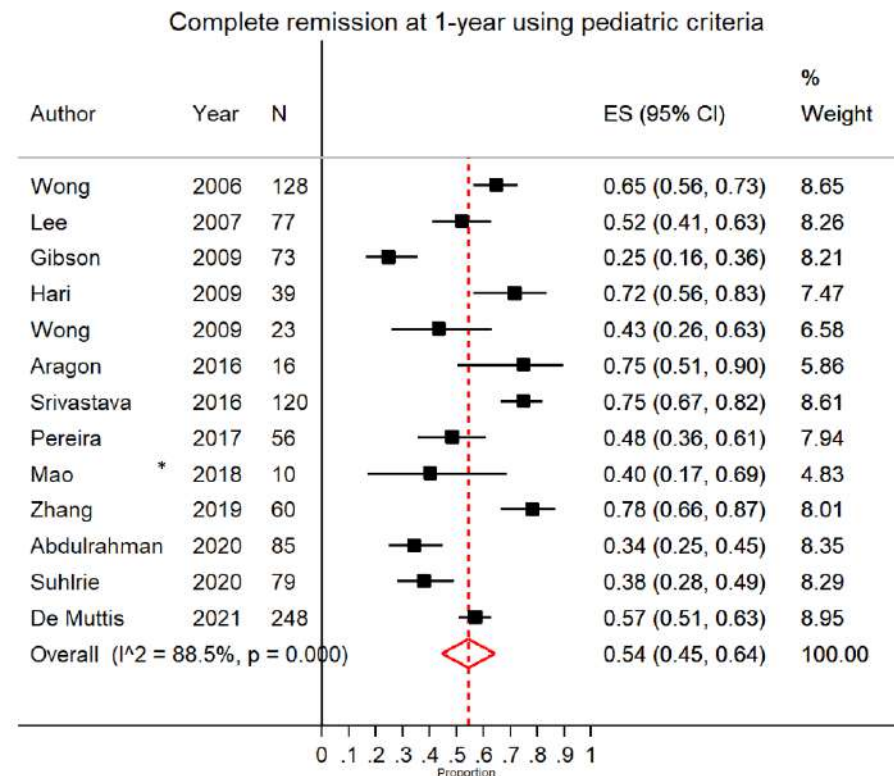
Criteria	Definition
Complete response*	<ul style="list-style-type: none">• Reduction in proteinuria <0.5 g/g (50 mg/mmol) measured as the PCR from a 24-h urine collection• Stabilization or improvement in kidney function ($\pm 10\%$–15% of baseline)• Within 6–12 mo of starting therapy, but could take more than 12 mo
Partial response	<ul style="list-style-type: none">• Reduction in proteinuria by at least 50% and to <3 g/g (300 mg/mmol) measured as the PCR from a 24-h urine collection• Stabilization or improvement in kidney function ($\pm 10\%$–15% of baseline)• Within 6–12 mo of starting therapy

CARRA guidelines, KDIGO 2021

- **Normal renal function**
- **Proteinuria (up/uc <0.2) or 24-hour urine protein <500 mg/1.73 m²/day or <300 mg/m²/day**
- **Inactive urinary sediment <5 RBC/WBC & no casts**

Remission in pediatric LN

	Low- or middle-income countries		High income countries		Overall	
	Patients; studies (N)	Pooled proportion (95% CI)	Patients; studies (N)	Pooled proportion (95% CI)	Patients; studies (N)	Pooled proportion (95% CI)
CR at last follow-up ^a	2108; 31	58% (49-66%) ^d	1330; 29	56% (42-69%)	3686; 61 ^c	57% (49-64%)
PR at last follow-up ^a	1398; 16	19% (11-28%) ^d	833; 19	26% (18-35%)	2479; 36 ^c	22% (16-28%)
Flare (renal or non-renal) ^b	1053; 20	27% (20-35%)	745; 18	35% (27-44%)	1798; 38	31% (25-37%)



Why is it important to achieve complete remission?

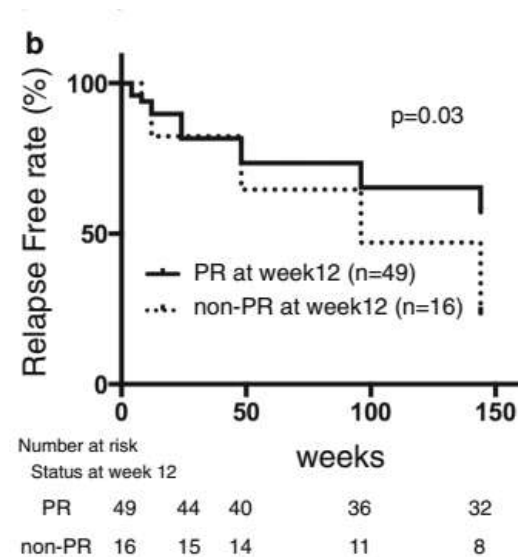
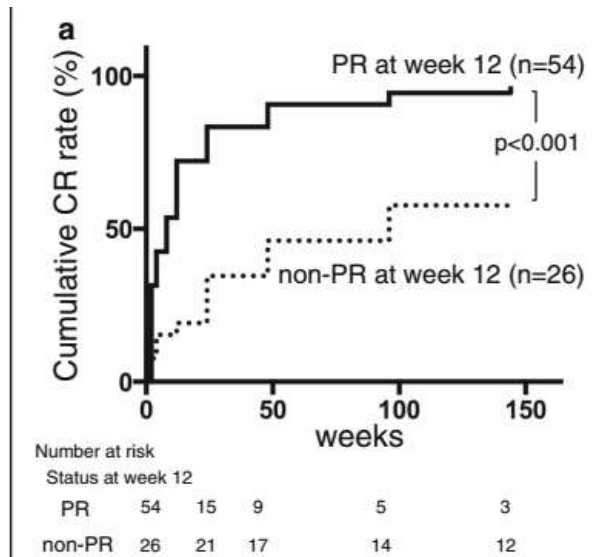
Patients with CR or PR

- **Better renal survival**
- **Better overall survival**
- **Better relapse free survival**

Risk of flare

5.5 times more likely with partial remission

44% with partial remission versus 5% with complete remission

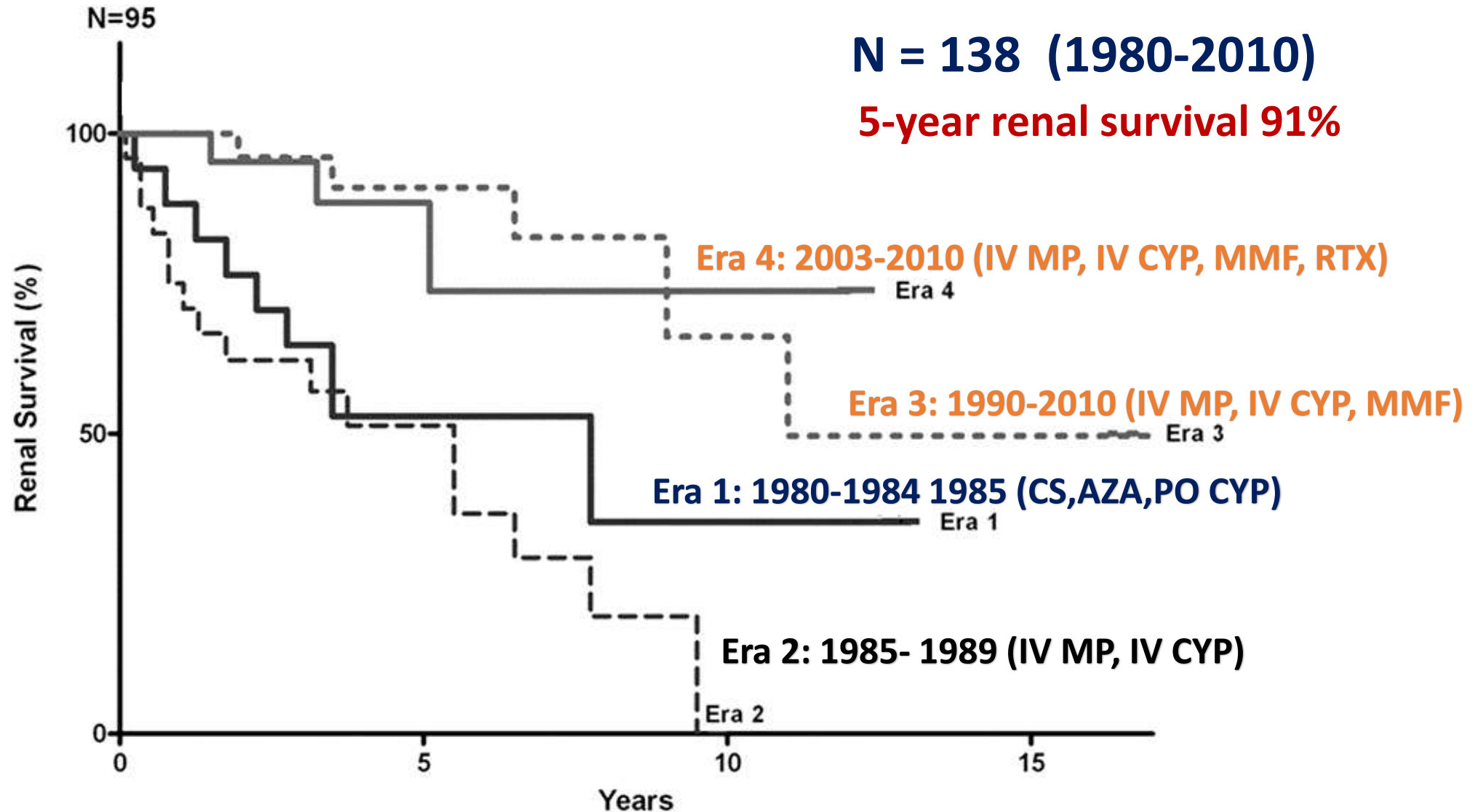


No partial remission at 3-months

3 times less likely for CR at 6 months

2 times more likely to relapse

Three decades of therapy of Pediatric lupus nephritis



Management: class II LN

Low quality evidence
Immunosuppression if significant proteinuria

EULAR/ERA-EDTA	ACR	KDIGO	GEAS	DWP	CARRA
Proteinuria >1 g/24 h despite RAAS inhibition, especially in the presence of glomerular haematuria; oral glucocorticoids (0.25-0.5 mg/kg/d) alone or in combination with AZA (1-2 mg/kg/d)	No immunosuppressive treatment (C)	Proteinuria (low level): treat as dictated by extrarenal manifestations Proteinuria (NS): corticosteroids + another agent (practice point)	Significant proteinuria (>1-2 g/24 h despite renal protective treatment) and/or deteriorated renal function that is not attributable to functional factors; steroids up to 0.5 mg/kg/d, possibly plus AZA or MMF for 6-12 months (2D)	Not provided	Not provided

Management: class II LN



Class II lupus nephritis with non-nephrotic proteinuria

Up/Ucr ratio 0.2 to 0.5 mg/g

No steroids unless indicated for extrarenal manifestations

Class II lupus nephritis with nephrotic range proteinuria

Up/Ucr ratio >0.5 mg/g

Oral prednisolone 1 mg/kg/day X 4-6 weeks

+

MMF (1200 mg/m²) OR AZA 1-2 mg/kg/day

Treatment of class III or IV LN

INDUCTION

3-6 months

IV Methylprednisolone 30 mg/kg (max 1g) x 3-6 days
Oral steroids @ 1 mg/kg/d (max 60 mg) X 4 weeks
Taper to ~7.5 to 10 mg/day by 6 months

Inj Cyclophosphamide
500 mg/m² q 4 weekly for 6 doses

MMF
600 mg/m² q BD for 6 months

Average time to CR/PR:
8 mo (95% CI 4-12)

Remission?

Oral steroids
(A/D once dose is <10 mg)

Refractory disease

Switch induction agents
Tacrolimus
OR **IV Rituximab**

MAINTENANCE

Duration?

MMF
800-1000 mg/m²/day
(preferred)

AZA
1.5 - 2.5mg/kg/d

NIH trials: Cytotoxic therapy improved renal survival

Monthly IV CYP (0.5g-1g/m²) x 6 + every 4 months for 2 years

	Austin et al NEJM 1986	Boumpas et al Lancet 1992	Illei et al Int Med 2001
Years of follow-up	10	5	10
Deaths	20%	N/A	18%
Herpes Zoster	25%	5%	28%
Other infections	10%	5%	33%
Avascular Bone necrosis	NA	28%	29%
Premature ovarian failure	45%	39%	56%

MMF for induction of class III, IV and V LN

Chan et al 2000	N=42	MMF 2 g/day vs. oral CYC (2.5 mg/kg) for 6 months	1 yr	CR: 81% (MMF) = 76% (CP) CP: Infections (33%), amenorrhoea (23%), hair loss (19%), death (10%) leucopenia (10%)
Chan et al 2005			5 yr	Similar rates of ESRD and relapse
Ginzler et al 2005	N=140	MMF 1-3g/day vs HD CP	6 mo	CR: MMF (22.5%) > CP (5.8 %) Treatment lower, less infections
Appel et al 2009 (ALMS)	N=370	MMF 2.6 g/d vs HD CP	6 mo	CR: 56% (MMF) = 53% (CP) MMF: <ul style="list-style-type: none"> ▪ Equal infection rate ▪ More GI side effects ▪ Frequent withdrawals due to AE ▪ Less frequent ovarian failure ▪ Less frequent alopecia ▪ Less frequent leukopenia

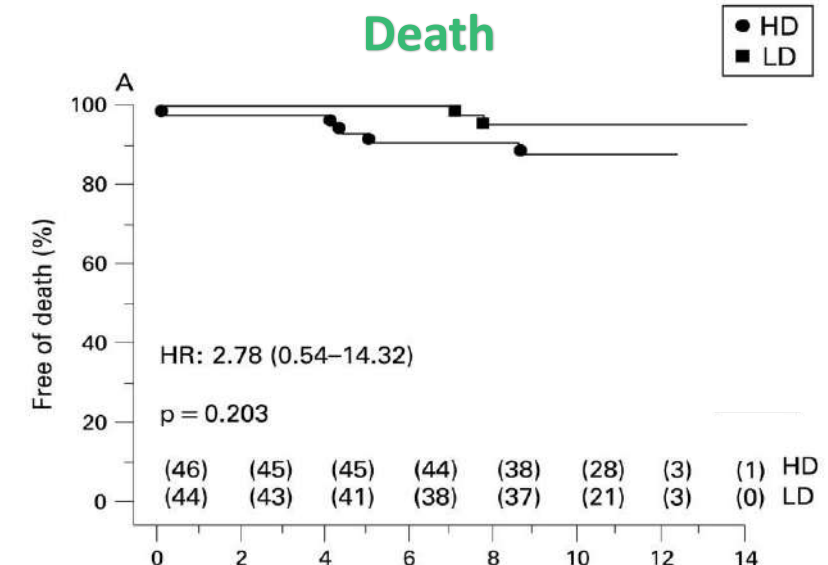
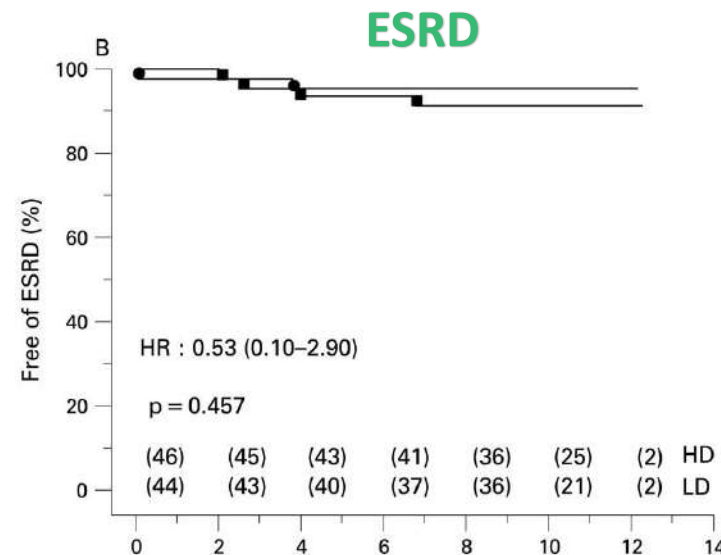
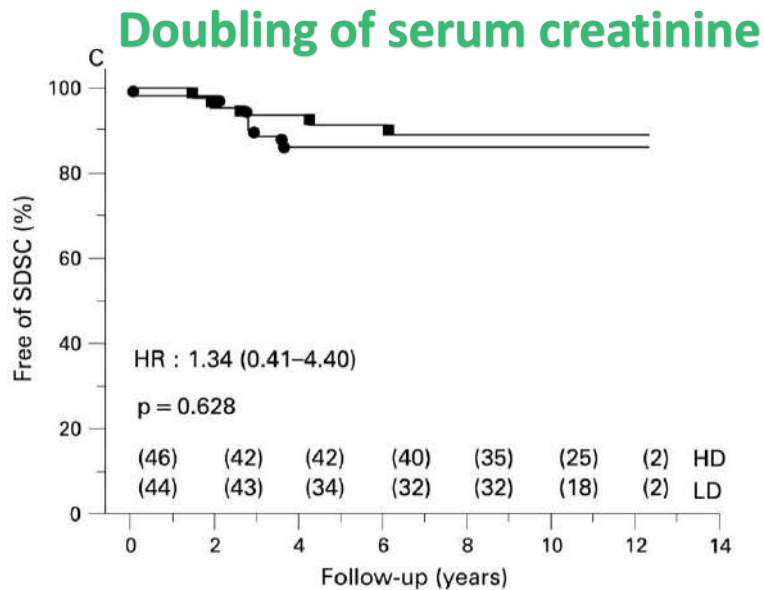
Euro-Lupus trial: non-inferiority of low dose IV CP at 10-years follow-up

	HD	LD
IV MP	3 x 750 mg	3 x 750 mg
IV CYP	(6+2) x 750 mg/m²	6 x 500 mg
Cumulative CYP dose	8.5 gr	3 gr
Complete remission	54%	71%
Severe infections *	22%	11%
Renal flares	29%	27%

The majority of patients:

- Less severe LN (↑creat: 22%; NS: 28%)
- Caucasians

Tailored to the severity of the disease



Effect of ethnicity or response criteria?

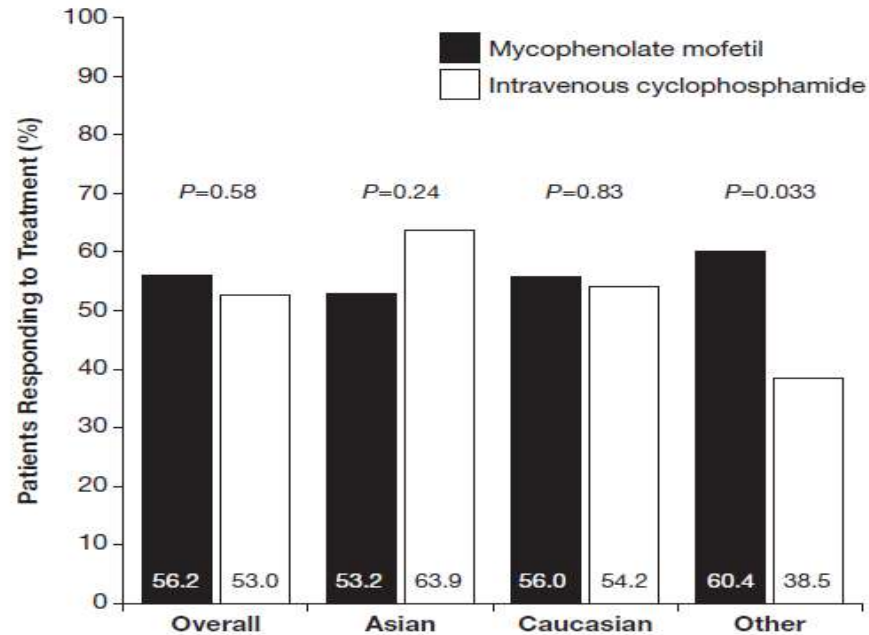


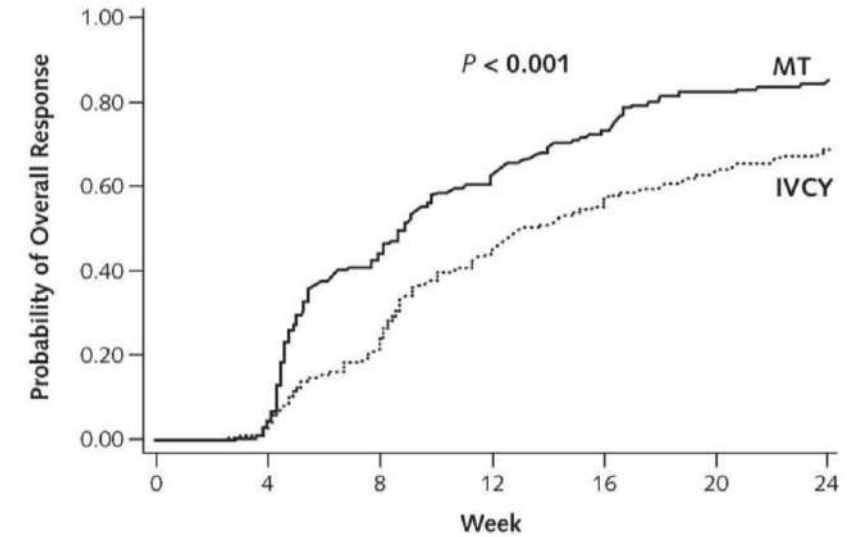
Table 3. Rates of complete response in the ELNT, ACCESS trial and ALMS, determined using the same response criteria

Treatment regimen	% with proteinuria >3 g/24 h at baseline ^a	Complete response rate (%) at 6 months ^b
ELNT, low dose (<i>n</i> = 36)	42	25
ELNT, high dose (<i>n</i> = 38)	45	24
ACCESS (<i>n</i> = 66)	52	23
ALMS, MMF (<i>n</i> = 169)	57	21
ALMS, CYC (<i>n</i> = 171)	60	22

ALMS trial

“Multitarget therapy” for induction treatment of LN

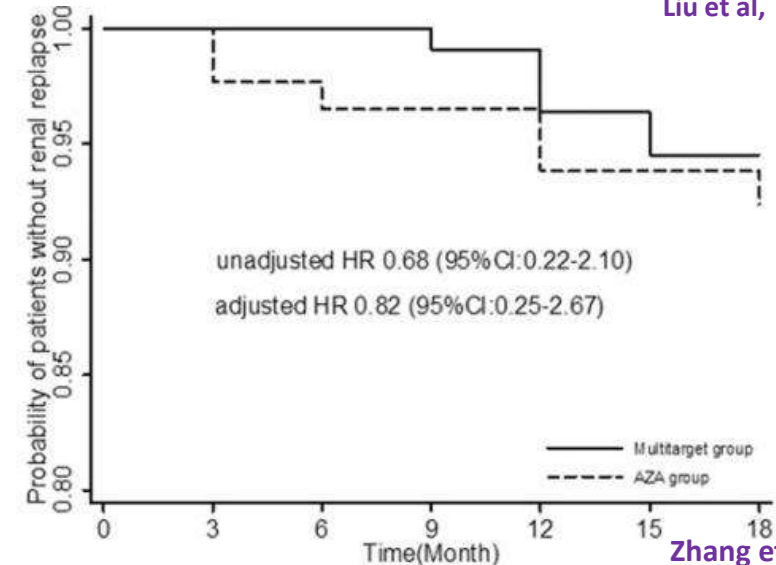
	Multitarget	Standard CYP
N	181	181
	Mt: 101	Mt: 64
Serum creat mg/dl	0.78	0.82
Proteinuria g/day	3.4	3.7
GFR $\geq 30, < 60$ ml/min	18%	19%
Class V	17%	20%
Treatment	3 x IV MP 500 mg PDN 0.6 mg/Kg/d TAC 4 mg/d, 3mg 6 mo, 2mg 1 yr MMF 1 g/d 750mg/d 6mo, 500 mg 1 yr	3 x IV MP 500 mg PDN 0.6 mg/Kg/d CYP 0.5-1 g/m²/m AZA 2mg/kg/d
Complete rem. at 6 m.	46%	26%
Median time to response	9 weeks	13 weeks
Renal relapse	5.5%	7.6%
Adverse events	50%	52%



Patients at risk, *n*

MT	181	175	98	67	45	29	20
IVCY	181	176	132	91	71	58	45

Liu et al, Ann Int Med 2015



Zhang et al, JASN 2017

Multitarget therapy may be better at inducing remission

Immunosuppressive treatment for proliferative lupus nephritis (Review)



Tunnicliffe DJ, Palmer SC, Henderson L, Masson P, Craig JC, Tong A, Singh-Grewal D, Flanc RS, Roberts MA, Webster AC, Strippoli GFM

Induction: 67 trials; N=4791

Complete remission

MMF + CNI 2.38 (95% CI 1.07 to 5.30) vs IVCP

MMF 1.17 (95% CI 0.97 to 1.42) vs IVCP

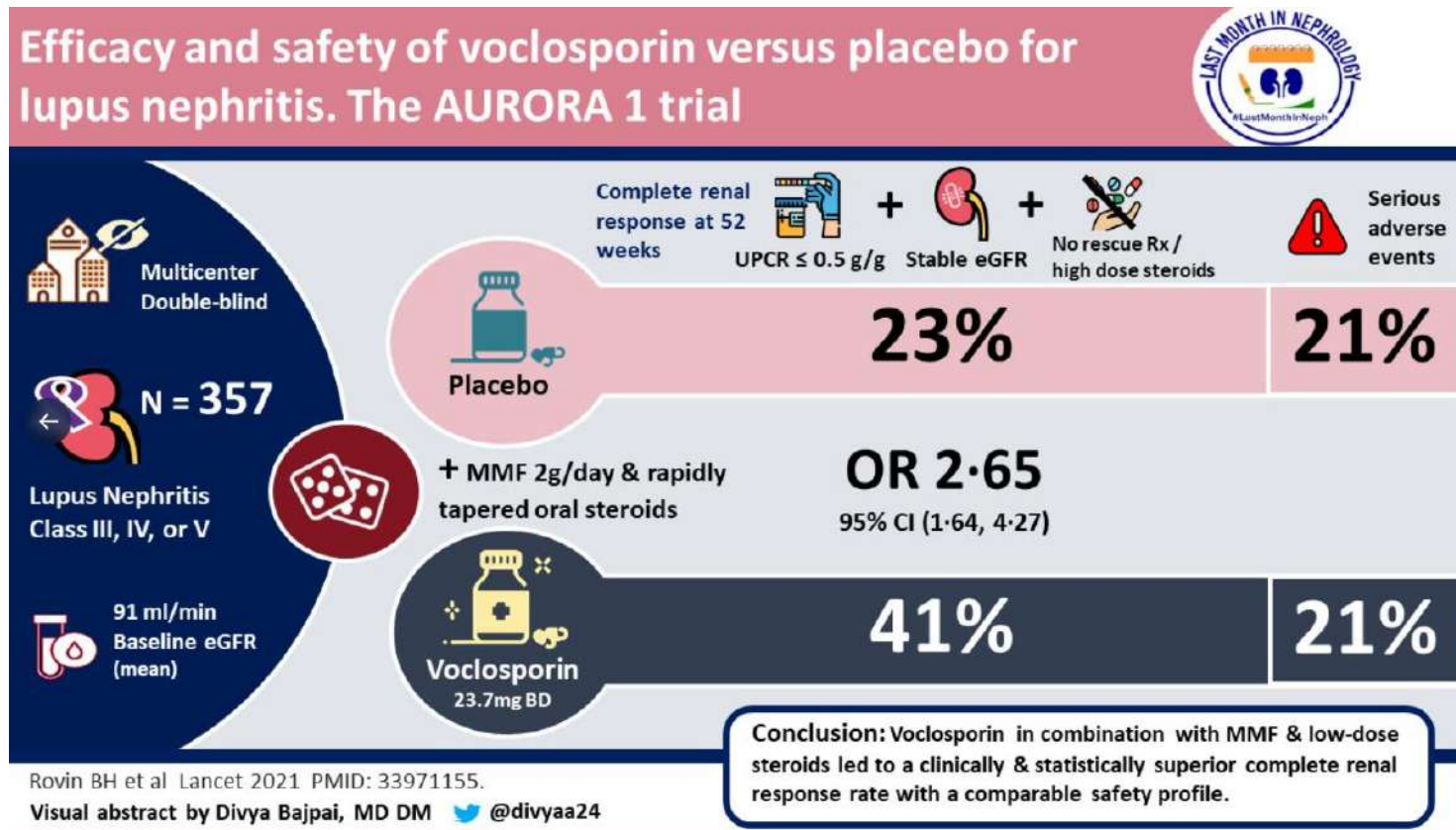
MMF less likely to cause **alopecia** (RR 0.29, 95% CI 0.19 to 0.46), **increase diarrhea** (RR 2.42, 95% CI 1.64 to 3.58)

Maintenance: 9 trials; N=767

MMF superior to AZA

Voclosporin: A new drug on the horizon

Aurinia Urinary Protein Reduction Active - Lupus With Voclosporin (AURA-LV): phase 2 RCT of 265 subjects



2 doses of IV MP (500 mg/dose) followed by 20–25 mg prednisone rapidly tapered to 2.5 mg/d by 16 weeks

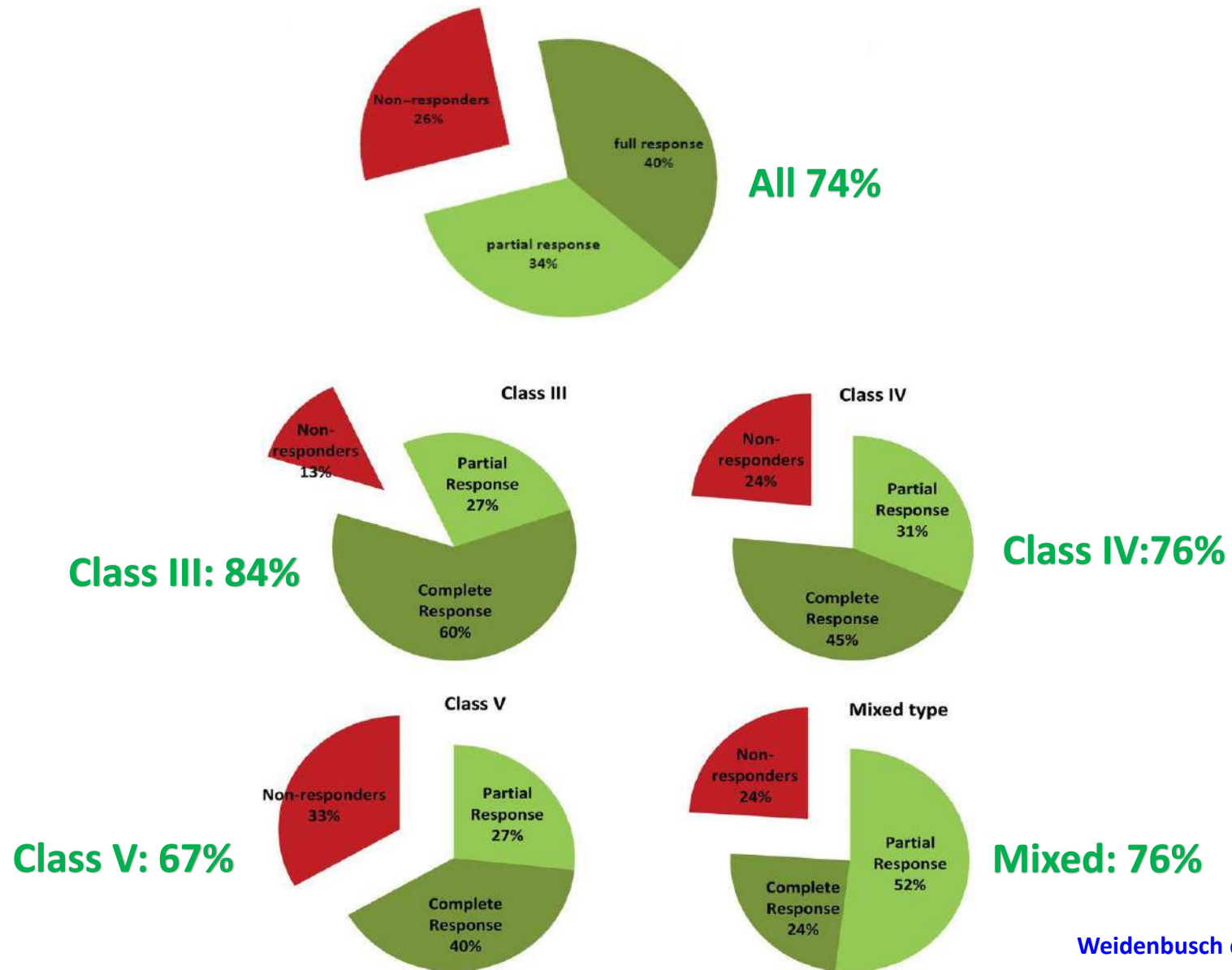
Pooled analysis

N=534

Renal response of 44% at 1 year vs. 23% in placebo

FDA approval in adults with LN II/IV/V with eGFR >45 ml/min/1.73m²

Rituximab beyond the LUNAR trial



Steroid minimization and withdrawal may hold promise

RITUXILUP protocol

IV MP (500 mg/1.73 m²)

RTX (1000 mg/1.73m²) at days 1 and 15

MMF (1200 mg/m²/day)

Steroids tapered rapidly

Median dose **0.3 at 3 months**, 0.10 at 6 months and **0 by 12 months**

N=50

At 12-months: 52% CR and 34% PR








No relapse

FU: 24 months

Belimumab: The BLISS-LN trial

Does addition of belimumab to standard therapy improve kidney outcomes in lupus nephritis?



Methods and Cohort		Intervention	Partial Renal response	Complete Renal Response
Multicentre, double-blind RCT, n=448 		Placebo 	 32%	 20%
Lupus Nephritis Class III to V	GFR >30 ml/min/1.73 m ²	versus	OR 1.6 95% CI 1.0 to 2.3 p = 0.03	OR 1.7 95% CI 1.1 to 2.7 p = 0.02
Mean age 33.4±10.6 yrs Females: 88%	50% Asian 30% White 14% Black	Belimumab 	 43%	 30%

Study duration = 104 weeks

Conclusions: In active lupus nephritis, more patients who received belimumab plus standard therapy had a primary efficacy renal response than those who received standard therapy alone

Reference: Furie R, Rovin BH *et al.* Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. *NEJM*, 2020
 VA by Swasti Chaturvedi @SwastiThinks

NOBILITY: Obinutuzumab (anti-CD20) Phase 2 Trial in LN



- Obi was added to standard therapy of MMF + steroids
- Steroids were tapered starting Day 16, reducing to 7.5 mg/d by Week 12
- Rescue with high-dose steroids was allowed
- Primary objective: evaluate the effect of Obi compared with PBO when added to MMF in patients with class III or IV LN as assessed by the proportion of patients who achieve CRR at week 52

	Obi + MMF N = 63	Placebo + MMF N = 62	Difference, % (80% CI)	P Value
CRR, n (%)	22 (34.9)	14 (22.6)	12.3 (2.1 to 22.6)	.1145
Overall response (CRR or PRR), n (%)	35 (55.6)	22 (35.5)	20.1 (8.9 to 31.3)	.0246
mCRR, n (%)	25 (39.7)	16 (25.8)	13.9 (3.2 to 24.5)	.0900

Furie R, et al. *Arthritis Rheumatol*. 2019;71(suppl 10): Abstract 939.

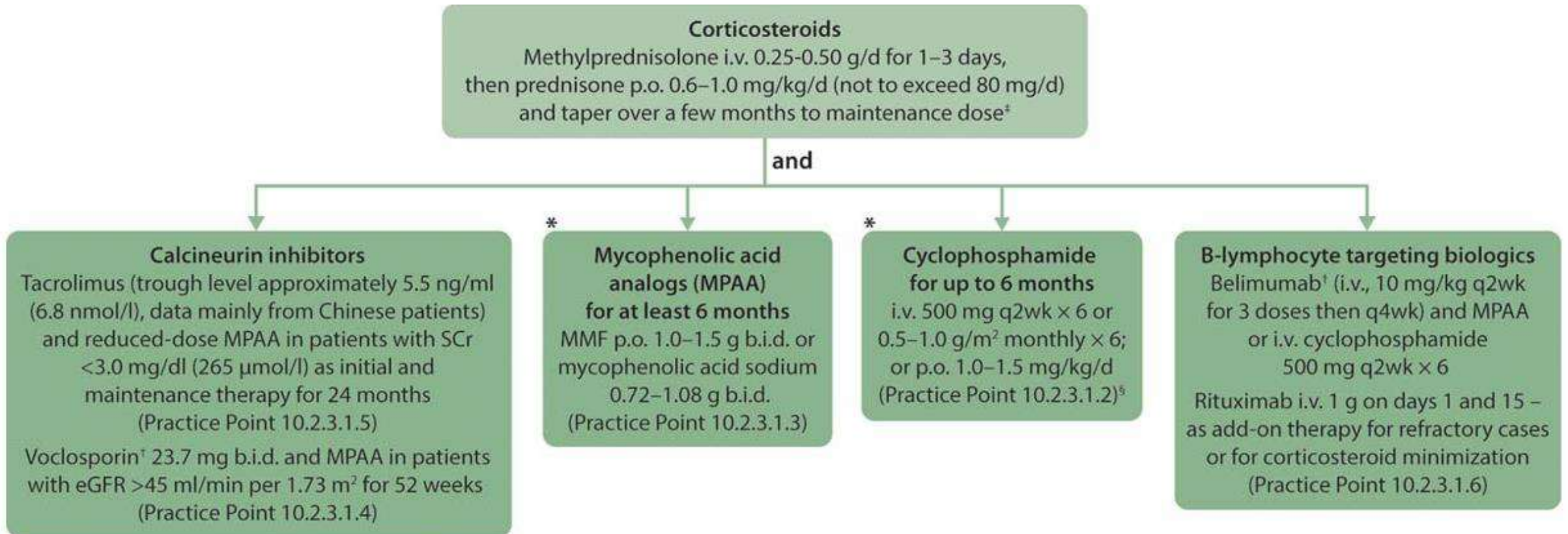
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An ongoing phase III study of Obinutuzumab (REGENCY trial)....

What is the BEST therapy?

- MMF is equivalent to low-dose cyclophosphamide for induction
- Issues of compliance
- GI intolerance with very high dose in children
- Lack of RCTs in children
- Lack of long-term data in severe disease
- TAC/voclosporin + MMF: probably better in controlling proteinuria
- Need more long-term data for CNI-based therapies
- Option of belimumab..

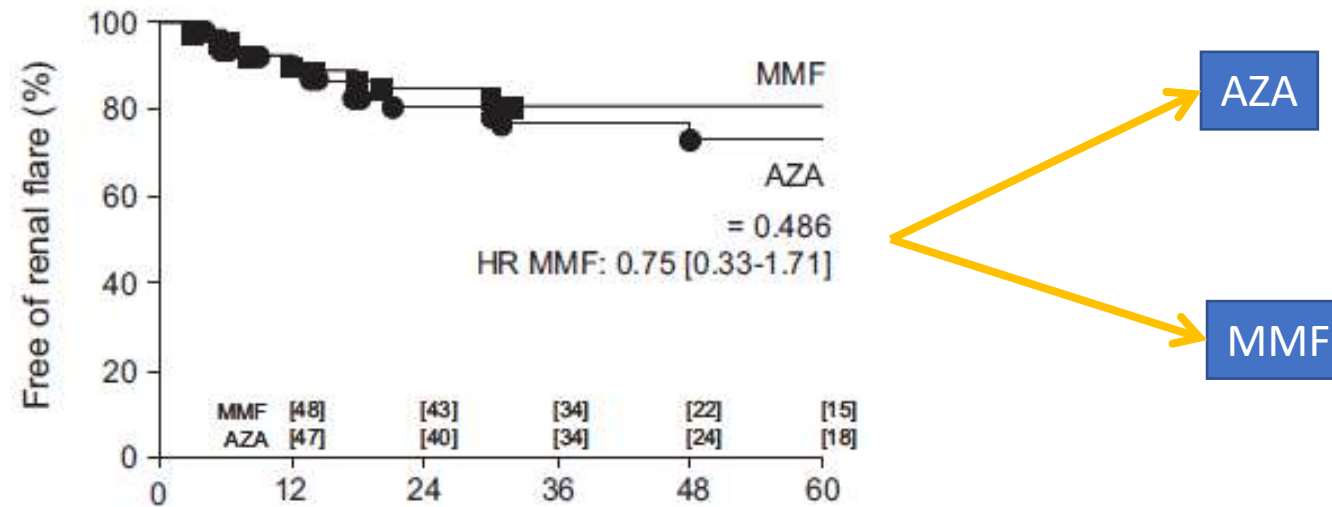
What is the BEST therapy?



Maintenance therapy

MAINTAIN

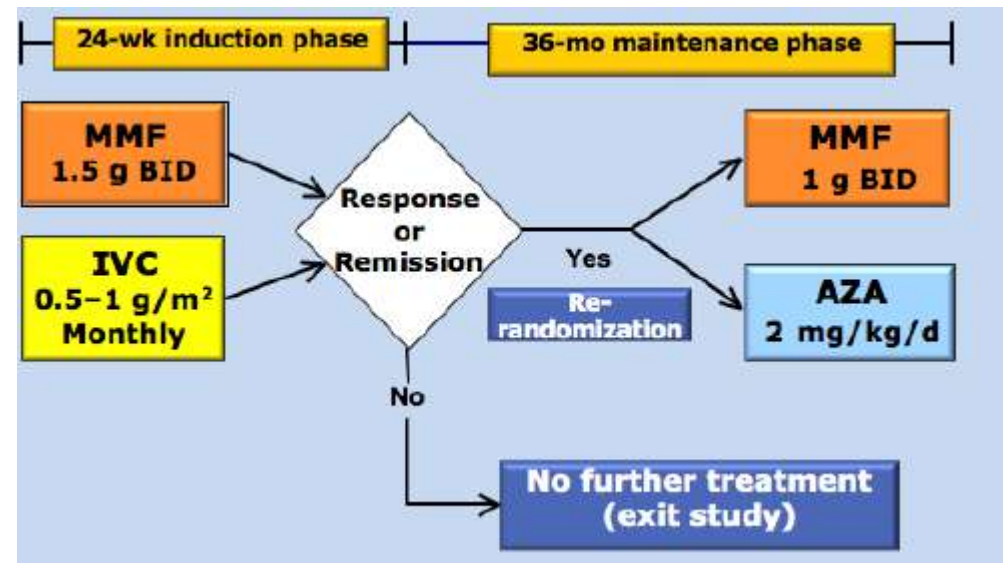
Primary end point
time to renal flare



MMF=AZA

ALMS

Primary end points
Death, ESRD, sustained doubling of
Creatinine, renal flare, rescue CS
Secondary end points
Time to event, CR, major extra renal flare
And adverse events



MMF>AZA

MMF superior to AZA regardless of induction treatment

Treatment for lupus nephritis: an overview of systematic reviews and meta-analyses

Six studies MMF vs AzA

MMF: lower relapse rate RR = 0.70, 95% CI 0.49-1.00

& leucopenia rate RR = 0.12, 95% CI 0.04-0.39

No differences in ESKD and mortality rate

Pure Membranous Lupus Nephritis

Membranous Lupus Nephritis: The Same, But Different

Frank Ward, MB, BCh, and Joanne M. Bargman, MD, FRCPC

AJKD, 2016

IV CP	40-70%	5 RCT, 3 observational
MMF	40-70%	5 RCT, 2 observational
CNI	40-83%	3 RCT, 3 observational

EULAR/ERA-EDTA	ACR	KDIGO
MMF 3 g/d (2B) High dose IVCP (2A) Cyclosporin (2A) Tacrolimus (3B) Rituximab (4C)	MMF 2-3 g/d (A)	MMF/CNI/IV CP/RTX (practise point) 40-60% response

Can we ever stop all therapy?

Table 1 Results of the studies in which the maintenance therapy of lupus was reduced or stopped

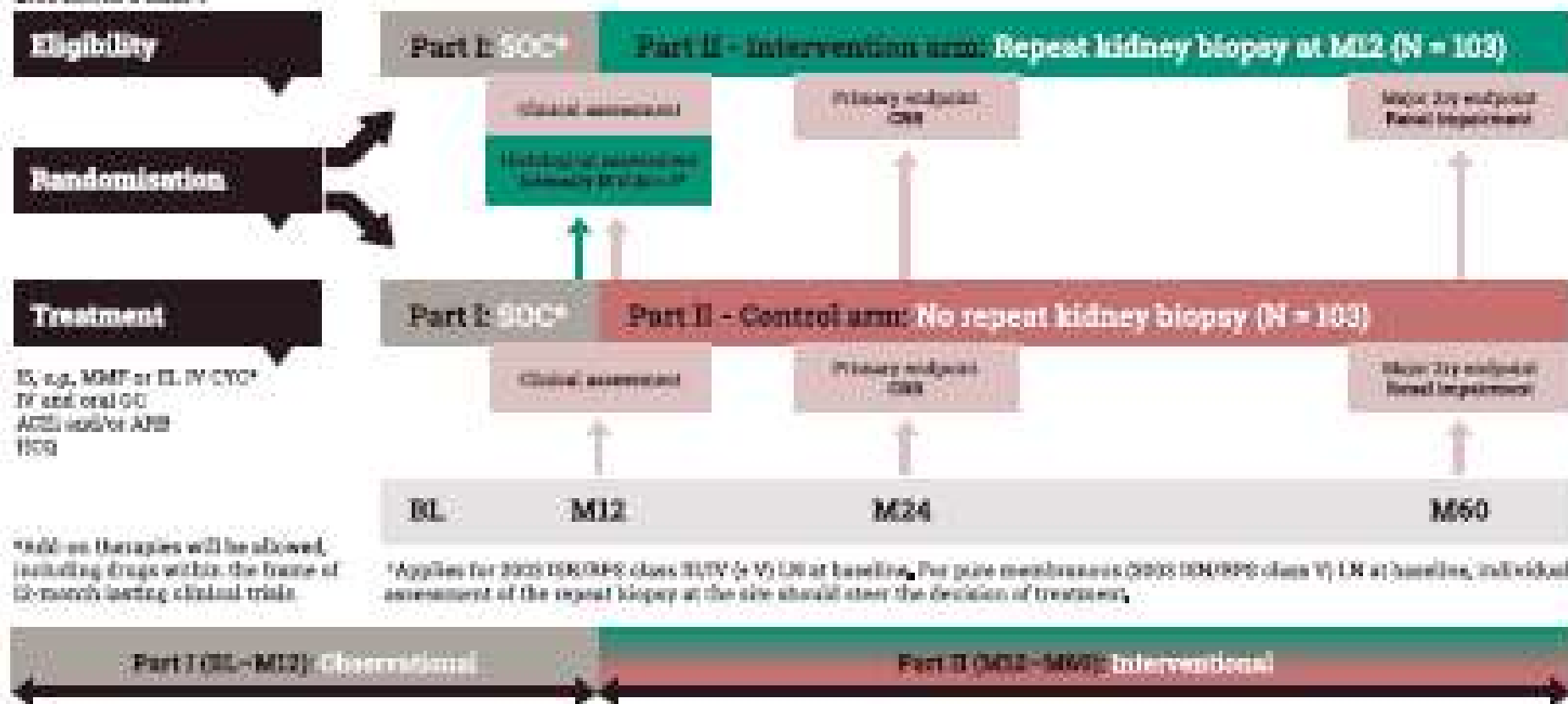
Authors [Refs.]	Induction therapy	Maintenance therapy	Patients	Follow-up months	Remission	Flares
Condon et al. [29]	RTX 1 g \times 2 MPP 1 g \times 2	MMF 2 g/day	50	40.7	90 %	Renal 22 % Extra renal 12 %
Roccatello et al. [30]	RTX 375 mg/m ² \times 6 MPP 15 mg/kg \times 3 iv Cy 750 mg \times 2 prednisone 50 mg/day	Prednisone 5 mg/day	8	36.2	100 %	Renal 12.5 % Extra renal 12.5 %
Pablos et al. [31]	Oral Cy 2–3 mg/kg/day for 35–45 months + prednisone 1 mg/kg/day	Prednisone 10 mg/day	11	49.5 \pm 20	100 %	Renal 36 %
Mosca et al. [32]	MPP 1 m ² g \times 3 iv Cy 750 mg/m ² \times 6–9	Prednisolone 4–8 mg/day	33	51	Remission 39 %, response 61 %	Renal 45 %

At least CR for 3 years
At least maintenance for 5 years

Re Bio Lup

Per-protocol repeat kidney biopsy in incident cases of lupus nephritis

2009 ISN/RPS class III/IV (A or A/C) & V
2009 ISN/RPS class V

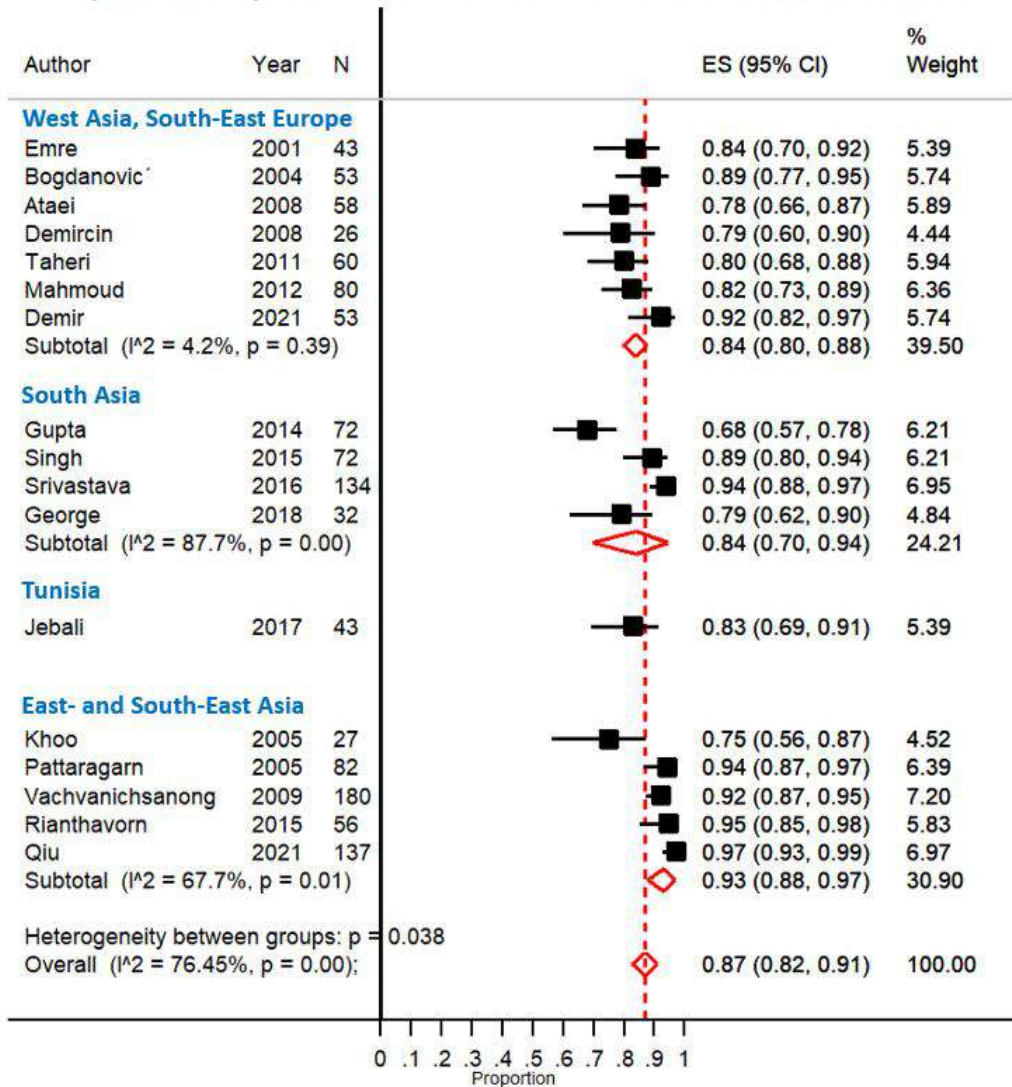


Abbreviations

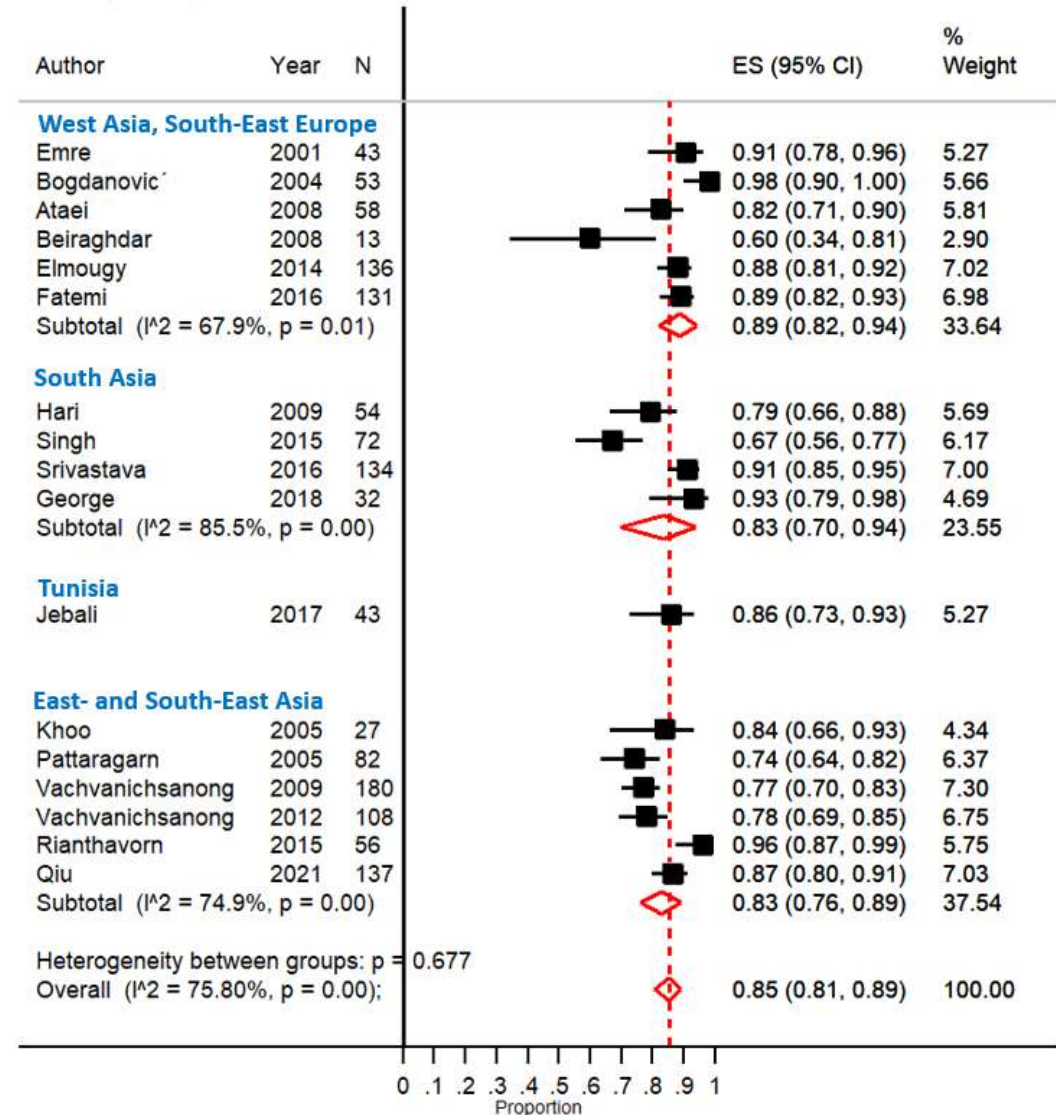
LN: lupus nephritis; ISN: International Society of Nephrology; RPS: Renal Pathology Society; MMF: methotrexate; IL-2: Interleukin-2; CYC: cyclophosphamide; GC: glucocorticoids; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; RAS: hydroxychloroquine; CRP: acute phase reactant; CRP: complete renal response; IS: immunosuppression; IV: intravenous; oral: oral; SOC: standard of care; BL: baseline; M: month.

Outcomes of pediatric LN

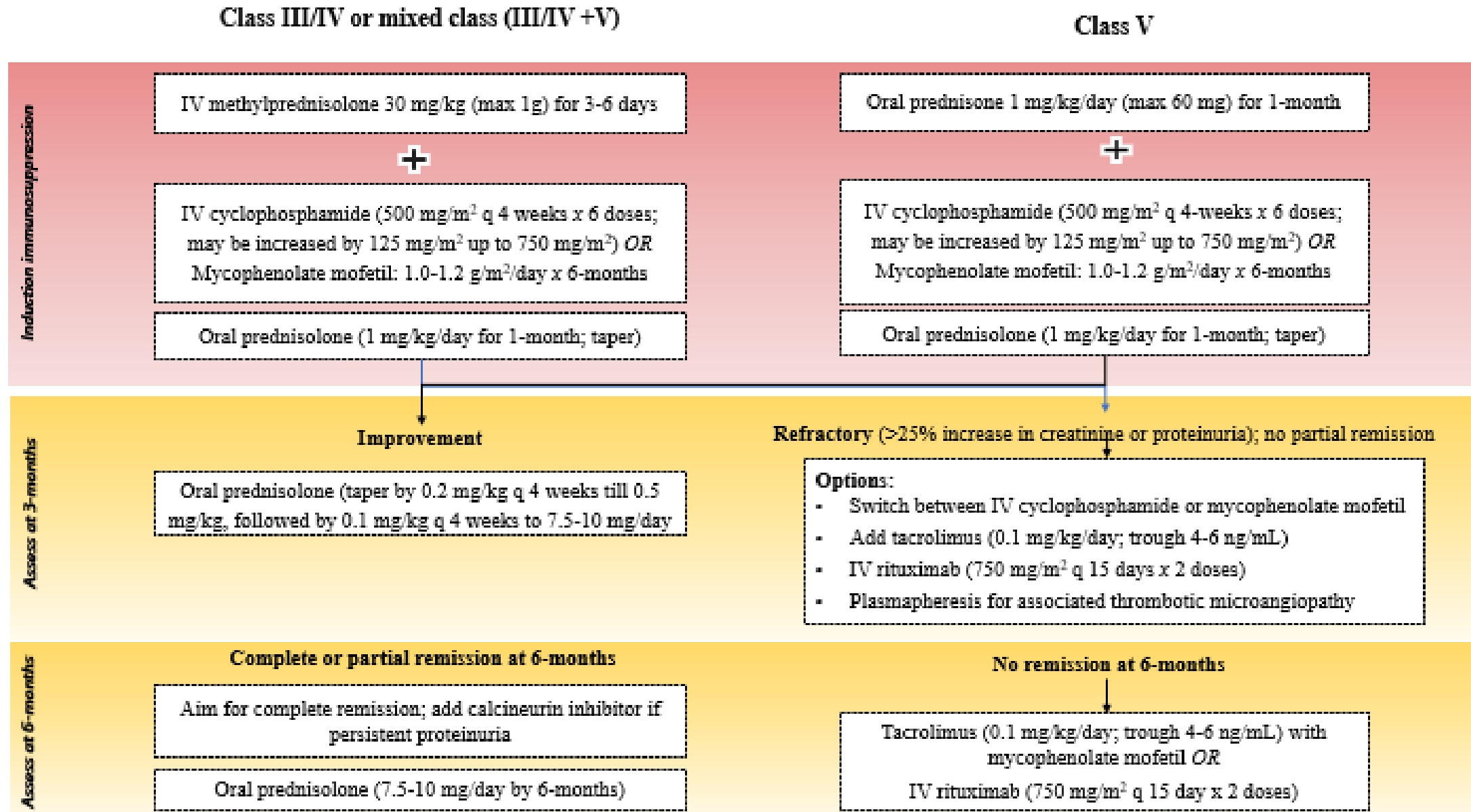
5-year kidney survival in low- and middle income countries



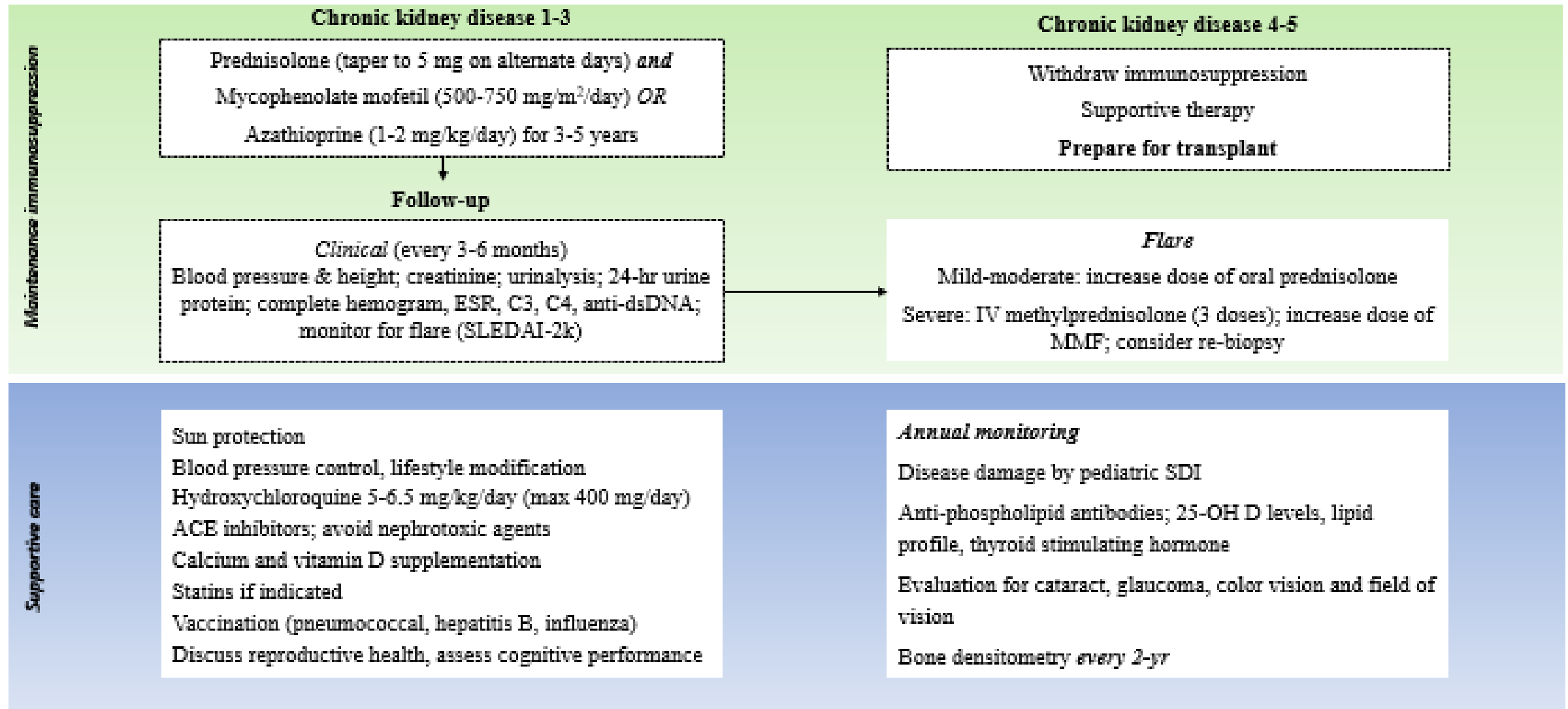
5-year patient survival in low- and middle income countries



Summary of management



Early recognition of flares & supportive therapy



Key Points

Intensive treatment in younger children

MMF similar to low-dose cyclophosphamide (side effect profile, cost, compliance)

Calcineurin inhibitors may have a role in induction therapy; multitarget therapy promising

B-cell inhibition might be useful, in refractory disease

Focus on steroid minimization

Target: complete remission

MMF better for maintenance

Withdrawal of all immunosuppression is debatable

Monitor for disease flare, HCQ, bone health, sun protection, APLA, vitamin D

Thank you